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Original Article

Coagulopathy in the absence of overt DIC in postoperative neurosurgical patients is a strong predictor of poor outcome

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Abstract: Objectives: To assess the prevalence of coagulopathy in postoperative neurosurgical patients and correlate it with the outcome. Materials and method: This longitudinal study was conducted in a tertiary care hospital in the Department of Pathology and Neurosurgery. Ethical approval was taken from the Institutional Ethical Committee - Human Research. Seventy-two (72) participants were recruited within 48 hours of surgery after obtaining consent. Complete clinical and surgical details were recorded. A 6.5 mL venous sample was collected and dispensed in two separate vials. The EDTA sample was run within 2 hours of collection on an automated hematology analyzer to obtain complete blood counts, including platelet count. The citrated sample was run on a fully automated coagulometer to determine PT, APTT, plasma fibrinogen, FVIII assay, and D-dimer levels. Subjects with a DIC-ISTH score of 5 or more were excluded. Coagulopathy was defined as three or more coagulation parameters deranged in a patient. All patients were followed up for the outcome. The outcome was correlated with coagulopathy, and a *p*-value less than 0.05 was considered statistically significant. Results: The study found that the number of hemostatic parameters deranged correlated with outcome ($P < 0.001$). The proportion of patients with coagulopathy was 32/72 (44.4%), while those without coagulopathy were 40/72 (55.6%). Of patients with coagulopathy, 87.5% (28/32) had an adverse outcome, while 12.5% (4/32) had a favorable outcome. The difference was found to be statistically significant ($P < 0.001$). Conclusions: Coagulopathy, defined as the derangement of three or more parameters, is a predictor of poor outcomes in postoperative neurosurgical patients. This timely recognition of coagulopathy can help triage patients requiring appropriate blood products, significantly reducing morbidity and mortality associated with postoperative neurosurgical patients.

Keywords: Disseminated intravascular coagulation, hemostatic parameters, coagulopathy, neurosurgery, outcome, mortality

Introduction

According to the Lancet Commission on Global Surgery held in 2015, 13.8 million people undergo neurosurgery worldwide every year. An estimated 3.5 million new cases are expected annually from South East Asia alone [1].

Surgical patients often show coagulation abnormalities in the postoperative period, but those undergoing neurosurgical procedures have higher coagulation abnormalities than those undergoing general surgical procedures [2]. This is because of various unique cellular and biochemical characteristics of the brain that make it more prone to uncontrolled bleeding and coagulopathy. The brain receives the second highest percentage (20-25%) of cardiac output that is auto-regulated based on the oxygen content of the blood. Due to uncontrolled bleeding during acute injury to the brain or neurosurgery, these auto-regulatory mechanism fails resulting in reduced oxygen delivery to the brain causing cognitive dysfunction and hypoxic injury to the brain [3]. Also, the brain is known to have the highest concentration of tissue thromboplastin. Any injury to the brain parenchyma, either due to traumatic brain injury or during brain tumor resection and necrosis, can cause a massive release of tissue thromboplastin into circulation which results in the activation of the extrinsic pathway of the coagulation process & progression to DIC [4-6]. The brain & spinal cord is also known to have a large amount of platelet-activating factor (PAF) as compared to other tissues in the body. On exposure to ischemia or hypoxia, PAF gets released those leads to platelet aggregation. PAF also contributes to the hypoxia-induced breakdown of the blood-brain barrier, potentially resulting in the release of PAF and other brain-derived prothrombotic molecules to the systemic circulation [7, 8]. After adipose tissue, the brain has the highest lipid content consisting of cholesterol, sphingomyelin, and phospholipids. Any injury to cerebral tissue leads to exposure of anionic phospholipids on the outside of the cell membrane. These phospholipids are highly susceptible to lipid peroxidation which is associated with poor outcomes [7, 9]. Loss of platelets and coagulation factors caused by excessive bleeding during surgery and dilution of these elements secondary to massive transfusion of red cells and plasma substitutes are associated with coagulopathy and mortality after neurosurgery [10].

Overt DIC remains the most dreaded and severe complication in patients who undergo neurosurgery, who mostly succumb to uncontrolled bleeding resulting in poor outcomes. However, those patients who do not have overt DIC may also have underlying coagulopathy, contributing to a poor post-surgical outcome [8, 11].

