Increased Risk for Postoperative Hemorrhage After Intracranial Surgery in Patients With Decreased Factor XIII Activity
Implications of a Prospective Study

Rüdiger Gerlach, MD; Fabian Tölle; Andreas Raabe, MD; Michael Zimmermann, MD; Annelie Siegemund, MD; Volker Seifert, MD, PhD

Background and Purpose—The functional integrity of the hemostatic system is a prerequisite for the safe performance of neurosurgical procedures. To monitor the individual coagulation capacity of each patient, standard tests are effective to detect deficiencies involving the generation of fibrin. However, fibrin clot strength depends primarily on coagulation factor XIII, which cross-links fibrin monomers and enhances clot resistance against fibrinolysis. Therefore, factor XIII is functionally involved in both the hemostatic and fibrinolytic systems. The objective of this prospective study was to determine the incidence and clinical relevance of perioperative decreased factor XIII with respect to standard coagulation parameters and the occurrence of postoperative hematoma.

Methods—In 876 patients, 910 neurosurgical procedures were performed. Prothrombin time (PT), partial thromboplastin time (PTT), platelet count, fibrinogen, and factor XIII were tested in each patient preoperatively and postoperatively.

Results—Postoperative intracranial hematoma (defined as requiring surgical evacuation) occurred after 39 (4.3%) of 910 surgical procedures. Patients with postoperative hematoma had significantly lower factor XIII and fibrinogen levels preoperatively and postoperatively than patients without hematoma. In patients with postoperative hematoma, PT and platelets differed significantly only postoperatively, whereas PTT was different neither preoperatively nor postoperatively. Of the 39 patients with a postoperative hematoma, 13 (33.3%) had a postoperative factor XIII <60% compared with 61 (7%) of 867 patients without hematoma (P < 0.01, Fisher’s exact test). The relative risk of developing a postoperative hematoma is therefore increased 6.4-fold in patients with postoperative factor XIII <60%. The risk is increased 12-fold in patients who additionally have postoperative decreased fibrinogen levels (<1.5 g/L) and 9-fold in patients with platelet count <150×10^9/L and factor XIII <60%.

Conclusions—This is the first prospective study that demonstrates the association of decreased perioperative factor XIII with an increased risk of postoperative hematoma in neurosurgical patients. The risk is further increased in those patients with low factor XIII and additional abnormalities of fibrinogen, PT, platelets, and PTT. Factor XIII testing and specific replacement, as accepted for other clotting factors, may reduce the risk of postoperative hematoma. (Stroke. 2002;33:1618-1623.)

Key Words: coagulation ■ craniotomy ■ factor XIII ■ factor XIII deficiency ■ fibrinolysis ■ hematoma ■ neurosurgical procedures
The objective of this prospective study was to determine the incidence and clinical relevance of perioperative decreased factor XIII with respect to standard coagulation parameters and the occurrence of postoperative hematoma in a large cohort of neurosurgical patients.

Subjects and Methods

Patients
In 876 patients, 910 intracranial neurosurgical procedures were performed between June 1997 and December 2000 (for details, see Table 1). This prospective study included 431 neurosurgical procedures performed between June 1997 and December 2000 (for details, see Table 1). This prospective study included 431 neurosurgical procedures performed between June 1997 and December 2000 (for details, see Table 1).

Table 1. Intracranial Surgical Procedures and Development of Intracranial Hematoma

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>135</td>
<td>14.8</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td>Glioma</td>
<td>132</td>
<td>14.5</td>
<td>6</td>
<td>15.4</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>110</td>
<td>12.1</td>
<td>6</td>
<td>15.4</td>
</tr>
<tr>
<td>Metastasis</td>
<td>102</td>
<td>11.2</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Head injury</td>
<td>90</td>
<td>9.9</td>
<td>9</td>
<td>23.1</td>
</tr>
<tr>
<td>Pituitary tumor</td>
<td>50</td>
<td>5.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Infratentorial surgery</td>
<td>47</td>
<td>5.2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Shunting procedures/biopsy</td>
<td>212</td>
<td>23.3</td>
<td>4</td>
<td>10.3</td>
</tr>
<tr>
<td>Hemicraniectomy/revision</td>
<td>32</td>
<td>3.5</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Total</td>
<td>910</td>
<td>100.0</td>
<td>39</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Percentages do not total 100% because of rounding.

