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Presence of Tumor Necrosis Factor α and Tumor Necrosis Factor Soluble Receptors in Erythrocyte Concentrates

To the Editor.—The proinflammatory cytokines tumor necrosis factor α (TNF), interleukin-1 β (IL-1), and interleukin-6 (IL-6) are assumed to be important mediators for the pathophysiologic changes seen in trauma.¹ Treatment strategies affecting this trauma response may have implications for critically ill patients. The occurrence of TNF² as well as IL-1²,³ and IL-6²,³ in platelet concentrates has been described. Stack et al⁴ found IL-1 and IL-8 in erythrocyte concentrates, whereas IL-6 was not detectable. TNF was not investigated. Published data concerning cytokine concentrations in blood components yield no information with regard to coexisting soluble cytokine receptors possibly being able to modulate tentative effects of measured cytokines.

The concentrations of TNF and soluble TNF receptors I and II (sTNF-R I and sTNF-R II) in ten buffy coat-depleted erythrocyte con-

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centrates prepared from ten healthy nonmedicated blood donors, two women and eight men, aged 36 yr (range 26–58 yr) were investigated. The erythrocyte concentrations were stored for 40 days at 4°C, and samples were obtained day 1 and subsequently every 10th day.

The concentrations of TNF and its soluble receptor were analyzed using ELISA and enzyme immunoasay kit (EASIA, Medgenix, Fleurus, Belgium). The detectable concentrations for TNF, sTNF-R I, and sTNF-R II were 3, 50, and 100 pg/ml, respectively. The coefficients of variation, interassays, and intraassays were less than 10%.

Values are presented as medians with ranges in parenthesis. Median concentrations (pg/ml) in erythrocyte concentrates and controls, respectively, were compared using Wilcoxon's two-sample (Mann-Whitney) test. The level of significance was set at 5%.

The concentrations (pg/ml) every 10th day, over the period of storage are given in table 1. Compared to a control group of 12 healthy volunteers, aged 36 yr (range 18–56 yr) TNF concentrations were increased days 1 (P < 0.05) and 40 (P < 0.01) compared to controls (table 1). Soluble TNF receptors were not analyzed in controls. According to the manufacturer, the reference ranges for sTNF-R I and sTNF-R II are 300–2,900 pg/ml and 1,900–8,500 pg/ml, respectively. Compared to these reference values, the current results indicate that median sTNF-R I concentrations are within the reference limits, whereas the median sTNF-R II concentrations were slightly below all days except day 1.

The current results indicate the presence of TNF as well as its soluble receptors in stored erythrocyte concentrates. TNF exerts its activities by complex interactions with specific receptors, which also exist in soluble forms with the ability to bind and inactivate TNF. Estimating only TNF concentrations without investigating coexisting soluble TNF receptors may be of little clinical relevance.

Excessive production of TNF in response to injury and infection is considered of extreme importance with regard to development of organ dysfunction. However, TNF mediates both harmful and beneficial effects. Supporting the importance of optimal TNF concentrations in trauma and infection to avoid a prolonged inflammatory response. A bifunctional role of soluble TNF receptors has been found in the modulation of TNF bioactivity, in which high concentrations of soluble TNF receptor forms antagonize and low concentrations promote the biologic effects of TNF.

The measured concentrations of TNF and its soluble receptors in erythrocyte concentrates in the current study were fairly low. Patients undergoing major surgery and critically ill patients are sometimes in need of massive transfusion of blood components. The trauma response in these patients is associated with an activation of the cytokine network. Transfusion of large amounts of erythrocyte concentrates containing both TNF and its soluble receptors may change the balance between TNF and soluble TNF receptor concentrations synthesized and released by the patient, which could influence the total cytokine load and, thus, the inflammatory response. The clinical impact of dysregulation and impaired control of the inflammatory response in trauma, ultimately resulting in a systemic inflammatory response syndrome may be considerable.

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Table 1. Median Concentrations (pg/ml) with Ranges in Parenthasis of TNF, sTNF-R I, and sTNF-R II in Samples from Erythrocytes over a Storage Period of 40 Days at 4°C.

<table>
<thead>
<tr>
<th>Controls (day)</th>
<th>TNF</th>
<th>sTNF-R I</th>
<th>sTNF-R II</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (&lt;3–22)</td>
<td>1.550 (405–2,640)</td>
<td>4.100 (500–7,000)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.685 (570–5,244)</td>
<td>1.650 (250–4,500)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>860 (390–4,760)</td>
<td>1.600 (500–2,100)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>935 (306–6,010)</td>
<td>1.500 (500–10,000)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>1,205 (420–3,080)</td>
<td>1.850 (600–4,100)</td>
<td></td>
</tr>
</tbody>
</table>

TNF concentrations in controls are given.

TNF concentrations are compared to values in healthy controls using the Wilcoxon's two-sample test.

* P < 0.05.
† P < 0.01.

TNF = tumor necrosis factor.

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