Research Article

Role of perioperative plasma D-dimer in intracerebral hemorrhage after brain tumor surgery: A prospective study

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Abstract

Background: Intracerebral hemorrhage (ICH) is one of the most feared complications after brain tumor surgery. Despite several factors being considered to influence bleeding, an increasing number of clinical studies emphasize that hemostatic disorders, developed during surgical aggression and tumor status, could explain unexpected ICH. The objective of this prospective study was to evaluate the influence of perioperative D-dimer levels on ICH after brain tumor surgery.

Methods: This prospective, observational, 18-month study, at a single third-level hospital, included all consecutive adults operated on brain tumors and postoperative stay in an intensive care unit. Three blood samples evaluated D-dimer levels (A-baseline, B-postoperative and C-24 hours after surgery). The normal range considered was 0-500ng/ml. ICH, as a primary outcome, was defined as bleeding that generates radiological signs of intracranial hypertension either by volume or by mass effect on the routine CT scan 24 hours after surgery. Other tumor features and hemostasis variables were analyzed. Chi-squared and Fisher’s exact test were used in the inferential analysis for qualitative variables and Wilcoxon and T-Test for quantitative ones. P-value < 0.05 was considered significant for a confidence interval of 95%.

Results: A total of 109 patients operated on brain tumor surgery were finally included, 69 male (63.30%) and 40 female (36.70%), with a mean age of 54,60 ± 14,75 years. ICH was confirmed in 39 patients (35,78%). Their average of DDimer was A-1.526,70 ng/dl, B-1.061,88 ng/dl, and C-1.330,91 ng/dl (A p0.039, B p0,223 C p0.042, W-Wilcoxon test). The male group was also associated with ICH (p0,030 X2 test). Of those 39 patients with ICH, 30 in sample A (76,9%), 2 0 in sample B (51,28%) and 35 in sample C (89,74%) had a D-dimer > 500 ng/dl (p0.092, p1, p0,761 X2 test) and the relative risk of developing a postoperative hematoma in this patients was increased 0,36-fold presurgery, 0,25-fold postsurgery and 0,40-fold 24hours after surgery. D-dimer variation, had no statistical significance (p0,118, p0,195, p0,756 T-test). Platelets and prothrombin activity were associated with D-dimer levels only in sample A (p 0.02 and p 0.20, W Wilson).

Conclusion: High levels of perioperative D-dimer could be considered a risk marker of ICH after brain tumor surgery. However, more studies would be worthwhile to confirm this association and develop primary prevention strategies for stroke.
Background

Cancer incidence is increasing globally, being a leading cause of death worldwide [1-3]. Though brain tumors are uncommon, they cause morbidity and mortality disproportionate to their incidence [4,5]. Despite individualized management and optimal surgical measures, a removal of a brain tumor carries a higher risk of intracerebral hemorrhage (ICH) [6,7]. Multifactorial and sometimes unexplained, it is likely the most feared complication leading to poor functional prognosis, even risk of death [8,9].

Functional integrity of the hemostatic system and normal standard coagulation tests are both required for safe neurosurgical procedures, but other specific acquired hemostatic disorders, not routinely measured, could be developed during cancer surgery and increase or predict bleeding risk [10-12].

D-dimer, a fibrinogen compound with high molecular weight, formed during activation of the coagulation system, derived from the degradation of crosslinked fibrinogen when the dissolution of a fibrin clot, at the end of the coagulation cascade. Its activity is a global reflection of clot formation and lysis. It can’t be generated in vitro conditions after blood collection so, that formation is considered a reflection of in vivo hemostatic activity. So, it appears to be one of the most valuable parameters in thrombosis research [13,14].

Until a few years ago, plasma D-dimer variation was explained by prothrombotic and inflammatory tumoral state, insufficient control of an antiinflammatory response, multifactorial coagulopathy, surgery, or biological conditions. In spite of that, plasma measurement of D-dimer has become essential in clinical to exclude deep vein thrombosis, pulmonary embolism and disseminated intravascular coagulation. It is considered a biomarker of worse-outcome in cardiovascular disease, with a convincing evidence of association with ischemic stroke, but conflicting and potentially more complex with ICH, until now [15-18].