Dependent fibrin clot stabilization. Thus, decreased enzymatic activity of factor XIII was discussed as a cause of postoperative hematoma in abdominal, gynecological, plastic, and urological surgery and also recently in the field of neurosurgery. The objective of this prospective study was to determine the incidence and clinical relevance of perioperative decreased factor XIII with respect to standard coagulation parameters and the occurrence of postoperative hematoma requiring surgical evacuation in a large cohort of neurosurgical patients.

Laboratory Procedures

The Sarstedt Monovette system was used for all blood sampling procedures. Samples (3 mL) used for all coagulation assays, including the factor XIII test, contained 0.3 mL of citrate solution. Samples were transferred immediately for further diagnostic processing. Before any of the tests were performed, the samples were centrifuged for 20 minutes at 3500 U/min at room temperature. Factor XIII assay was performed immediately, and samples were stored at −70°C. Platelets were automatically counted according to standard procedures after blood was sampled in blood collection systems containing EDTA.

To characterize abnormalities in the fibrinolytic system, plasminogen, plasmin-antiplasmin (PAP) complex, and α1-antiplasmin testing was additionally performed in 18 blood samples (46.2%) of patients with postoperative hematomas. Therefore, the samples that were obtained immediately before reoperation and stored at −70°C were used.

All laboratory tests were performed according to the protocol of the manufacturer. For measurement of plasma factor XIII, a photoclinometric test of Dade Behring (Berichrom FXIII) was used. This test system is not affected by postoperative heparin administration and is a validated procedure. The low number of platelets remaining in the plasma samples after centrifugation did not influence the accuracy of the test. Plasminogen and α1-antiplasmin were tested with the Berichrom plasminogen assay and Berichrom α1-antiplasmin assay, respectively. PAP complex was tested with the use of the Dade Behring Enzygnost PAP assay.

Statistical Evaluation

Statistical analysis was performed with the use of commercially available software (SPSS Inc, version 10.0). Data of all parameters were tested as mean ± SD. To compare independent preoperative and postoperative parameters, the unpaired Student’s t test was used. Probability values <0.05 were considered significant. Parameters compared with the t test were proven to be normally distributed.

Fisher’s exact test was used to compare the frequencies of postoperative hematoma and factor XIII, fibrinogen, platelets, PT, and PTT. Therefore, it was necessary to define cutoff values, which are given individually for each parameter in Results. The cutoff values for each of these parameters preoperatively and postoperatively were also used to calculate the relative risk of developing a postoperative hematoma. For all postoperative parameters, the lowest measured factor XIII, fibrinogen, platelet count, and PT and the highest PTT were used for statistical calculation up to the detection of a hematoma in this group and during the postoperative course in the group of patients without hematoma, respectively.

Preoperative and postoperative factor XIII, fibrinogen, platelet count, PT, and PTT were entered into a multivariate discriminant analysis (stepwise inclusion, Wilks λ method [probability for inclusion=0.05 and for exclusion=0.10]). A total of 760 (83.5%) of the 910 surgical procedures were included; 180 (19.8%) were excluded because of at least 1 missing parameter.

Logistic regression analysis (forward inclusion, Wald method) was performed to determine predictive factors for the occurrence of postoperative hematoma.
**TABLE 2. Perioperative Changes of Factor XIII and Standard Coagulation Parameters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative Coagulation Parameters</th>
<th>Postoperative Coagulation Parameters</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Hematoma</td>
<td>Hematoma</td>
<td></td>
</tr>
<tr>
<td>Factor XIII, %</td>
<td>113.7±27.3</td>
<td>97.89±25.0*</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.43±1.17</td>
<td>2.92±1.22*</td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10^9/L</td>
<td>241.9±76.2</td>
<td>222.4±79.8</td>
<td></td>
</tr>
<tr>
<td>PT, %</td>
<td>95.3±45.1</td>
<td>91.2±19.5*</td>
<td></td>
</tr>
<tr>
<td>PTT, s</td>
<td>33.2±6.6</td>
<td>33.1±7.6*</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.01 vs no hematoma (preoperative).  †P<0.01 vs no hematoma (postoperative).  ‡P<0.05 vs no hematoma (postoperative).