Furthermore, many studies have found that transfusion is also associated with prolonged hospitalization, increased postoperative complication, and increased rate of mortality in both elective as well as emergency cranial surgery [10, 12]. Thus, deciding what to transfuse and when to transfuse in presence of deranged coagulation parameters is paramount.

In this regard, some studies in the past have tried to evaluate the utility of coagulation parameters like prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen levels, and plasma factor VIII levels in predicting outcomes in postoperative neurosurgical patients but have found conflicting results. While some studies have shown that prolongation in PT & APTT is associated with adverse outcomes in post-operative neurosurgical patients, others have found that mild elevation in PT-INR after neurosurgery does not correlate with post-operative hemorrhagic complications and adverse outcomes. Thus, their utility in predicting outcomes in postoperative neurosurgical patients is controversial [13-15]. Plasma fibrinogen is the first coagulation factor to decrease below critical levels during blood loss as may be seen in these patients. Studies have observed that plasma fibrinogen levels are significantly lower in patients who developed postoperative hematoma as compared to those without bleeding complications [16, 17]. Plasma factor VIII levels have been estimated in only an occasional study with limited data on neurosurgical patients [18, 19].

Though much-conducted research has tried to evaluate individual parameters of coagulation pathways, no single comprehensive study has assessed the effect of all coagulation parameters simultaneously in postoperative neurosurgical patients and compared them with the outcome. Hence, the study was planned to assess all the coagulation parameters, including platelet count, prothrombin time, activated partial thromboplastin time, plasma fibrinogen levels, plasma factor VIII assay, and plasma D-dimer levels, to define the prevalence of coagulopathy in postoperative neurosurgical patients and their correlation with outcome.

Materials and methods

Setting

This observational and longitudinal Study was carried out in the Department of Pathology in association with the Department of Neurosurgery, in a tertiary care hospital in New Delhi from November 2019 to April 2021. The hospital is a 1500 bedded hospital that caters to a huge population from Delhi and the adjacent NCR region as well as adjacent states of UP and Haryana. It conducts approximately 30 neurosurgeries per month.

Ethics

Ethical clearance was taken from Institutional Ethical Committee. The protocol was registered under CTRI after obtaining ethical clearance.

Place

Participants were recruited from the neurosurgical ward of the hospital, between 24 to 48 hours after surgery. Written informed consent was taken from every participant or their guardian before their inclusion in this study.

Inclusion criteria

Patients who had undergone neurosurgery with dissection/resection of the brain in the last 48 hours.

Exclusion criteria

1. Patients with any prior known congenital bleeding or thrombophilic disease. 2. Patients on anticoagulants/antiplatelet drugs. 3. Patients with abnormal platelet count, PT, and APTT preoperatively. 4. Patients undergoing surgery with minimal brain manipulation.

Procedure

A detailed history, including drug history and any previous bleeding disorder, was obtained, and recorded for all patients.

A venous sample (6.5 ml) was collected under strict aseptic conditions and dispensed in respective vials for the following tests.

1. For complete blood counts including platelet count, 2 ml blood was collected in a K_2-EDTA vial and mixed by gentle inversion.

2. For coagulation studies, 4.5 ml of blood was placed in a trisodium citrate vial and mixed by gentle inversion. The sample was rendered platelet free by centrifugation for 15 min at 2000 g and the platelet-poor plasma (PPP) was obtained.

3. The samples were stored at -70°C till further analysis and thawed at the time of testing. Platelet counts were obtained from three part fully automated hematology analyzer (MS95, Melet Schloesing laboratoires, France), and tests of coagulation (PT, APTT, plasma fibrinogen levels, plasma factor VIII levels, and plasma D-dimer levels) were done on fully automated coagulometer (STA-Compact Max^3, Diagnostica Stago S.A.S, France).

Patients with overt DIC as per ISTH-DIC score (based on the patient's platelet count, international normalized ratio (INR), fibrinogen, and D-dimer. A score of ≥ 5 indicates overt DIC) after workup were also excluded from the study.