Poor neurological outcome and high disability scores after ICH have lately increased the interest to determine new biomarkers of bleeding. The recent literature suggested that D-dimers can be used to evaluate and predict clinical prognosis in neurosurgical patients, including after subarachnoid hemorrhage, ICH, ischemic stroke, trauma, dural arteriovenous fistula and intracerebral neoplasms [19-23].

Increasing incidence and morbi-mortality of brain tumors conducted this study to evaluate perioperative plasma D-dimer as risk biomarker of bleeding after brain tumor surgery.

It should be noted during the COVID-19 pandemic, early and effective predictors of clinical outcomes were urgent needed for risk stratification. It has been reported COVID-19 was associated with hemostatic abnormalities and elevated D-dimer levels were observed in non-survivors. It was considered, with a nonwell established optimal cut-off, the earliest and most helpful biomarker to predict poorer outcomes and improve management. Thanks to the pandemic, the relevance of D-dimer was considered again [24-27].

Methods

A prospective, observational, 18-month study (July 2013-December 2014) was conducted in the Neurointensive Care Unit (N-ICU) at Miguel Servet University Hospital, a single third-level center in Spain. The study included all consecutive adults operated on elective brain tumor surgery by trained and experienced neurosurgeons with postoperative stay in the N-ICU. Dead people in the operating room, incomplete coagulation test (by lost or mistake) or nontumor tissue were exclusion criteria.

Two blood samples were drawn from a jugular central venous catheter placed prior to surgery (A-presurgery or baseline, B-postsurgery and C-24 hours after surgery). The cut-off value of D-dimer was < 500 mg/dl. D-Dimer was immediately measured with two autoanalyzers ACL-TOP 500 y 700 CTS by latex particle immunoassay. Competence and quality management of medical laboratory was accredited by ISO 15189: 2012 certification. Patients did not receive any prophylaxis or hemostatic therapy.

ICH, as a primary outcome, was defined as bleeding that generates radiological signs of intracranial hypertension (IH) either by volume or by mass effect on the routine head computerized tomography (CT) scan 24 hours after surgery. All CT scans were assessed by a comitte of neuroradiologists and neurosurgeons. Other filiation data were collected (age, gender, previous coagulopathy, origin and tumor tissue, routine hemostasis and hemogram parameters). Perioperative management of antiplatelet and anticoagulant agents was properly considered.

Categorical variables were presented as frequencies and percentages. The association between qualitative variables was determined by Pearson Chisquared test ($X^2$) or Fisher’s exact test. Wilcoxon-test and T-Test were considered to establish correlation between quantitative variables. $P$- value < 0.05 was significant for confidence interval of 95%.

Data collection worksheets were stored and analyzed by SPSS® Statistic Software 21.0.0. Each participant was assigned a registration number to to data anonymization. Ethical approval for this study was obtained from Ethics Committee of Clinical Investigation in Aragon (CEICA, n° CP14/2013).

Results

A total of 120 patients were operated on neurosurgery during 18 months. But finally 12 of them were excluded, 10 due to incomplete blood sample and two due to absence of tumor tissue in the histopathological analysis. From 109 patients, 69 were male (63,30%) and 40 female (36,70%)
with a mean age of 54.60 ± 14.75 years; 34 patients (31.2%) were < 50 years old.

Primary tumor resection (68.80%) was more common than recurrent tumor (21.10%) and metastases (10.09%). There were different histological types of brain tumor, being high-grade glioma the most prevalent (39.44%) followed by meningioma (27.52%). The least common was mesenchymal (4.58%). Volume were < 30 ml in most of them (64%) and subtotal removal (≥ 90% of volumen) was possible in more than 85%. Most patients (71.5%) did not have postoperative neurological complications: focal neurologic deficit 24.77% was the most prevalent, followed by headache (5.5%). Only eleven patients (10%) suffered from critical care complication, 8 of them sepsis. According to hemostasis and bleeding disorders, one patient had unexplained preoperative anemia 8.9 g/dl and another one a previous inherited condition (glucose-6phosphate dehydrogenase deficiency G6PDD).