**Results**

In this prospective study, 910 intracranial operations were performed in 876 patients (Table 1). In 39 of the procedures (4.3%), patients developed a postoperative intracranial hematoma, which was removed surgically. The location of the hematoma was epidural in 22 (56.4%), subdural in 10 (25.6%), and intracerebral in 7 (18%) cases. The hematoma was evacuated before heparin administration on the day of previous surgery in 4 (10.3%) of the 39 patients. All other patients underwent reoperation after the anticoagulation therapy was started (12 patients on day 1; 4 on day 2; 9 on day 3; 4 on day 4; 3 on day 5; and the remaining patients on days 6, 7, and 9).

**Perioperative Changes of Factor XIII and Standard Coagulation Parameters**

In the group of patients with postoperative hematoma, factor XIII was significantly lower preoperatively (97.89±24.98% versus 113.66±27.31%) and postoperatively (71.4±20.57% versus 93.46±24.37%; P<0.01, t test) (Table 2) compared with the group without hematoma. As shown for factor XIII, fibrinogen also differed statistically significant preoperatively (2.92±1.22 versus 3.43±1.17 g/L; P<0.01, t test) and postoperatively (2.07±0.93 versus 2.53±0.99 g/L; P<0.01, t test), respectively (Table 2). No perioperative significant differences were found for platelet count and PT. Postoperative platelet count was statistically significantly lower in patients with hematoma (150.5±53.7×10^9/L) than in patients who did not suffer from rebleeding after surgery (185.6±68.3×10^9/L; P<0.01) (Table 2). PT was also significantly lower in the hematoma group (71.7±11.6%) than in the group without hematoma (76.4±12.6%; P<0.05) (Table 2). No difference was seen for PTT either preoperatively or postoperatively in either group.

The overall decrease in postoperative factor XIII, fibrinogen, platelets, and PT is likely to be due to perioperative blood loss or consumption. Therefore, to calculate the relative risk it seems rational to define a higher threshold of preoperative parameters that might be critical for postoperative hematoma formation than we have used for calculation of the same parameters postoperatively. For factor XIII, the average decrease in all patients is from 112.99±27.38% preoperatively to 92.50±24.66% postoperatively (approximately 18.1%), regardless of any postoperative bleeding complication. A preoperative factor XIII <80% was significantly associated with a postoperative hematoma (P<0.01, Fisher’s exact test) (Table 3). Therefore, the risk of developing a postoperative hematoma is increased 3.9-fold in those patients. In contrast, a preoperative PT <80% was not associated significantly with hematoma formation. A preoperative fibrinogen <3.0 g/L also had a significant association with postoperative hematoma formation (P<0.01, Fisher’s exact test), resulting in a 2.9-fold increased risk for those patients (Table 3). Patients with platelet count >200×10^9/L preoperatively were not at risk of developing a postoperative hematoma.

Of the 39 patients with postoperative hematoma, 13 (33%) had a postoperative factor XIII <60% compared with 61 (7%) of 867 patients without hematoma. This difference was statistically significant (P<0.01, Fisher’s exact test). Therefore, those patients with a postoperative factor XIII <60% have 6.4-fold increased risk of developing a postoperative hematoma. Furthermore, patients with postoperative platelet count <150×10^9/L (P<0.01) and fibrinogen <1.5 g/L were at a 3.0- and 2.5-fold increased risk of developing a postoperative hematoma, respectively (P<0.01, Fisher’s exact test) (Table 4). In this series, no statistically significant association was found between decreased postoperative PT or prolonged PTT and the occurrence of postoperative hematoma.