Coagulopathy

Coagulopathy was defined as derangements in 3 or more hemostasis parameters, including platelet count, PT, APTT, plasma FVIII levels, plasma fibrinogen levels, and plasma D-dimer level [13].

Outcome

All patients were followed up for one month to assess the outcome. A favorable outcome was defined as recovery post-surgery, while an adverse outcome was defined as death or deterioration in health during the stipulated period.

Statistical analysis

The collected data was transformed into variables, coded, and entered into spreadsheets in Microsoft Excel. Data were analyzed and statistically evaluated using the SPSS-PC-19 version. Quantitative data were expressed in mean ± standard deviation. The differences between the two comparison groups were tested by Student's t-test (unpaired). Qualitative data were expressed in percentages, and the Chi-Square test tested the statistical differences between proportions. The risk ratio was calculated for different parameters for mortality prediction, and a *p*-value less than 0.05 was considered statistically significant.

Results

The present study was conducted on 72 patients who underwent neurosurgery with the primary aim of assessing the association of routinely done coagulation parameters, namely platelet count, PT, APTT, plasma FVIII levels, plasma fibrinogen levels, and plasma D-dimer levels, with clinical outcome in the absence of overt DIC.

The age of the patients ranged from 8 to 75 years, with a mean ± SD of 39.0 ± 17.0 years. Of these seventy-two patients, 44 (61.1%) were males, and 28 (38.9%) were females.

Outcome

Among 72 subjects, 57% (41/72) had an adverse outcome, while 43% (31/72) showed a favorable outcome (recovery post-surgery).

Table 1. Screening coagulogram in all neurosurgical patients

Parameter	Number (n = 72)	%
Isolated PC↓	22	30.6
PC↓ + PT↑	5	6.9
Isolated PT↑	3	4.2
PC↓ + APTT↑	2	2.8
PT↑ + APTT↑	2	2.8
Isolated APTT↑	1	1.3

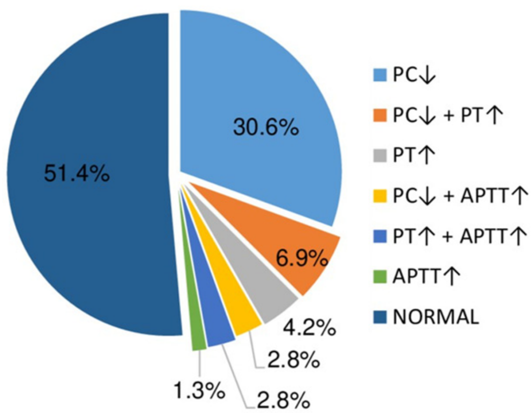

Figure 1. Distribution of hemostatic abnormalities in screening coagulogram (n = 72).

Correlation of outcome with age and gender of subjects: To find the association of outcome and age, the subjects were divided into three groups - < 25 years (20/72; 27.7%), 25-50 years (36/72; 50%), and 51-75 years (16/72; 22.3%). The percentage of patients showing adverse outcomes significantly correlated with the age of the patient, with 6/19 (31.6%), 24/37 (64.9%) & 11/16 (68.7%) deaths in 1-25, 26-50 & 51-75 years of age groups, respectively (p value < 0.05).

As regards gender, the frequency of adverse outcomes was higher in females as compared to males; 71.4% (20/28) in females and 47.7% (21/44) in males, indicating a significant correlation between gender and outcome ($P < 0.05$).

Correlation of outcome and type of surgery: There were 33/72 (45.8%) patients with glioma resection and 34/72 (47.2%) patients who had undergone drainage and evacuation of hematoma following traumatic brain injury or ruptured aneurysm, and 5/72 (7%) patients who had undergone shunt surgery for hydrocephalus.

Table 2. Total number of deranged hemostatic parameters in postoperative neurosurgical patients

Total number of deranged hemostatic parameters	Number (n = 72)	%
0	2	2.1
1	13	18.1
2	25	34.7
3	16	22.2
4	15	20.8
5	1	1.4

There was a statistically significant (p-value: 0.02) higher percentage of deaths reported in patients with intracranial bleeding (21/34, 61.7%) than in those with tumors (20/33, 60.6%), while no deaths occurred post-shunt surgery.

