CHAPTER 7

EARLY POST-TRAUMATIC THROMBOCYTOPENIA IS NOT AFFECTED BY HIGH-DOSE METHYL-PREDNISOLONE

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Submitted
ABSTRACT

Background: After trauma and sepsis platelet counts (PC) decrease during the first two days. Except in massive bleeding, this is primarily due to inflammation-induced platelet sequestration. Changes in PC are strongly related with outcome. In contrast to animal experiments, the effect of early steroids on PC in critically ill patients has not been studied. Spinal cord injury is currently the only widely accepted indication for the administration of high-dose steroids. We investigated if early methylprednisolone (MPS) affected platelet sequestration in patients with spinal injury.

Methods: In the MPS-group, patients with vertebral and spinal cord injury received 30 mg/kg of MPS followed by an infusion of 5.4 mg/kg/hr for the next 23 hrs. Controls were patients with vertebral fractures who received no steroids. Patients who received any platelet transfusion or excessive red cell transfusion were excluded. PC and hemoglobin were determined on day 0, 1 and 2.

Results: In 24 patients MPS was administered on average 3.8 hrs after the injury. 41 patients were included in the control group. Both groups were comparable in age, Injury Severity Score and blood loss. Between day 0 and day 2 the PC decreased by 41% and 37% in the MPS and control group respectively. In both groups hemoglobin decreased by 14%.

Conclusion: High-dose MPS started within 4 hours does not inhibit platelet sequestration during the first 2 days after trauma. This inability of MPS to prevent platelet sequestration may be related to the failure of MPS to affect mortality in clinical trials.

INTRODUCTION

In major trauma and sepsis, platelet sequestration is intimately linked with systemic inflammation and possibly with disseminated intravascular coagulation (DIC) [1]. As a result of the trauma the platelet count (PC) decreases during the first days. In severely injured patients the extent of early thrombocytopenia is strongly associated with the subsequent occurrence of multiple organ dysfunction syndrome [2]. In a recent study on 1415 patients admitted to the surgical intensive care unit (ICU) we found that the rate of change in platelet count was associated with mortality [3]. This phenomenon was observed in all subgroups: abdominal surgery, vascular surgery, liver transplantation and trauma. In medical ICU patients it has also been observed that the magnitude of decreases in PC constitutes an important, independent marker for mortality [4].

Experimental trauma and sepsis studies have shown that very early (i.e. before or <60 minutes of the insult) administration of corticosteroids has a positive effect on mortality in parallel with a very marked reduction of platelet sequestration [5,6]. On the other hand, well-conducted clinical intervention studies in critically ill patients have all consistently failed to improve survival. In addition to high-dose corticosteroids [7,8,9] these interventions included anti-endotoxin antibodies, several cytokine inhibitors, platelet activating factor (PAF) antagonist and bradykinin antagonist [10]. These studies did not report on the effect of the intervention on quantitative changes in platelet counts.
To our knowledge, acute spinal cord injury is the only widely accepted indication for the administration of high-dose corticosteroids after acute injury in particular and acute critical illness in general. The second and third National Acute Spinal Cord Injury Studies [11,12] (NASCIS-2 and -3) reported a significantly better neurologic outcome for patients treated with methylprednisolone (MPS) within 8 hours of the injury (30 mg/kg bolus followed by 5.4 mg/kg/hr for 23 hrs or 48 hrs if started more than 3 hrs after the injury). Although the design and interpretation of the NASCIS studies have been questioned [13], the NASCIS-protocol is widely applied, not in the least because of the devastating nature of this trauma. The effect of MPS on platelet counts was not studied by the NASCIS investigators. In the current study we investigated patients with spinal cord injury who received MPS according to NASCIS guidelines. Patients with vertebral fractures and otherwise comparable injuries, but without spinal cord injury were used as controls. The aim of the study was to assess if high-dose corticosteroids inhibit early platelet sequestration.