**Postoperative Hematoma and Complex Hemostatic Impairment**

After hours of surgery, complex coagulation derangement may occur, and therefore it is important to know to what extent those abnormalities increase the overall risk of rebleeding. Postoperative factor XIII <60% and fibrinogen <1.5 g/L not only showed a significant association with postoperative hematoma formation, as it did for each of the factors alone, but increased the relative risk of developing a hematoma to 12-fold. Patients with postoperative platelet counts <150×10^9/L and factor XIII <60% were also at a significantly higher (9-fold) risk of having postoperative hematoma.

**TABLE 3. Preoperative Coagulation Parameters and Relative Risk for Postoperative Hematoma**

<table>
<thead>
<tr>
<th>Preoperative Coagulation Parameter</th>
<th>Relative Risk for Postoperative Hematoma</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor XIII &lt;80%</td>
<td>3.9</td>
<td>1.86–8.07</td>
</tr>
<tr>
<td>Fibrinogen &lt;3.0 g/L</td>
<td>2.9</td>
<td>1.45–5.83</td>
</tr>
</tbody>
</table>
bleeding complications. Patients with postoperative decreased factor XIII and PT (both <60%) also had a 6-fold increased risk. Factor XIII <60% and PT >35 seconds were associated with an almost 5-fold increased risk for postoperative hematoma (Table 5).

### Postoperative Factor XIII and Fibrinolysis

In a subgroup of 18 (46.2%) of the patients with a postoperative hematoma, plasminogen, α2-antiplasmin, and PAP were tested. Patients with postoperative hematoma and postoperative factor XIII <70% had a lower plasminogen (85.6 ± 23.56% versus 108 ± 12.7%; \(P < 0.05\)) and α2-antiplasmin level (87.9 ± 33.1% versus 117.6 ± 14.8%; \(P < 0.05\), t test) than patients with postoperative hematoma and factor XIII >70%. Because PAP is a specific marker of fibrinolysis, it was chosen instead of the more global fibrinolytic marker D-dimer. Consistent with increased fibrinolytic activity, PAP was higher (1417.5 ± 1793 versus 586.57 ± 452.9 \(\mu\)g/L) in the group of patients with factor XIII <70% but showed a high variation. Although statistically not significant, elevated PAP levels in patients with decreased factor XIII and postoperative hematoma indicate increased fibrinolytic activity.

In a multivariate discriminant analysis of preoperative and postoperative factor XIII, fibrinogen, platelets, PT, and PTT, only postoperative factor XIII was included. Correct discrimination was 65.7% with an exact assignment to the group of patients with or without postoperative hematoma. In a logistic regression analysis, none of the parameters (preoperative and postoperative factor XIII, fibrinogen, platelets, PT, and PTT) was identified as an independent predictive factor for the development of a postoperative hematoma.

### Perioperative Factor XIII Substitution

Because this study was not considered to prove the efficacy of normal plasma factor XIII concentration in preventing postoperative hematoma, factor XIII was replaced in only 23 patients. In 7 of these 23 patients, substitution was performed after hematoma evacuation to prevent a second rebleeding. Ten patients with postoperatively decreased factor XIII (<60%) received factor XIII replacement, and no postoperative hematoma occurred. Six patients with preoperative factor XIII <60% underwent substitution therapy; the postoperative plasma level remained >60%, and no hematoma occurred.

### Discussion

A postoperative hematoma is a potential life-threatening complication after intracranial surgery and is frequently associated with poor outcome and death of neurosurgical patients.1 Therefore, it is of vital importance to identify risk factors that can be avoided or specifically treated. In addition to coagulopathies, disseminated intravascular coagulation2–4 and drugs interfering with platelet function1,17,18 are identified as risk factors for bleeding complications. However, most of these abnormalities can be detected by routine coagulation tests or medical history. In this series of 39 postoperative hematomas, 1 patient was on antiplatelet medication, another patient was treated with oral anticoagulants, and a third patient had a severe liver dysfunction resulting in hemostatic impairment, which was specifically treated and controlled preoperatively.

