Case Report

Hypertensive crises following platelet transfusions in a patient on erythropoietin therapy

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Introduction

The mechanism by which recombinant human erythropoietin (Epo) increases blood pressure in a substantial proportion of uraemic patients is still unclear. In vitro studies support changes in endothelial function [1,2]. Increased vascular responsiveness to endogenous vasoconstrictors has also been shown in uraemic patients receiving Epo [3,4].

We previously observed that antiplatelet therapy may protect these patients from the development of hypertension induced by Epo [5,6]. One hypothesis to explain this finding may be the influence of hyperactive platelets on the function of an abnormal endothelium.

We study the effect of Epo in an end-stage renal failure patient with severe thrombocytopenia and the changes in her blood pressure after platelet transfusions.

Case report

A 15-year-old female patient with Flechner’s syndrome (macrothrombocytopenia, deafness and Alport-like nephropathy) was referred to our service for end-stage renal failure. She underwent splenectomy at the age of 10. Renal failure was detected at the age of 13, with progressive deterioration in the last few months. Epo therapy (25 U/kg/b.i.w) was begun 3 months earlier due to severe anaemia. Blood pressure was normal prior to Epo therapy and a slight increase was observed in the last few weeks for which 20 mg/day nitrendipine was administered. The patient had uneventfully received several platelet transfusions in the previous years.

She was admitted to the hospital for peritoneal catheter placement. At admission, her blood pressure was 140/90 mmHg and laboratory studies showed: haematocrit 26%, haemoglobin 88 g/l, platelet count $3 \times 10^3$/mm$^3$, and creatinine clearance 8.5 ml/min. Six platelet packs were transfused before a peritoneal catheter was surgically placed, using local anaesthetic.

A marked increase in blood pressure was observed immediately after operation, needing the institution of more intensive antihypertensive therapy (Figure 1). The patient was discharged 12 days later, with her blood pressure controlled with captopril 100 mg/day. Five days later, she was readmitted for peritoneal dialysis treatment. Her blood pressure was 140/80 mmHg. Because of peritoneal outflow obstruction, omental wrapping of the catheter was suspected and a laparatomy was performed. One hour prior to laparatomy six platelet packs were transfused, the patient again developing severe hypertension, which did not respond to analgesic or anxiolytic drugs (Figure 1).

In order to rule out the influence of volume expansion on the hypertensive crises following platelet transfusions, 350 ml of saline 0.9% (the estimated plasma
volume of six packed platelet units) were infused over 2 h, 15 days after the last hypertensive crisis. A peak blood pressure of 150/100 was recorded 2 h after the infusion, with the patient remaining normotensive (BP < 130/80 mmHg) for the following 2 days.

Despite the continued Epo therapy, there was no need for antihypertensive drugs during the following months.

Seven months later, the patient received six platelet packs before the extraction of a tooth. She had normal blood pressure (120/70 mmHg) prior to platelet transfusion and her haematocrit was 28%. Two hours after platelet transfusion, the blood pressure was 180/110 mmHg. She was discharged the next day on propanolol 120 mg plus nifedipine 60 mg/day. During the following 24 h, the patient remained severely hypertensive at home despite treatment, complaining of epigastric pain, vomiting and 36 h later was readmitted with tonic-clonic convulsions and a blood pressure of 250/150 mmHg. Although she was treated with intensive antihypertensive therapy (sodium nitroprussiate and labetalol), the control of blood pressure was very difficult. Epo therapy was withdrawn. Fifteen days later, blood pressure was normal (120/80 mmHg) without medication.

One month later, it was necessary to remove the peritoneal catheter due to complicated peritonitis with catheter malfunction and Candida overgrowth. The patient received six platelet packs before the removal of the peritoneal catheter. No modifications in the blood pressure were observed after transfusion, remaining normotensive without antihypertensive drugs. Her haematocrit was maintained above 25% by these changes in endothelial function do not seem to be important enough by themselves to cause significant clinical events in most patients treated with Epo. It is likely, however, that these changes, may impair vascular responsiveness to endogenous vasoconstrictors, such as noradrenaline or angiotensin II [3,4].

In order to confirm the association between hypertensive crises and platelet transfusions only when she was on Epo therapy, we asked parents for permission to re-institute Epo therapy for 1 month (25 U/Kg/b.iw) and then closely check blood pressure changes following the transfusion of three platelet packs. Before platelet transfusion, the patient’s blood pressure was 120/70 mmHg without medication. Immediately after the transfusion, blood pressure rose to 180/120 mmHg and remained so for 4 h, until nifedipine, propanolol, and hydralazine were instituted. During the following 5 days these drugs were required for blood pressure control and were tapered thereafter. Ten days later, the patient’s blood pressure was normal with no need of antihypertensive medication, despite the continued Epo therapy.

**Discussion**

This end-stage renal failure patient with macrothrombocytopenia developed severe auto-limited crises of arterial hypertension after platelet transfusions only when she was receiving Epo therapy. Platelet transfusions without Epo no longer triggered arterial hypertension. This observation raises two major questions: (1) what is the mechanism by which platelet transfusions increased blood pressure in this thrombocytopenic end-stage renal failure patient? and, (2) why did the blood pressure increase only in conjunction with Epo therapy?

Hypertensive crises following blood transfusions are very uncommon. Increases in blood pressure along with encephalopathy or cerebral haemorrhage following blood transfusions have been described only in patients with several types of haemolytic anaemia and normal renal function (prototype of chronic endogenous overproduction of erythropoietin) [7–10]. The infusion of vasoactive substances from platelets has been mentioned for explain these clinical events [7]. Platelet packs are very rich in substances which potentially have vasopressor effects (serotonin, thromboxane). In addition, intracellular concentrations of these substances are high in normal platelets, and through the mechanism of aggregation, they can be locally released in peripheral circulation. Therefore the infusion or release of these substances from aggregated platelets may explain the increase in blood pressure only if the recipient of the transfusion was especially susceptible to their vasoactive effects. According to the events observed in this case, it seemed that Epo made the patient susceptible to the potential vasopressor effect of platelet transfusion.

A shift in prostanoid balance and increased synthesis and release of endothelin-1 (ET-1) are thought to be primary effects of Epo in endothelium [1,2]. However, these changes in endothelial function do not seem to be important enough by themselves to cause significant clinical events in most patients treated with Epo. It is likely, however, that these changes, may impair vascular responsiveness to endogenous vasoconstrictors, such as noradrenaline or angiotensin II [3,4]. Furthermore, increase in local synthesis and secretion of ET-1 may amplify the effects of other potential vasoconstrictors, such as serotonin [11]. At the same time, the interaction of more active platelets with endothelium could lead to the release of other substances from aggregated platelets such as TGFβ, PDGF, FGF, etc., which are known to potentiate ET-1 synthesis and promote the proliferation of endothelial cells [12,13]. In addition, thrombin, which is formed after activation of the coagulation cascade can also stimulate the formation of ET-1, even potentiating the *in vitro* effects of Epo on ET-1 synthesis and secretion [2].

The results from the studies quoted above, may help to explain hypothetically the co-stimulatory effect of more active platelets in Epo-induced hypertension. On a theoretical and speculative basis, they may also explain why this patient showed hypertensive crises after platelet transfusions. However, further studies will be necessary to unveil the role of platelets in the physiopathology of arterial hypertension and the link between platelets and Epo-induced hypertension in end-stage renal failure patients.
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References


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