<table>
<thead>
<tr>
<th>Heparin preparation</th>
<th>Severity of trauma</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major (N)</td>
<td>Minor (N)</td>
</tr>
<tr>
<td>A. Anti-PF4/heparin antibody seroconversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>17/100 (17.0%)</td>
<td>4/216 (1.9%)</td>
</tr>
<tr>
<td>LMWH</td>
<td>5/124 (4.0%)</td>
<td>0/174 (0%)</td>
</tr>
<tr>
<td>P</td>
<td>0.0014</td>
<td>0.132</td>
</tr>
<tr>
<td>B. Clinical HIT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>4/100 (4.0%)</td>
<td>0/216 (0%)</td>
</tr>
<tr>
<td>LMWH</td>
<td>1/124 (0.8%)</td>
<td>0/174 (0%)</td>
</tr>
<tr>
<td>P</td>
<td>0.175</td>
<td>1.0</td>
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</table>

Anti-PF4/heparin antibodies were measured using a combination of enzyme-immunoassays, and thus indicate antibodies of either IgG, IgA, and/or IgM classes.

* Abbr.: HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin (certoparin); UFH, unfractionated heparin

The data clearly indicate that both heparin type and trauma severity are strong and independent predictors of the anti-PF4/heparin immune response. Consequently, the highest risk of immunization (17%) and of clinical HIT (4%) was seen in patients who received UFH thromboprophylaxis after major trauma. At the other end of the spectrum, not even a single immunization event occurred in 174 patients who received LMWH thromboprophylaxis after minor trauma.

A quick survey of the data in the table suggests that the effect of trauma severity was at least as great as that due to heparin type. Most notably, the frequency of anti-PF4/heparin immunization was approximately twice as high in patients who received LMWH after major trauma (5 of 124, 4.0%) compared with those who received UFH after minor trauma (4 of 216, 1.9%). Indeed, when the Greifswald group applied logistic regression analysis, adjusting for confounders such as age, sex, and type of heparin, the odds ratio for developing any immune response in major trauma compared with minor trauma was 7.98 (95% CI, 2.06–31.00; P = .003). This mirrors the approximately 10-fold greater frequency of HIT that has been shown with UFH compared with LMWH.1,2,3

The authors speculate that increased release from platelets of PF4 in the context of major surgery, or perhaps a greater degree of inflammation—a plausible potentiator of the anti-PF4/heparin immune response—might be responsible. Perhaps a “double HIT”—simultaneous antigen exposure plus a proinflammatory “danger signal”—is needed for triggering a strong immune response. To date, this concept of proinflammatory potentiators has been largely suggested in case reports. For example, acquired hemophilia has been observed anecdotally to occur in the context of infection, surgery, and malignancy.4 More powerfully, this study by Lubenow et al demonstrates through compelling clinical trial data that a nondrug factor—severity of trauma—is of major importance in potentiating the heparin-induced immune response.

**REFERENCES**


**TRANSFUSION MEDICINE**

**Comment on Canault et al, page 1835**

**p38: signaling improved platelet storage?**

Lea M. Beaulieu and Jane E. Freedman Boston University

During storage, platelets become gradually impaired in activation and signaling responses. In this issue of *Blood*, Canault and colleagues demonstrate that storage-induced shedding of platelet receptors GPIbα and GpV is mediated by p38 MAP kinase and inhibition of this pathway improves the function and posttransfusion recovery of stored platelets.1

Therapeutically, platelet concentrates are crucial for transfusion into thrombocytopenic patients, particularly when bleeding. However, the efficacy of these transfusions is limited by the shelf life of the platelet concentrates and their diminishing function over time. Therefore, it is crucial to understand how to optimally store platelets to preserve their hemostatic function once transfused. In addition, it is important to maintain the suppression of platelet markers that could contribute to their clearance after transfusion.

Platelet storage lesion is a term that describes both the biochemical and structural changes that occur in platelets during storage. Morphologic and functional alterations have been characterized in stored platelets and include shape change, reduction in activation by agonists, secretion of platelet granules, blebbing, and exposure of surface phosphatidylserines. Less is known about the biochemical properties regulating these changes. Recently, inhibition of PI3-kinase–dependent Rap1 activation has been reported to reduce both αIIbβ3 activation and α-granule release, improving platelet survival during storage.2

During storage, platelets shed adhesive surface glycoproteins. In this issue of *Blood*, Canault et al investigate another signaling pathway responsible for platelet receptor shedding that is known to alter platelet function. They examine the role of p38 MAP kinase in GPIbα and GpV shedding from the
Although these properties, that is, vasodilation, may be beneficial in the setting of elevated blood pressure, vessel dilation can be dangerous in the setting of hemorrhage. Clearly, the global effect of p38 MAP kinase inhibition on the vasculature relevant to bleeding would need to be examined.

Can MAP kinase inhibition be used to maintain the integrity and functionality of platelets stored for transfusion? Whereas this article presents some exciting mechanistic data, more questions are raised concerning the clinical relevance of this approach. As there are many other factors that can affect platelet function during storage, such as bacterial contamination and activation by plasma products, that are independent of p38 MAPK signaling, these interesting data stress the importance of taking a broad view of the problems involved with platelet transfusion.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES

COMMENT ON CAI ET AL, PAGE 1669

Separation of GVHD and GVL

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CD4+Foxp3+ Treg suppress antitumor responses using a granzyme B–dependent mechanism while the regulatory control of GVHD by Treg exploits a distinct mechanism that is granzyme B–independent.

Alogeneic bone marrow transplantation (BMT) is a viable therapeutic option for the treatment of a variety of hematologic malignancies. A major complication of allogeneic BMT is graft–versus-host disease (GVHD), in which the alloreactive T cells transferred along with the bone marrow graft respond to antigenic differences expressed on host tissues. Although this post-transplantation complication is a significant cause of morbidity and mortality after allogeneic BMT, GVHD does appear to have a significant antitumor benefit, often termed a graft–versus-leukemia (GVL) effect. Relapse rates in patients who develop GVHD are considerably lower compared with rates in patients who do not develop this complication after transplantation. Over the past several decades, attempts to identify and separate specific immune effector mechanisms that mediate GVHD and GVL have been largely unsuccessful. Sometimes the best way to make progress in a field is not to keep trying to get further down the same road, but to take the road less traveled. In this issue of Blood, Cai and colleagues have uncovered the fact that suppression of GVHD and GVL appear to function by different mechanisms. If these differences in the regulation of GVHD and GVL effector mechanisms can be exploited, the potential for therapeutic enhancement of allogeneic
p38: signaling improved platelet storage?
Lea M. Beaulieu and Jane E. Freedman