Fifteen units of blood products were transfused, 12 of 14 were intraoperative red blood cells (RBC) and also, intraoperative, 1 pooled platelets (PP). 5 patients needed TXA and 1 prothrombin complex (PC). Noone needed neither frozen plasma (FP) nor FVIIa.

The average length of stay in ICU was 3.34 ± 2.77 days. All patients, except two who died due to massive ICH, were discharged from ICU to neurosurgery hospital floor (Table 1).

Most of patients suffered from minimal disorders in routine hemostasis and hemogram parameters (hemoglobin (Hb), hematocrit (Ht) platelets (P), international normalized ratio (INR), activated partial thromboplastin time (APTT), Prothrombin Activity (PA) and fibrinogen (Fb)) but within normal ranges (Tables 2-4). It should be highlighted that antiplatelet and anticoagulant therapy were both adequately stopped. Despite normal routine and specific baseline hemostasis and coagulation, male with G6PDD suffered from ICH and needed 2 intraoperative RBC.

ICH was finally confirmed in 39 patients (35.78%). The average of D-dimer in those patients was A-1.526,70 ng/dl, B-1.061,88 ng/dl and C-1.330,91 ng/dl. HDD-dimer levels were lower in patients without ICH A-543,97 ng/dl, B-572,02 ng/dl and C-965,23 ng. Maximum value of D-dimer in sample A was 15.053 ng/dl and minimum 39 ng/dl, 5.043 ng/dl and 46 ng/dl in B and 5.494 ng/dl and 36 ng/dl in C respectively (Table 5).

Inferential analysis determined that none of the clinical and tumor data analyzed were statistically associated with ICH, except male group (p0.030 X2 test) and ICU stay (< 0.01 W-Wilconxon) (Table 1).

Postoperative D-dimer levels were extremely elevated in the two patients who suffered from ICH associated with ischemic stroke and also in the three blood samples in those who died. It should be noted that among patients with ICH, 30 of them (76.9%), in sample A, 20 (51.28%) in sample B and 35 (89.74%) in sample C had D-dimer levels > 500 ng/ dl, compared with D-dimer levels < 500 ng/dl (p0.092, p1, p0.761 X2-test).
The relative risk of developing a postoperative hematoma was increased 0.36-fold presurgery, 0.25-fold postsurgery and 0.40-fold 24 hours after surgery in patients with D-dimer > 500 ng/dl, respectively.

Regression analysis showed plasma D-dimer levels were statistically associated only with baseline P and PA (p<0.02, p<0.00, Pearson correlation) (Tables 8-10). Significant association between standard coagulation and ICH was demonstrated only with baseline APTT and postoperative P (p<0.02, p<0.00, Wilcoxon test) (Tables 11-13).

Discussion

Poor neurological outcomes after ICH increased the interest in new biomarkers which could identify the risk of life-threatening complications and reliable prognostic criteria. Sequential D-dimer levels have been traditionally determined to detect thromboembolism, structural disorder in traumatic brain injury, as a worse-outcome marker in cardiovascular disease and, despite being uncommon in neurosurgery field, also in prognosis after stroke, but mainly ischemic [28-31].

Juvela, et al. (Stroke 2006) [32] analyzed D-dimer after aneurysmal ICH, with worse long-term results and more advanced stages if elevated, being probably useful as a risk marker of poor outcome. Delgado, et al. (Neurology 2006) [33] predicted early neurologic deterioration and poor outcome after ICH with increased D-dimer levels in 98 consecutive acute ICH. Chiu, et al. (J Clin Neurosci 2012) [34] confirmed higher D-dimer level after spontaneous ICH was associated with 30-day mortality and Castelnouvo (Thromb and Haemost 2017) [20]. The largest meta-analysis, ischaemic and haemorrhagic stroke, similar findings to Zakai, et al. (Front Neurol 2018) [36] revealed that high level of D-dimer was associated with risk of ICH, so it was suggested to be a potential biomarker of bleeding in ICH.

Qi Zhou, et al. (Brain and Behavior 2021) [21] confirmed recently in a retrospective design with 1.332 patients the elevation of D-dimer is an independent risk factor for poor functional prognosis and mortality in spontaneous ICH.

Table 4: Routine hemogram and hemostasis. C- Sample.

Table 5: D-dimer levels in ICH/no ICH group.