### Perioperative Coagulation Parameters and Risk of Postoperative Hematoma

Preoperative factor XIII and fibrinogen were significantly lower in the group of patients with postoperative hematoma than in patients without postoperative hematoma. Therefore, in these patients the presence of a hemostatic impairment to a certain degree can be assumed, which was clinically not relevant before operation. Postoperative factor XIII, fibrinogen, platelets, and PT were significantly lower in patients with hematoma, which may have amplified any preoperative impairment. Lower platelet count indicates diminished platelet adherence at damaged vessels, decreased generation of thrombin, and low platelet-associated factor XIII, which promotes clot stabilization and platelet interaction. Platelet-associated factor XIIIa increases the amount of cross-linking in a fibrin clot, thereby contributing to aging of the clot and reduction in the degree of platelet binding.19

Furthermore, the importance of platelet-mediated thrombin generation has recently been reported,20–22 and it was demonstrated that administration of recombinant activated factor FVII may compensate for a lowered platelet count with regard to thrombin generation.23 Decreased generation of thrombin, however, may also interfere with factor XIII activation and fibrin cross-linking. This may explain the exponential risk of postoperative hematoma in patients with combined decreased factor XIII, fibrinogen, platelets, and PT and increased PTT postoperatively. The correlation of fibrin clot stability with factor XIII concentration has been demonstrated in vitro12,24 and was also of clinical relevance in patients who underwent cardiopulmonary bypass surgery.25 Therefore, the decrease of fibrinogen, the precursor of fibrin, which is the main substrate for factor XIII, as well as low plasma factor XIII increases the risk of postoperative hema-

| TABLE 4. Postoperative Coagulation Parameters and Relative Risk for Postoperative Hematoma |
|-----------------------------------------------|-------------------------------|
| Postoperative Coagulation Parameter         | Relative Risk for Postoperative Hematoma | 95% CI  |
| Factor XIII <60%                          | 6.4                            | 3.1–13.02 |
| Platelet count <150 × 10^9/L              | 3.0                            | 1.5–5.77  |
| Fibrinogen <1.5 g/L                      | 2.5                            | 1.2–5.40  |

| TABLE 5. Complex Hemostatic Impairment and Relative Risk for Postoperative Hematoma |
|-----------------------------------------------|-------------------------------|
| Deficient Postoperative Coagulation Parameters | Relative Risk for Postoperative Hematoma | 95% CI  |
| Factor XIII <60% and fibrinogen <1.5 g/L     | 12.2                          | 4.61–32.3 |
| Factor XIII <60% and platelet count <150 × 10^9/L | 9.7                           | 3.91–24.1 |
| Factor XIII <60% and PT <60%                | 6.2                           | 1.94–19.4 |
| Factor XIII <60% and PTT >35 s              | 4.8                           | 1.97–11.5 |
toma because of a decreased number of cross-linked fibrin clots.

In the literature, the minimum factor XIII level that is necessary to achieve sufficient hemostasis ranges from a low level of 2%26 to moderately decreased levels of 30% to 50%.27,28 Thus, the level of preoperative and postoperative factor XIII that is sufficient to achieve safe hemostasis after brain surgery is unclear. Whether a patient with postoperative decreased factor XIII develops a postoperative hematoma might be determined to a certain extent by normal levels of fibrinogen and platelets. Therefore, particularly those patients with factor XIII <60% and low fibrinogen or decreased platelets are at high risk of developing a postoperative hematoma. However, until now no report has described a correlation between plasma factor XIII and factor XIII activity in the wound bed, where fibrin cross-linking also occurs. Interestingly, it was shown in a rat model of bilateral frontal craniotomy and corticotomy that the local application of factor XIII significantly reduced the occurrence of postoperative hematoma.29

Consistent with the findings of a retrospective study,30 patients with postoperative factor XIII <60% had a 6.4-fold increased risk of developing a postoperative hematoma in this prospective study.

Factor XIII polymorphism may also be a cause of decreased plasma concentration. Recently, in a few studies a slightly higher incidence of factor XIII Val 34 Leu polymorphism in patients with primary intracerebral hemorrhage was related to impaired cross-linking of fibrin and/or coagulation proteins.30–32 However, in this study factor XIII polymorphism was not assessed, and no factor XIII genomic analysis was performed.