PATIENTS AND METHODS
Patient data were gathered from the hospital data base, from a dedicated trauma database that uses International Classification of Diseases (ICD-9) codes and from patient files. Patients with ICD-9 code 806 (vertebral injury with spinal cord lesion) who received MPS (methylprednisolone sodium succinate, Pharmacia-Upjohn, Peapack, New Jersey, USA) according to the NASCIS protocol were included in the MPS group. Patients with ICD-9 code 805 who received no steroids since they had no spinal injury, were included in the control group. To minimize confounding effects of excessive injury and bleeding necessitating red cell or platelet transfusion the following patients were excluded: patients who died within one week, patients who received any platelet transfusion and patients who received more than 4 units of red cells per day during the first three days. In all patients the injury severity score (ISS) was determined [14]. Platelet count and hemoglobin were determined on day 0, 1 and 2. Statistical differences between mean values were assessed with the Student t-test.

### Table 7.1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>MPS group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>Age (+/-SD)</td>
<td>38 +/- 15</td>
<td>39 +/- 19</td>
</tr>
<tr>
<td>Male/Female</td>
<td>18/6</td>
<td>35/6</td>
</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vertebal fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Thoracic</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Lumbal</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Sacral</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mean ISS ±SD (range)</td>
<td>24±11 (9-41)</td>
<td>21±8 (4-34)</td>
</tr>
<tr>
<td>Patients operated on day 0, 1, 2</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

*MPS: methylprednisolone; ISS: injury severity score.*
RESULTS
The MPS group and control group included 24 and 41 patients respectively. Groups were comparable in age and ISS (Table 7.1). The mean delay between injury and MPS-treatment was 3.8 hrs (range 0.5-7 hrs). Two MPS patients died and one control patient died during hospital stay (after 9, 13 and 29 days respectively). In the MPS group 9 patients received a total of 23 red cell units on day 0, 1 and 2; in the control group 13 patients received 38 units over the same period. For the two groups taken together, the mean±SD platelet count dropped from 215±56 on day 0 to 133±41 ·10³/mm³ on day 2 (a 38% decrease; p<0.001). Over the same period overall hemoglobin dropped from 11.0±2.6 to 9.4±1.9 g/L (a 14% decrease; p<0.001). The difference between the relative decrease in PC and the relative decrease in hemoglobin was more than a factor 2 and significant (p<0.001).

Fig. 7.1 displays the changes of platelet count and hemoglobin for the MPS and the control groups. No differences between the two groups were observed in the decrease of platelet count and hemoglobin. Also within both groups the relative or fractional drop in platelet count was again significantly higher than the relative drop in hemoglobin (p<0.001 and p<0.001 respectively). To
further minimize confounding effects of transfusion or operation we also analyzed patients who received no red cell transfusion and who were not operated (11 MPS patients and 22 control patients). Again, no significant differences between the MPS and the control group were seen; the relative drop in PC of 34% was significantly higher than the 15% drop in hemoglobin (p<0.001).

**DISCUSSION**

Platelet counts significantly decreased after admission in the patients studied. The observed decrease in platelet count is much greater than can be explained on the basis of blood loss alone. The 38% drop in platelet count in all patients is more than double the fractional decrease in hemoglobin. When the effect of the spleen as an exchangable pool of platelets is taken into account, even more platelets must have disappeared from the circulation compared to red cells. Since in comparable groups the same decrease in platelet count was observed with or without MPS, MPS clearly was not effective in preventing platelet sequestration.

Both the unparalleled success of steroids and the difficulties in replacing corticosteroids with more modern treatments are related to the very broad spectrum of their anti-inflammatory actions. These effects include inhibition of many cytokines and mediators, reduction in vascular permeability and inhibition of several leukocyte types [15]. In the patients studied, even if additional or ‘secondary’ inflammatory responses are suppressed by high-dose MPS the initial events apparently irreversibly induce sustained platelet sequestration. Whatever the nature of any pharmacologic intervention after trauma, administering it much earlier than 3.8 hours post-trauma appears will be difficult in the majority of cases. In the NASCIS-2 and -3 studies, where the participants were obviously aware of the importance of rapid treatment, the delay to MPS-administration was 8.7 and 3 hrs respectively [11,12].