Table 6: D-dimer and ICH.

Table 7: D-dimer variation in ICH/no ICH group.

Table 8: Standard coagulation and D-dimer –A.

Table 9: Standard coagulation and D-dimer –B.
Obviously, it is very difficult to discard the influence of all those factors on the results but, despite several limitations, this is the first prospective study in the literature to evaluate how perioperative D-dimer behaves in the presence of ICH and with the rest of the hemostatic parameters in order to consider it as a risk marker of unexplained bleeding.

Baseline and 24-hour after aggression samples were statistically associated with ICH, so high D-dimer could be considered as risk marker of bleeding and poor prognosis in the perioperative of brain tumor. Regression analysis only confirmed significant association with baseline P and PA, probably explained by hipercoaguability and inflammation. A larger sample would be necessary to be replaced.

In regard to standard parameters, several patients suffered from a minimal disorder during perioperative period, however statistical association with ICH only could be demonstrated with baseline APTT and postoperative P. This association seems to be coherent (by consumption coagulopathy during surgical aggression in that tumoral state) but too specific without data to compare in the literature, so these results can not consider the standard parameters as risk markers.

This study is based on a small sample size of a single-center and there is no data available to compare with other brain tumor patients, so findings should be interpreted with caution. There is also no literature for gender and ICH. An increased prevalence of cardiovascular disease and spontaneous ICH is described in males so, it could explain our association [38-40]. But a larger sample size would be necessary to compare this and the other features after ICH. Obviously, several comorbidities, biological conditions, bleedings disorders, drugs, skills and surgical factors could influence bleeding.

Although it is very difficult to control all these interfering factors, heterogeneity was minimal and epidemiologic and tumor features were similar to general population [1-6,37], perioperative management of antiplatelet and anticoagulant agents was adequately considered, preoperative samples were carefully analyzed and neurosurgeons were experts on applying the latest knowledge and minimally invasive neurosurgical techniques in brain tumors.

With regard to the main variable, the lack of established criteria in the literature lead to measure ICH objectively by a committe of neuroradiologists and neurosurgeons, avoiding evacuation criteria very controversial between studies. Other types of intracranial hemorrhage (epidural, subdural and subarachnoid) and ischemic stroke were also evaluated in the CT scan. Fortunately, no more types of hemorrhage were considered as risk marker of bleeding and poor prognosis in the perioperative of brain tumor.
diagnosed. High levels of postoperative D-dimer found in two patients with ischemic stroke and ICH were not considered for the analysis, however this result would support previous studies to consider high D-dimer as a potential risk marker for both ischaemic and haemorrhagic stroke with poor functional prognosis.

G6PD deficiency, considered latent and more severe in males, would manifest as hemolytic anemia. Despite normal preoperative hemostasis and coagulation, surgical aggression and/or some drugs could bring out this latent deficiency and lead to ICH. However, guidelines do not recommend prophylactic transfusion before major surgery. The association analysis was not considered with an only case [41,42].

All these findings would confirm that perioperative D-dimer levels could be a risk marker of ICH with a high impact on future research to screen patients at risk of stroke. More studies would be worthwhile to confirm this association and develop primary prevention strategies.

Conclusion

High levels of perioperative D-dimer could be considered a risk marker of ICH after brain tumor surgery. However, more studies would be worthwhile to confirm this association and develop primary prevention strategies for stroke.

Declarations

Ethics approval and consent to participate: Written informed consent was required for all participants. Comité de Ética de Investigación de la Comunidad de Aragón (CEICA) approved the study (NºCP14/2013).

Availability of data and materials: All data generated or analyzed were included in this published article.

Authors contributions

Author’s contributions this study are

EVJ: main author, design, methodology and writing

ANP: coordination and design

JCP: collection and analysis of neurosurgery data

CRL: statistical analysis

NFM: blood sample analysis

LSG: visualization, writing-review, expert in brain injury

MQD: visualization, writing-review and editing, expert in hemotherapy

JCL: visualization, writing-review and editing.

Acknowledgement

Thanks to Coagulation Laboratory, Intensive Care, Hematology and Neurosurgery Departments at Miguel Servet University Hospital. Thanks also to Faculty of Medicine at University of Zaragoza.

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