

Severity of anemia and hemostatic parameters are strong predictors of outcome in postoperative neurosurgical patients

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ABSTRACT

Objective: Post-operative neurosurgical patients are commonly associated with haemostatic derangements; many a times leading to development of overt disseminated intravascular coagulation (DIC) and eventually death in some of them. The present study has analysed the factors that would predict the outcome in post operative neurosurgical patients with deranged haemostatic parameters.

Methods: This is a prospective, descriptive study over a period of 15 months on 115 post operative neurosurgical patients who were clinically suspected to have DIC and investigated for the haemostatic parameters. Patients with at least one parameter abnormal were included in the study and complete data was available in 85 patients was analysed.

Results: Majority of deaths (22/33, 66.7%) were related to bleeding and end organ failure attributed to DIC. The most common haemostatic abnormalities found were thrombocytopenia with prolonged Prothrombin time (PT) in 48/115 (42.7%) patients. The parameters found significantly different between those who survived and those died were age, post-operative development of chest infections, severe anemia, and renal function abnormalities. Also, patient outcome correlated strongly with marked prolongation of prothrombin time (PT) and Partial thromboplastin time (PTT). However, presence of ≥ 3 coagulation abnormalities, presence of significant drop in haemoglobin post operatively and /or development of chest infection predicted death in postoperative neurosurgical patients with accuracy of 80.4% and this was highly significant ($P = 0.000$).

Conclusion: Presence of ≥ 3 coagulation abnormalities, significant drop in hemoglobin post operatively and /or development of chest infection post-operatively were strong predictors of death in postoperative neurosurgical patients.

Key words: Disseminated intravascular coagulation, hemostatic parameters, neurosurgery, partial thromboplastin time, plasma prothrombin time, thrombin time, thrombocytopenia

Introduction

The occurrence of hemostatic abnormalities in surgery has been described since 1930.^[1] Intracranial surgery in particular,

whether for trauma,^[2] vascular pathology,^[3] or malignancy^[4,5] has been shown to be associated with a higher incidence of coagulation disorders compared with general surgical procedures.^[6] A combination of factors contributes to triggering disseminated intravascular coagulation (DIC), including the release of fat and phospholipids from tissue into the circulation, hemolysis, and endothelial damage.^[7] Furthermore,

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because postoperative neurosurgical patients are to be kept on ventilator or are catheterized for a longer time are likely to get hospital acquired infection which predisposes them to sepsis-induced DIC as well. Hence, neurosurgical patients are commonly associated with hemostatic abnormalities.^[8-10]

There are sufficient data on the diagnosis of DIC; however, there are limited data on how serial monitoring of hemostatic parameters affects the clinical outcome. This is especially relevant as heavy transfusion support would alter or mask the laboratory features of overt DIC. This study is an observational/prospective study carried out on postoperative neurosurgical patients to study the outcome of postoperative neurosurgical patients with deranged hemostatic parameters and to correlate it with the laboratory and clinical parameters.

Materials and Methods

This is a prospective observational study of 85 postoperative neurosurgery patients who were clinically suspected of DIC with at least one deranged hemostatic parameter namely platelet count (PC), prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time (TT). None of these patients had any known preexisting hemostatic disease, stroke, and vasculitis. The patients were enrolled from August 2011 to November 2012.

The detailed clinical and laboratory data were analyzed in these 85 patients. The complete hemogram and baseline hemostatic laboratory parameters were done as and when requested by the treating clinician. Postsurgical data, especially with reference to biochemical parameters, transfusion requirements and outcome, were noted from the case records. The hemogram was done on Sysmex 1800i. PC was also compared with the manual assessment on peripheral smear. PT, PTT, and TT were performed using the kit (Diagnostica Stago) on fully automated coagulometer. The normal values of PT and a PTT were 11–15 s and 29–35 s, respectively. Statistical analysis was performed using Chi-square tests, Student's *t*-test, Kruskal–Wallis test along with multivariate tests using logistic regression and receiver operating characteristic curve analysis on SPSS Software version 16.0.