Hemostatic abnormalities in routine screening coagulogram among postoperative neurosurgical patients

Abnormality in screening coagulogram (platelet count, PT & APTT) was observed in 48.6% (35/72) subjects, of which 10 (28.5%) died. Isolated thrombocytopenia was the most common laboratory abnormality seen in 22/72 (30.6%) patients, followed by thrombocytopenia with prolonged PT in 5/72 (6.9%) and isolated prolongation in PT in 3/72 (4.2%). No patient had all three parameters deranged. Thirty-seven (51.4%) patients showed no abnormality in the screening coagulogram (**Table 1**; **Figure 1**).

Hemostatic parameters derangement and outcome

Table 2 shows the number of hemostatic parameters deranged in the subjects. Maximum subjects had two hemostatic parameters deranged, followed by three and four.

Table 3 shows the association of the number of hemostatic parameters deranged in a patient with mortality. Further, it was seen that the patients with adverse outcomes had a significantly higher number of deranged hemostatic parameters than those with favorable outcomes.

Table 3. Association of hemostatic parameters with mortality

The total number of parameters deranged	Survivors		Non-survivors		*p*-value
	No.	%	No.	%	
0	2	100.0	0	0	
1	9	69.3	4	30.7	
2	16	64.0	9	36.0	
3	0	0.0	16	100.0	
4	4	20.0	11	80.0	
5	0	0.0	1	100.0	
The mean number of hemostatic parameters deranged	1.87 ± 1.12		2.88 ± 0.95		< 0.001*

*p value < 0.05.

Table 4. Association of coagulopathy with the outcome

Coagulopathy	Survivors		Non-survivors		*p*-value	Risk ratio
	No.	%	No.	%		
Absent (n = 40)	27	67.5	13	32.5	< 0.001*	2.69 (1.69-4.29)
Present (n = 32)	4	12.5	28	87.5		

*p value < 0.05.

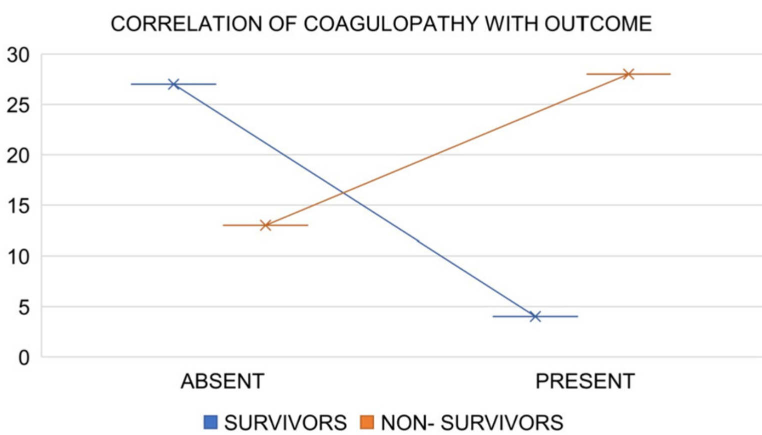

Figure 2. Association of coagulopathy with the outcome (n = 72).

Prevalence of coagulopathy and its correlation with the outcome

Coagulopathy was seen in 44.4%, i.e., 32 out of 72 patients. While 55.6% had less than three deranged parameters.

Amongst the patients who died (n = 41), 28 (68.3%) had coagulopathy (≥ three hemostatic parameters deranged), and 13 (31.7%) did not have coagulopathy. The study observed that mortality was significantly higher in patients with coagulopathy (28/32; 87.5%) as compared to those without coagulopathy (13/40; 32.5%) (P < 0.001) (**Tables 3**, **4**; **Figure 2**).

Discussion

The coagulation screening tests, including platelet count, PT, APTT, and thrombin time, are routinely used to guide transfusion in postoperative neurosurgical patients. However, there are conflicting reports on using PT and APTT alone to predict outcomes in postoperative neurosurgical patients. Few authors have found severe prolonged PT and APTT correlate with a worse prognosis. While in contrast, others have found that mild elevation in PT-INR after neurosurgery does not correlate with postoperative hemorrhagic complications and adverse outcomes [13-15]. In our study, it was also observed that 35 patients had an abnormality in screening coagulation parameters; however, mortality was observed in only ten patients.

