Evaluation of the Safety of Fibrinogen Concentrate Administration for Bleeding Control in Neurosurgery

Avaliação da Segurança da Administração do Concentrado de Fibrinogênio no Sangramento em Neurocirurgia

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ABSTRACT
Background and Objective: Bleeding control is extremely important in any surgical procedure, especially in neurological surgery. Hemodilution with colloid and crystalloid may predispose to functional impairment of fibrinogen, which replacement may be beneficial. We evaluated the safety of fibrinogen concentrate administration in patients who underwent a neurosurgical procedure.

Method: We reviewed the medical charts of a series of consecutive patients who received prophylactic fibrinogen concentrate and underwent a neurosurgical procedure for different pathologies in our institution from July 2009 to July 2010. Adverse effects, red blood cells and platelet transfusions were carefully recorded in all cases.

Results: Twelve patients were included in our study. There were seven (58%) men and five (42%) women, with a median age of 37 years. All patients had a normal baseline laboratory tests. There was no case of allergic reactions or any adverse events related to fibrinogen administration. None of them required red blood cells or platelet transfusions after surgery, and there were no thrombotic events during 30 days of follow-up.

Conclusion: The prophylactic use of fibrinogen concentrate appears to be safe in neurosurgery and may reduce the need of blood derivatives transfusion. Additional prospective studies should be performed to assess the efficacy of this strategy.

Key words: Blood coagulation; Fibrinogen; Hemorrhage; Neurosurgery

Introduction
Immediate hemostasis in neurosurgery is essential since small amounts of blood within the brain parenchyma may lead to permanent neurological damage or even death. As micro neurosurgical interventions in the brain require clear fields of vision, continued bleeding may obscure the target structures, with potential tissue damage. In patients with intracranial lesions requiring immediate surgery, this condition is often associated with plasma coagulation and/or thrombotic disorders caused by drugs such as aspirin and warfarin. Impairment of hemostasis in a bleeding patient during surgery may be due to various factors such as loss, consumption or dilution of the coagulation factors, platelets and other blood cells involved in the overall hemostatic regulation. Bleeding tendency can be exacerbated by anemia, hypothermia and acidosis. The management of bleeding patients involves...
the correction of hypothermia and acidemia, resuscitation
with crystalloids and colloids, and infusion of red blood cells
(RBCs), fresh frozen plasma (FFP), and platelets. Treatment
may also include infusion of antifibrinolytic drugs and clotting
factor concentrates such as fibrinogen concentrate, prothrombin
complex concentrate, or recombinant activated factor VII.

Fibrinogen, also known as factor I, is an acute-phase protein
synthesized in the liver that plays a pivotal role in the final stages
of the coagulation process. In normal subjects, fibrinogen
concentration ranges from 1.5 to 4.5 g/L, with up to 10-fold
increase in the setting of tissue damage, infection, and in the
inflammatory response induced by cytokines. Fibrinogen
facilitates platelet aggregation by binding to glycoprotein IIb/
IIIa receptors and triggering fibrin polymerization through
thrombin generation. Acquired deficiency of fibrinogen is
more common than hereditary α- or hypofibrinogenemia
and may occur due to loss, consumption, hyperfibrinolysis,
or the compromised synthesis of fibrinogen. A low plasma
concentration of functional fibrinogen is associated with
bleeding in major surgeries. During the process of excessive
blood loss, fibrinogen is the first clotting factor approaching
a critical threshold, reaching low serum concentrations of
approximately 1 g/L. Recent studies have suggested that
hemodilution with colloidal plasma expanders predisposes to
functional impairment of fibrinogen.

Given the pivotal role of fibrinogen in hemostasis, its
replacement may be beneficial to patients with critically low
levels or a functional deficiency of fibrinogen. Thus, the use
of fibrinogen concentrates derived from human plasma has
increased over the years. Haemocomplettan P® (CSL Behring,
Marburg, Germany) is a fibrinogen concentrate derived from
human plasma that can be quickly reconstituted without
thawing and with no need for compatibility testing. According
to pharmacovigilance data obtained over a period of 22 years,
Haemocomplettan P® proved to be a safe product, since only
nine cases of thrombosis have been reported as possibly related
to the drug. Few studies have evaluated the safety of using
fibrinogen concentrates specifically in neurosurgery. To the
best of our knowledge there are no studies evaluating the use
of fibrinogen concentrates in Brazilian health services. Thus,
the objective of this paper is to evaluate the safety and efficacy
of the use of a fibrinogen concentrate in patients undergoing
neurosurgeries.