Results

There were 66 males and 49 females with age ranging from 2 months to 80 years and a median of 45 years. There were 63 postoperative cases of brain tumors, 42 patients who had undergone craniotomy for treatment of head injury, drainage of hematoma, hydrocephalus, and shunt surgeries. Ten patients had primary central nervous system (CNS) infections.

Outcome and clinical parameters

Age

The median age was 43 (4–80) years, of those who survived and 53 (2 months–80) years for those who were dead ($P = 0.051$).

Figure 1 shows that in younger age almost all deaths were DIC related however; with advancing age there were others factors that influenced death.

Clinical presentation of patients suspected of developing disseminated intravascular coagulation postoperatively

Fifty-three patients had intracranial bleeds in the form of postoperative hematomas or re-bleeds or sub-arachnoid hemorrhage. On the other hand, 13 patients had bleeds from sites other than intracranial sites. The percentage deaths were slightly higher in the latter category (5/13, i.e. 38.5%), but the difference was not statistically significant ($P = 0.676$). 80% (4/5) deaths in patients who had bleeding in non-CNS sites died due to DIC [Table 1].

Thirty eight patients did not show any apparent signs of infection. Of the remaining 47, 33 patients had chest infection (70.2%), which was significantly higher. Furthermore, chest infections were associated with higher mortality (54.5%) compared to infections at other sites (35.7%). This difference was statistically significant. ($P = 0.05$). Furthermore, the presence of co-morbidities in the form of diabetes, hypertension,

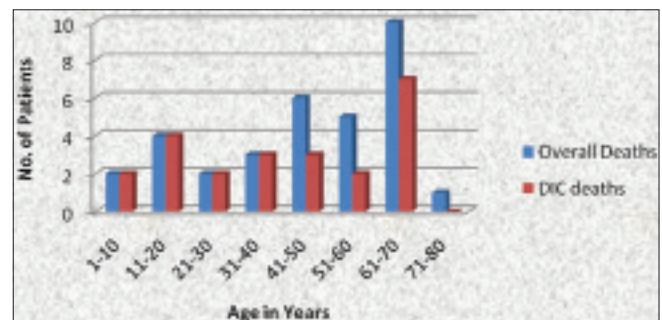


Figure 1: Correlation of patient outcome in different age groups of patients with hemostatic abnormalities in neurosurgical patients

Table 1: Correlation between clinical characteristics and outcome in postoperative neurosurgical patients with hemostatic abnormalities

Clinical characteristic	Total patients	Dead	Percentage of deaths	<i>P</i>
Total patients	85	33	38.8	-
Clinical presentation of DIC				
Infection/sepsis	36	10	27.7	0.169
Bleeding	34	18	52.9	
Laboratory parameters	15	5	33.3	
Site of bleeding				
Intracranial	53	19	35.8	0.676
Non-CNS sites	13	5	38.5	
Site of infection				
Chest infections	33	18	54.5	0.05
Infection in other sites	14	5	35.7	
Presence of co-morbid condition	26	19	73.1	0.00

DIC – Disseminated intravascular coagulation; CNS – Central nervous system

liver, and kidney disease was significantly related to death ($P = 0.001$).

Correlation of anemia and outcome

21/85 (25%) patients in our study group had normal hemoglobin for age and sex and continued to have normal hemoglobin during the course in hospital. Only 1 of these patients died due to DIC. Development of anemia during the hospital stay was highly correlated with the adverse outcome ($P = 0.006$). Rapid drop in hemoglobin postoperatively was even more significant [Table 2].

Outcome and hemostatic parameters

The most common laboratory abnormality found in our patients was thrombocytopenia with prolonged PT followed by isolated prolonged PT. There was no patient who had normal PC with both prolonged PT and PTT. 33/85 (38.8%) patients had died in the study group of which 25.9% (22/85) died because of DIC. Hence, 66.7% of deaths (22/33) were because of DIC [Figure 2].