**Factor XIII and Fibrinolytic Activity**

Hyperfibrinolysis was reported to be associated with postoperative hematoma in patients who underwent surgery for brain tumors.7,33 Clot resistance to fibrinolysis is enhanced by platelet factor XIII–mediated cross-linking of α2-antiplasmin to fibrin.19 At low factor XIII concentrations, only γ-chain cross-linking of fibrin monomers occurs, while α-chain cross-linking is dependent on high factor XIII concentrations.24

The almost 70% correct classification of patients with postoperative hematoma due to postoperative factor XIII concentration, as the only included parameter in a multivariate discrimination analysis, emphasizes the importance of factor XIII interaction with the hemostatic and fibrinolytic systems. Therefore, it would be likely to find abnormalities of the fibrinolytic system in patients with low factor XIII. Indeed, PAP complex testing in patients with postoperative hematoma revealed an almost 2-fold higher level and a significantly lower plasminogen and α2-antiplasmin level in those patients with decreased factor XIII. Although the increase of PAP was not statistically significant in patients with postoperative hematoma and low factor XIII compared with normal factor XIII, the elevated PAP demonstrates increased fibrinolytic activity in patients with low factor XIII. Moreover, increased plasmin-mediated fibrinolysis leads to a decrease of α2-antiplasmin incorporation into the clot, which may have an additional effect on clot destabilization. Fuji et al34 found a parallel decrease of plasminogen and hematomcr, which could be a possible explanation for the significantly decreased plasminogen in the group of patients with hematoma and postoperative decreased factor XIII. However, no significant difference in hematomcr was seen in patients with postoperative hematoma and factor XIII <60% and >60% in this study (data not shown). A strong correlation between factor XIII, fibrinogen, and plasminogen was found in patients of different races,34 which may explain the significantly decreased plasminogen in patients with low factor XIII in this study, although such correlation has not yet been described for the European population. An impaired hepatic synthesis of factor XIII and plasminogen would also explain such a correlation.

Postoperative decreased PT alone was not associated with hematoma in this series. Because this is a known risk factor during the postoperative course, administration of fresh frozen plasma and prothrombin complex concentrates was commonly performed if the decrease was obvious by standard testing. None of the patients who received factor XIII, either preoperatively or postoperatively, developed a postoperative hematoma, and the patients who were underwent substitution after hematoma evacuation did not suffer from rebleeding again. Postoperative PTT was not associated with hematoma formation.

Although the incidence of postoperative hematoma of 4.3% in this series seems high, it must be considered that all patients were included prospectively. Therefore, the rate is consistent with other reports in which the occurrence of postoperative hematoma was between 1% and 12%.1,7 The patients underwent major surgical procedures for a variety of different pathologies (Table 1). As demonstrated in other studies,1 the incidence of hematoma formation was highest after meningioma surgery (30.8%); this was followed by surgery for brain injury (23.1%).15

Beside fibrin clot stabilization, factor XIII has recently been found to reduce endothelial permeability independently of its role in the coagulation cascade.30 Thus, decreased factor XIII may also influence the blood-brain barrier, especially in patients with brain neoplasm with respect to brain edema or postoperative bleeding complication. In this series >62% of all patients with postoperative decreased factor XIII (<60%) underwent surgery to treat meningiomas (14.5%), glioblastomas (18.4%), metastasis (15.8%), and severe head injuries (18.4%), which are conditions with at least a focal blood-brain barrier disruption. However, the correlation of plasma factor XIII with the extent of brain edema needs to be addressed in more detail in another study, using a specific protocol of preoperative MR image acquisition.

**Conclusion**

This is the first prospective study that emphasizes the importance of plasma factor XIII for sufficient fibrin clot stabilization after intracranial surgery. The results indicate that decreased factor XIII is currently underestimated and is associated with postoperative hematoma formation. In particular, those patients with decreased factor XIII, fibrinogen,
and platelets are at high risk of developing a postoperative hematoma. Therefore, factor XIII testing and specific replacement may reduce the risk of postoperative hematoma.

References


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