We prefer to use the term platelet sequestration since it includes both adhesion of platelets to the vascular wall, and aggregation of platelets in clots. Although DIC is not uniformly defined [16], demonstrating the consumption of platelets as well as coagulation factors is essential for the diagnosis. To some extent DIC is present in many patients after major trauma [2], but we did not measure coagulation parameters to assess the extent of possible DIC in our patients. But DIC is not a prerequisite for platelet sequestration, since thrombocytopenia often occurs in the absence of DIC [17]. The 'target' organs of platelet sequestration after trauma or sepsis are many: 111Indium-labelled platelets have been located in the gut, lung, liver and spleen, especially in patients with poor outcomes [18]. Regardless of the target organ, the endothelial cell is (by definition) the main cell with which platelets interact. Various inflammatory stimuli can induce endothelial cell activation [19] that can trigger coagulation and platelet adhesion, e.g. by inducing release of tissue factor [20]. Correlating the prolonged platelet sequestration observed in vivo with in vitro studies is not trivial since it is very difficult to realistically reproduce the interaction between endothelial cells and platelets. In an interesting in vivo experiment [21] endothelial dysfunction developed after a 1-hr perfusion with endotoxin of the forearm vessels in healthy persons. This endothelial "stunning" lasted for more than 48 hours. Thus activation of platelets and activation of endothelial cells may be present in the absence of significant DIC.

As indicated above, in many trauma and sepsis experiments but not in clinical studies, limiting the decreases in platelet count has been used as a surrogate goal. In observational studies low early
platelet counts were predictive of poor outcome in patients with sepsis or patients with a ruptured abdominal aortic aneurysm [22,23]. In prognostic models in critical care, the platelet count has emerged as an important component. For example the multi-organ dysfunction [24] and the sequential organ failure assessment scores [25] use the platelet count and not the leukocyte count as one of their components parameters, which in contrast to the older Acute Physiology and Health Evaluation (APACHE) score [26]. Recent studies have shown that the rate of change in the platelet count is even a better marker of outcome. Failure of the platelet count to recover sufficiently after reaching nadir values was associated with poor outcome in medical [4] and surgical [3] intensive care patients. In surgical ICU patients we found that the rate of change in platelet count had the same predictive power for mortality as APACHE-II scores [3]. However, in the immunomodulatory clinical intervention trials [10] platelet count has not been used as a major parameter. No intervention effects on the platelet count have been reported - although the platelet count was measured in many trials as part of semiquantitative hematological or coagulation scores. It would be of interest to re-analyse existing clinical trial databases and compare quantitative changes in platelet count with the intervention and with outcome.

Thus many lines of evidence point to a relation of platelet count with outcome in a variety of seriously ill patients. The pathophysiologic importance of platelet sequestration in regard to outcome can only be proven by selectively blocking this process. Promising interventions 'downstream' the inflammatory cascade may be possible at clinically feasible times. Inhibitors of tissue-factor activity may be very effective in limiting DIC and platelet sequestration [16]. Antithrombin-III and especially glycoprotein IIb/IIIa (GP IIb/IIIa) -inhibitors have both shown anti-inflammatory effects. The GP IIb/IIIa-inhibitors that selectively inhibit platelet adhesion have shown dramatic effects on coronary platelet sequestration and mortality in several clinical trials [27].

In conclusion we have shown that high dose steroids started within hours after major injury do not influence subsequent systemic platelet sequestration. We believe that limiting the decrease in platelet count as a goal in intervention studies remains useful. How instrumental the role of platelet sequestration is in systemic inflammation, needs to be addressed by specific intervention studies.
REFERENCES