Patient outcome correlated with the severity of coagulation abnormalities significantly. Severe prolongation of PT and PTT (>2 times) correlated significantly with the deaths due to DIC ($P = 0.001$ and 0.004 , respectively). Prolongation of TT, however, was not significant, the reason being that numbers of patients who also had prolonged TT were few.

No particular combination of hemostatic parameters was associated with worse outcome. The analysis was thus stratified according to the number of coagulation abnormalities present into the two categories.

- Group A with <3 coagulation abnormalities and,
- Group B with ≥ 3 abnormalities.

Maximum number of deaths occurred when ≥ 3 coagulation parameters were deranged i.e., 14/22 (63.6%) [Table 3]. Number of coagulation factor abnormalities were also significantly present in patients who developed chest infections postoperatively ($P = 0.002$). Drop in platelets which

is otherwise highly suggestive of DIC, did not correlate with the presence of higher number of coagulation parameters derangements ($P = 0.040$) present. Thereby suggesting that there were other factors leading to thrombocytopenia apart from DIC and its presence did not necessarily signify impending DIC.

So at the end of this univariate analysis, it was found that presence of chest infection and presence of anemia and ≥ 3 coagulation abnormalities had a strong bearing on the overall mortality of patients suspected with DIC.

Multivariate analysis for predictors of DIC deaths in this cohort showed that presence of ≥ 3 coagulation abnormalities was the most significant parameter ($\beta = 2$) that influenced the outcome due to DIC. The presence of chest infection ($\beta = 1.4$) and the presence of severe drop in hemoglobin postoperatively ($\beta = 1.6$) were the other two parameters which influenced the outcome. Hence, it was concluded that ≥ 3 coagulation abnormalities along with the presence of either drop of hemoglobin postoperatively or development of chest infection postoperatively were strong predictors of death due to DIC. This assessment system predicted DIC deaths with accuracy of 80.4% and this was highly significant ($P = 0.0001$).

Discussion

There is no single laboratory test that can establish or rule out the diagnosis of DIC. Furthermore, DIC is an extremely dynamic

Table 2: Correlation of blood cell count parameters with outcome in postoperative neurosurgical patients

	Total patients	Total deaths (%)	Significant	Deaths due to DIC (%)	P
Mild anemia	28	10 (35.7)	0.006	7 (70)	0.026
Moderate to severe anemia	35	20 (57.1)		14 (40)	
Rapid drop in Hb	60	30 (50)	0.001	20 (66.7)	0.005
↑TLC	59	24 (40.7)	0.390	15 (62.5)	0.631
↓platelet count	57	25 (43.9)	0.130	17 (68)	0.384

DIC – Disseminated intravascular coagulation; TLC – Total leukocyte count; Hb – Hemoglobin

Table 3: Comparison of between Group A (<3 coagulation abnormalities) and Group B (≥ 3 Coagulation abnormalities) categories with patient outcome

	Total patients (85)	Total deaths (33) (%)	Significant	DIC – deaths (22) (%)	P
Group A (<3 coagulation abnormalities)	63	19 (30.2)	0.006	11 (57.9)	0.008
Group B (≥ 3 coagulation abnormalities)	22	14 (63.6)		11 (78.6)	

DIC – Disseminated intravascular coagulation

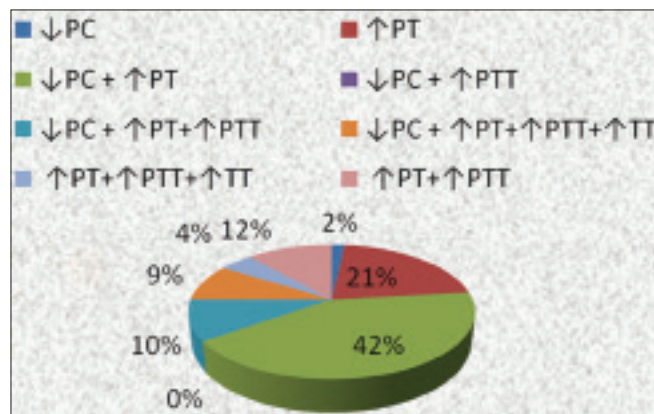


Figure 2: Distribution of hemostatic abnormalities in neurosurgical patients

situation and the tests are a snapshot of this dynamic state. Hence, a combination of tests which when repeated in a patient suspected with DIC can be used to diagnose the disorder with reasonable certainty in most cases.^[11,12] However, in clinical practice, all these laboratory findings are seldom found reflective of the underlying state because with the slightest suspicion of DIC the patient is transfused with platelets and fresh frozen plasma which alter the interpretation of these tests.