**METHODS**

**Patient selection**

We reviewed the medical records of consecutive patients
who had undergone neurosurgery for different pathologies in
our institution over a 1-year period, from July 2009 to July
2010. In all cases, the same surgical and anesthetic teams
were involved in patient care. We selected for analysis only
those patients in whom the fibrinogen concentrate of interest
(Haemocomplettan P®) had been used as part of routine
care. The anesthesia records, along with perioperative and
postoperative notes were reviewed to determine the incidence
of complications and the need for transfusion of platelets,
coagulation factors and RBCs. The study was approved by the
institutional review board prior to start it.

**Routine procedures and patient assessment**

According to the standard hospital procedures, all patients
underwent preoperative assessment of complete blood
counts, determination of serum creatinine concentration, and
measurement of the international normalized ratio (INR)
and activated partial thromboplastin time (aPTT). A platelet
aggregation test was also performed. Evaluation of fibrinogen
concentration was not performed routinely because it is not
part of the hospital preoperative standard of care. During
neurosurgery, the fibrinogen concentrate was used empirically
for intraoperative bleeding (common in neurosurgery due to
the delicate nature of nervous tissue), since all patients had
previously received colloids and crystalloids for volume
expansion. Doses were used empirically, as thromboelastometry
was not routinely available. During the surgery, calcium and
bicarbonate were measured every three hours. The same blood
tests performed preoperatively were repeated after surgery and
on the day of discharge from the intensive care unit (ICU) in
all patients. All patients had a follow-up period of at least 30
days after surgery.

**Statistical analysis**

Descriptive analyses were made using tables of absolute and
relative frequencies, with results presented as mean ± standard
deviation (SD) or median and range, as appropriate.
RESULTS

Preoperative patient characteristics

Twelve patients fulfilled the criteria for analysis. Table 1 shows the demographic and clinical features before surgery. Only two patients showed decreased platelet aggregation and were treated prophylactically with platelet infusion prior to surgery. The median age was 37 years (ranging from 26 to 56 years-old), five patients (42%) were females and seven (58%) males. Their preoperative laboratory tests were all within normal ranges. Table 2 shows the types of neurosurgical procedures performed in the study. None of the patients had been previously treated with steroidal anti-inflammatory drugs, acetylsalicylic acid, or low-molecular-weight heparin. All patients received a synthetic colloid (hydroxyethyl starch, Voluven®) for plasma volume replacement, and crystalloids (Ringer’s solution) before surgery. In addition, seven patients had received other colloids (albumin), and four had been given RBC transfusions.

Intraoperative management of bleeding

The mean duration of neurosurgery was 511 minutes. Fibrinogen concentrate was used to treat microvascular bleeding during surgery to maintain normal cerebral perfusion pressure. Nine patients used 1 gram of fibrinogen concentrate and only three received 2 grams to achieve hemostasis (mean of 1.25 grams/ surgery). No allergic reactions or adverse events to the fibrinogen concentrate were observed. During surgery, all patients received Voluven® (on average 1000 mL) and only five required albumin. No patients received RBC or platelet transfusion during surgery. As described before, one patient had received a transfusion of platelets before surgery, but the bleeding did not stop. After administration of the fibrinogen concentrate, no further bleeding was observed. Calcium (mean ± standard deviation: 1.16 ± 0.04 mmol/L) and bicarbonate (mean ± standard deviation: 23.77 ± 1.94 mEq/L) levels were normal in all patients during surgery.

Post-surgery assessment

After surgery, decreased mean values of hemoglobin, and hematocrit, with normal values for platelets, creatinine, INR, and aPTT (Table 3) were observed. No patient required RBC or platelet transfusion after surgery or until the last day of follow-up (30 days). Only two patients were treated with low-molecular-weight heparin due to prolonged hospitalization. Hemoglobin, hematocrit, creatinine and INR values upon hospital discharge are shown in Table 3. All patients were treated prophylactically for deep-vein thrombosis, in nine of them the prophylaxis were performed with compression stockings, and in two patients with pneumatic compression boots. To note, there were no cases of thrombosis until the last day of follow-up.