Thus, neurosurgeons should not use these parameters alone to guide hemostatic intervention. This is because unnecessary transfusion of blood products during the postoperative period is an independent risk factor for postoperative complications and mortality in patients undergoing intracranial surgery [10, 20]. Multiple transfusions may lead to dilution of platelets and coagulation factors, thus further contributing to disseminated intravascular coagulation [DIC] [4, 7, 8].

Furthermore, an extended panel of coagulation tests includes plasma fibrinogen levels, plasma factor VIII levels, and plasma D-dimer levels. Minimal studies have evaluated these parameters in neurosurgical patients. Few have observed a significantly lower plasma fibrinogen level in patients who developed postoperative hematoma than those without bleeding complications [16, 17, 20, 21]. An occasional study has estimated plasma factor VIII levels. A study reported plasma factor VIII levels to be within the normal limit in 30 patients. In contrast, other studies found that factor VIII levels were significantly higher in neurosurgical patients than in general surgical patients [18, 19].

Thus, no single parameter alone can predict outcomes in postoperative neurosurgical patients. This paves the way for developing a comprehensive panel of coagulation tests to identify coagulopathy in neurosurgical patients and carefully balance the need for blood transfusion with the prevention of unnecessary blood products.

In a study on 85 postoperative patients by Kotru et al. [13], the authors evaluated platelet count, PT, APTT, and TT in all patients. They proposed that the presence of ≥ 3 coagulation parameters with either a severe drop in hemoglobin or the presence of chest infections could predict deaths in neurosurgical patients with a positive predictive value of 80.4%. They found their scoring system to be better than APACHE-II scoring for predicting the development of DIC in postoperative neurosurgical patients. While the role of DIC as a contributory factor to postoperative mortality is well established in these patients, there is a lack of data on how these coagulation parameters may influence prognosis in the absence of overt or impending DIC. After an extensive literature search, we found no study evaluating all coagulation parameters comprehensively. Hence, ours is a novel study where all hemostatic parameters, namely platelet count, PT, APTT, FVIII levels, fibrinogen levels, and D-dimer levels, were evaluated simultaneously. As a result, we found that the mean number of hemostatic parameters deranged being more significantly higher in non-survivor (2.88 ± 0.95) than in survivors (1.87 ± 1.12) with a *p*-value of < 0.001. The authors recommend using a cut of ≥ 3 deranged coagulation parameters to postoperatively predict adverse outcomes in patients undergoing intracranial surgery.

Our study also observed that deaths were significantly higher in patients with intracranial bleeding (61.7%) than in those with tumor resection (60.6%). This is possibly due to the increased release of tissue thromboplastin in patients with intracranial bleeding than in those with tumor resection [3, 5]. Furthermore, in several studies, it has been shown that malignancies are often more associated with a prothrombotic state and have more incidence of venous thromboembolism (VTE) than disseminated intravascular coagulation (DIC) [22, 23].

This study was designed to evaluate a comprehensive panel of hemostatic parameters which can direct transfusion needs in post-operative neurosurgical patients. It is the author's view that the hemostatic status of post-operative neurosurgical patients may be evaluated using these six coagulation parameters i.e., Platelet count, PT, APTT, plasma FVIII levels, plasma Fibrinogen levels & plasma D-dimer levels. A derangement in three or more than 3 parameters should be used to direct transfusion needs while patients having less than 3 deranged parameters may not need transfusion of blood products. Furthermore, these findings may also be used for the development of a scoring system better than the currently applied ISTH-DIC score for predicting prognosis in postoperative neurosurgical patients.

Due to the small sample size, findings in the present study need to be replicated on a larger group of neurosurgical patients for further validation & research in future.

Conclusions

Coagulopathy, defined as ≥ 3 deranged coagulation parameters, out of platelet count, PT, APTT, plasma FVIII levels, plasma fibrinogen levels, and plasma D-Dimer levels, can predict outcomes in postoperative neurosurgical patients. Early recognition of patients at higher risk of an adverse event will help guide transfusion with appropriate blood products and avoid unnecessary plasma transfusion.

Disclosure of conflict of interest

None.

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