In this study of 85 patients, prolonged PT was the most common abnormality found (97.6%). Prolonged PTT was relatively less common (35.3%). The severe abnormalities of PT and PTT (>2 times the normal control sample) significantly co-related to the adverse patient outcome ($P = 0.001$ and 0.004 , respectively). International Society on Thrombosis and Hemostasis scoring for DIC which is the most common scoring pattern used for DIC, has prolonged PT and thrombocytopenia as an important predictor of severity of overt DIC.^[12] However, thrombocytopenia did not correlate with the adverse patient outcome in our cohort of patients. Unlike study by Stephan *et al.*, who showed that in surgical Intensive Care Unit (ICU) patients with DIC, presence of thrombocytopenia was highly co-related with outcome ($P = 0.02$).^[13] Otherwise also, irrespective of the cause, thrombocytopenia is an independent risk factor for ICU-related mortality.^[14] Prolonged TT was the least common abnormality: (14.1%). However, when present it was associated with 85.7% of DIC related deaths in the category. Although the difference was not statistically significant, none of the patients with severe prolongation of TT survived. The reason for this discrepancy could be that the number of patients with prolongation of TT were few and hence, were statistically insignificant. In our cohort, prolonged TT was an ominous sign as it although present in few patients only, but was associated with high mortality. Furthermore, in general, these coagulation tests are prolonged when coagulation level factors are below 50%. Moreover, levels needed for adequate hemostasis is between 25% and 50%.^[15] Hence, although these tests poorly reflect *in vivo* hemostasis but form a useful low-cost guide for the need of transfusions. Another important factor in the diagnosis of DIC with the help of S. Fibrinogen and D-dimers is that serum fibrinogen is an acute phase reactant and despite ongoing consumption may remain within the normal range for a long time.^[13] Furthermore, raised D-dimer may be seen in ICU settings in other non-DIC conditions such as recent surgery, inflammation, and venous – thromboembolism. Moreover, D-dimers are metabolized in the liver and excreted in kidneys, hence would be falsely elevated in liver and kidney dysfunction.^[16] These conditions are not uncommon in postoperative neurosurgical patients, and hence offer limited value in diagnosis and management.

Outcome analysis of these patients showed that 33 patients died, of which 66.7% of deaths (22/33) were because of DIC. Patients died in spite of mild derangements in the hemostatic parameters in the majority. The type of coagulation parameter derangement

had no influence on the overall outcome ($P = 0.220$) and also with DIC deaths ($P = 0.334$). However, when the patients were stratified according to the number (3 or ≥ 3) of coagulation abnormalities present, the difference in the overall mortality ($P = 0.006$) and DIC related mortality ($P = 0.008$) was significant. Existing data have always stressed on the thrombocytopenia, PT, serum fibrinogen and D-Dimer for assessing the presence as well the severity of DIC. However, our data show that the presence of number of coagulation abnormalities with especially prolonged TT was sufficient and predictive of overall as well as DIC related mortality. Many studies carried out so far have emphasized that severity of coagulopathies measured by the degree of prolongation of PT or thrombocytopenia or low serum fibrinogen.^[17] However, none has mentioned that number of abnormalities deranged could have a bearing on overall prognosis. This is especially relevant as these patients quite often receive multiple transfusions which mar the efficacy of these tests in judging the severity of DIC.