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Table 1. Patients’ demographic and clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Value or N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range; years)</td>
<td>37 (26-56)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Hb (mean ± SD; g/100mL)</td>
<td>13.88 ± 1.90</td>
</tr>
<tr>
<td>Hct (mean ± SD; %)</td>
<td>40.71 ± 4.96</td>
</tr>
<tr>
<td>Platelets (mean ± SD; 1000/mm3)</td>
<td>231.50 ± 68.75</td>
</tr>
<tr>
<td>INR (mean ± SD)</td>
<td>1.14 ± 0.13</td>
</tr>
<tr>
<td>aPTT (mean ± SD; seconds)</td>
<td>1.05 ± 0.19</td>
</tr>
<tr>
<td>Serum creatinine (mean ± SD; mg/dL)</td>
<td>1.03 ± 0.23</td>
</tr>
</tbody>
</table>

aPTT: activated partial thromboplastin time; Hb: hemoglobin; Hct: hematocrit; INR: international normalized ratio; SD: standard deviation.

Table 2. Type of performed neurosurgeries.

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System Tumors</td>
<td>5</td>
</tr>
<tr>
<td>Spinal tumor</td>
<td>1</td>
</tr>
<tr>
<td>Decompressive Craniectomy</td>
<td>3</td>
</tr>
<tr>
<td>Arteriovenous malformation (AVM)</td>
<td>1</td>
</tr>
<tr>
<td>Venous malformation (Cavernous)</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
</tr>
</tbody>
</table>
Most coagulation defects resulting from bleeding during surgery are caused by dilutional coagulopathy. Fibrinogen is the first coagulation factor to become critically reduced during surgical blood loss. Some years ago, FFP and cryoprecipitate were the main options for correcting the fibrinogen deficiencies. Although the use of these products has been empirically justified, their hemostatic efficiency has not been fully evaluated in the surgical setting. An alternative to correct dilutional coagulopathy is the administration of fibrinogen concentrate, which has been shown to improve clot firmness and reduce blood loss using in vitro and in vivo animal models. Clinical studies have provided evidence for the efficacy and tolerability of fibrinogen concentrates both in congenital and acquired fibrinogen deficiency. To our knowledge, this is the first report on the use of fibrinogen concentrates in neurosurgery published in health services from Brazil.

Our results suggest that the use of fibrinogen concentrate during neurosurgical procedures is effective. Transfusions of RBC or platelets after surgery were not necessary for our patients, suggesting that hemostasis was adequately achieved with the administration of fibrinogen concentrate. Similar results were observed in a study with nine children who underwent major craniofacial surgery, and in all cases sufficient hemostasis was achieved by administering fibrinogen concentrates without fresh frozen plasma or platelet transfusions. The use of fibrinogen concentrate is guided by specific parameters, such as the Clauss assay and thromboelastometry (using the ROTEM® system), that determine fibrinogen concentration in plasma. In fact, no clear critical threshold has been determined for fibrinogen concentration, and in Brazilian health services the use of fibrinogen is usually done empirically, since in most of those services ROTEM® is not available and the use of Clauss method is impracticable during surgery due to the delay in obtaining the fibrinogen plasma concentration results. In our study, the empirical use of Haemocomplettan P® was thus justified and was done according to the common decision by the neurosurgeon and the neuroanesthesiologist.

The most important result of our study is the absence of adverse effects, which suggests that fibrinogen concentrate is a safe product for use in neurosurgery. According to pharmacovigilance data obtained over a period of 22 years, Haemocomplettan P® proved to be a safe product, since only nine cases of thrombosis have been reported as possibly related to the drug. Such evidence suggests that fibrinogen concentrates confer a low thrombogenic potential.

None of the patients required FFP transfusion, minimizing the risk of immune reactions and viral transmission. A recent study has demonstrated that FFP administration in surgical patients makes them more likely to develop an infection, in comparison with patients who do not receive FFP.

Study Limitations

Although our study suggested that fibrinogen concentrate administration is safe, our series is small and from a single center. Moreover, assessment of its efficacy is not possible with our study design. Even though no patient required FFP or red blood cells transfusion during or after surgery, suggesting potential benefits, other factors such as surgeons’ expertise and severity of the treated pathologies should be taken into account. For these reasons, evaluation of fibrinogen administration efficacy may require prospective comparative studies.

Conclusions

In conclusion, our study suggests that fibrinogen concentrate used for bleeding control is safe in neurosurgery. Furthermore, the use of fibrinogen concentrate may reduce the need for...
transfusions of other blood products in this setting, a hypothesis worthy of further investigations.

REFERENCES


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