Clinical correlates

The neurosurgical patients suspected with DIC showed that patients with a higher age group were more likely to die ($P = 0.051$). It was observed that all patients who died up to 40 years of age were because of DIC, however, as the age advanced there were additional factors contributing to the death apart from DIC. This could be explained by the fact that increasing age was associated with the presence of co-morbid conditions ($P = 0.0010$), which is explainable, as the incidence as well as the complications related to Diabetes, hypertension increase with age. There are no studies in literature which directly address this issue of affect of co-morbidities on outcome in DIC. However like any postsurgical risk of death which increases with the presence of co-morbidities holds true for this cohort of patients too. However, surprisingly this significance was also seen when the outcome of only DIC deaths was compared. Multivariate analysis performed thereafter did not show co-morbidity as a predictor of DIC related mortality.

The presence of chest infections came out to be significant risk factor for overall mortality as well as DIC related mortality. It also emerged as a strong predictor of DIC Deaths even in multivariate analysis ($P = 0.004$). The presence of infections at other sites for example, urinary tract infection was less frequent (14/33). Notably, the numbers were also few to account for any statistical significance. Postoperative primary CNS infections in our cohort of patient were also low; in fact, no patient suspected to have DIC had postoperative CNS infections. Neurosurgical patients admitted to the ICU are at risk of developing life-threatening nosocomial infections, especially with organisms resistant to commonly used antibiotics. In a study of 120 neurosurgical patients from West Indies showed that of 120 neurosurgical patients admitted to the ICU 28.8% developed infections after a mean of 5 days in the ICU.^[18]

Hematological parameters

25% of patients in our study group had normal hemoglobin for age and sex and continued to have normal hemoglobin during the course in hospital. Only three patients died in this category of which one died due to DIC. Otherwise, severity of anemia was highly correlated with the outcome ($P = 0.006$). The severity of anemia also emerged as a strong predictor of DIC related deaths on multivariate analysis. Salim *et al.* also showed in 1150 patients of traumatic brain injury that presence of anemia had a significant affect on overall morbidity and liberal use of Blood transfusion in fact worsened the clinical outcome.^[19] The cause of anemia in these patients was not evaluated, but drop of hemoglobin during hospital stay could be because of the perioperative blood loss or bleeding because of impaired hemostasis. The possible reason for low hemoglobin affecting outcome could be because the higher likelihood of patient having multi-organ failure exaggerated by to preexisting tissue hypoxia. There are studies which correlate anemia with traumatic brain injury as a predictor of worst prognosis, suggesting hypoxia as a cause of the second injury in the group.^[20] However, the data are minimal on the same. APACHE-II scoring also considers low hematocrit as a predictor of worse outcome^[21] but low hemoglobin as a predictor of DIC deaths in neurosurgical patients is unknown.

Predictors of disseminated intravascular coagulation deaths in postoperative neurosurgical patients

Multivariate analysis using the above-mentioned discriminators of DIC deaths showed that severity of anemia ($P = 0.011$), presence of chest infections ($P = 0.004$), and number of hemostatic parameters deranged (≥ 3) (0.004) were the only predictors of DIC-related mortality in neurosurgical patients suspected to have DIC. Presence of ≥ 3 hemostatic parameters deranged with either the severe drop of hemoglobin and/or presence of chest infections accurately predicted death in 80.4% death which was statistically significant ($P = 0.001$). This is scoring system developed for predicting DIC-related mortality in neurosurgical patients with suspected DIC is simple, cost effective, and helpful as compared to APACHE-II^[21] disease classification system which is very complex and does not look into neurosurgical patients specifically.

Conclusion

This study brings out certain pertinent points that although PC and prolonged PT, APTT are hallmarks of DIC but may not be reflective of the outcome in isolation. The study developed a dynamic and a practical scoring system to predict of DIC death that had a high predictive power and was also simple and cost effective. However, whether it has predictive efficacy only in neurosurgical patients or in other groups predisposed to DIC needs to be evaluated. Furthermore, it needs to be prospectively studied for further validation on larger group of patients.

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Conflicts of interest

There are no conflicts of interest.

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