LETTERS TO THE EDITOR

Safety Concerns About Perisurgical Epoetin Treatment: Should We Add Antiplatelet Drugs to Perisurgical Epoetin Alfa Treatment?

To the Editor:

Cardiac surgery in Jehovah's witness patients remains a challenge in the presence of low blood volume and reduced hemoglobin (Hb). Perisurgical rHuEPO has proven useful to accelerate red blood cell production and increase Hb to reduce the risk of allogeneic blood transfusion. We report a case of a 57-year-old female Jehovah's witness suffering from severe calcified mitral valve stenosis with severe pulmonary hypertension and massive tricuspid insufficiency. The patient showed a poor quality of health and auricular fibrillation undergoing acenocumarol treatment. The patient was scheduled for mitral replacement and tricuspid annuloplasty surgery, and she refused all blood derivatives. In the preoperative assessment, laboratory results showed that there was a normochromic normocytic morphology, with levels of Hb of 12 g/dL, ferritin levels of 360 ng/mL (normalized ratio [NR] of 15-200), transferrin of 2.54 g/L (NR of 1.93-3.08), and soluble transferrin receptor of 2.03 mg/L (NR of 0.83-1.76). The patient was treated with 2 doses of both 200 mg of intravenous iron and 40,000 U of subcutaneous epoetin alfa (rHuEPO), in a week, and a third dose 2 days after the second one. This treatment was approved as a merciful use. A week after the last dose, the patient suffered a sudden onset of left hemiplegia, with facial paralysis and gaze deviation to the right. The cranial computerized axial tomography did not show alterations. At that time, Hb was 12.4 g/dL, and the platelet count was 362,000/μL. Blood pressure was 107/60 mmHg. Control of anticoagulation gave an international normalized ratio value of 3.0. Three hours after disappearance of the symptoms the patient was discharged from the emergency room with the diagnosis of transient ischemic attack (TIA) and any additional treatment was added.

Three weeks later, the patient underwent surgery for mitral replacement and tricuspid annuloplasty, with a preoperative Hb level of 13.9 g/dL, and no blood derivatives were used. The minimum Hb value during the perioperative period was 10.7 g/dL and other blood-sparing techniques like intraoperative cell saver and aprotinin were used. It was suspected that treatment with rHuEPO could play a role in the episode of TIA because of a possible increase in platelet reactivity. The patient had never suffered from TIA before, and she was correctly anticoagulated with acenocumarol. The patient did not present any additional risk factor, such as arterial hypertension, and Hb levels had not risen yet at that time.

Apart from correcting the hematocrit, rHuEPO improves platelet function[1,2] even before the Hb rise can be observed,[2] suggesting a direct beneficial effect on platelets.[3] Long-term administration of rHuEPO in uremic patients has improved their hemostatic behavior,[4] although increased risks of hypertension and thrombotic events have been associated with this treatment.[5] However, very few clinical thrombotic events were reported in the large studies that led to rHuEPO registration for use in the perioperative period.[6,7] More recently, the incidence of thrombotic/vascular event occurrence in rHuEPO-treated patients undergoing major elective orthopedic surgery was 2 out of 460 in a European multicentric study[8] and 46 of 619 patients in an integrated analysis from 2 prospective, multicenter, randomized studies.[9] However, none of these studies used the reference method (eg, venography, echo-Doppler) to detect deep vein thrombosis.

It is feasible to think that although the dose of rHuEPO applied in perisurgery (40,000 U/wk) is much higher than that administered in chronic renal failure (2,000 U 3 times a week), the short-term treatment period prevents the appearance of adverse effects. However, there is evidence showing that the in vitro acute exposure of endothelial cells to rHuEPO activates the JAK/STAT signaling pathway, inducing the generation of a more thrombogenic extracellular matrix, which exhibits a higher presence of tissue factor.[10]

In surgical patients, the treatment with anticoagulants, generally low–molecular-weight heparin, is not initiated until the day before surgery, which is 3 weeks after the first dose of rHuEPO. Therefore, the potential early effect of rHuEPO on platelet reactivity could imply a thrombotic risk in the vessels, which would increase with the progressive Hb rise in the following days. Despite this fact, adequate anticoagulation with acenocumarol may not be sufficient to protect a patient under treatment with rHuEPO from episodes of TIA. For all these reasons, antiplatelet therapy could be a putative prophylactic treatment to prevent TIA or other thrombotic events in high-risk patients.

In conclusion, the referred case shows that rHuEPO administration is not risk free, even in the perisurgical setting. A careful evaluation of benefit/risk rate for each patient and more accurate definition of exclusion criteria for this drug are required. A

simultaneous prophylactic antithrombotic therapy could theoretically be considered in order to prevent the development of thrombotic events in high-risk patients.

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REFERENCES

1. Moia M, Mannucci PM, Vizzotto L, et al: Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. Lancet 330:1227-1229, 1987
2. Cases A, Escolar G, Reverter JC, et al: Recombinant human erythropoietin treatment improves platelet function in uremic patients. Kidney Int 3:668-672, 1992
3. Diaz-Ricart M, Etebanell E, Cases A, et al: Erythropoietin improves signaling through tyrosine phosphorylation in platelets from uremic patients. Thromb Haemost 82:1312-1317, 1999
4. Malyszko J, Malyszko JS, Borawski J, et al: A study of platelet functions, some hemostatic and fibrinolytic parameters in relation to serotonin in hemodialyzed patients under erythropoietin therapy. Thromb Res 77:133-143, 1995
5. Finelli PF, Carley MD: Cerebral venous thrombosis associated with epoetin alfa therapy. Arch Neurol 57:260-262, 2000
6. Faris PM, Ritter MA, Abels RI: The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. The American Erythropoietin Study Group. J Bone Joint Surg Am 78:62-72, 1996
7. De Andrade JR, Jove M, Landon G, et al: Baseline hemoglobin as a predictor of risk of transfusion and response to epoetin alfa in orthopedic surgery patients. Am J Orthop 25:533-542, 1996
8. Weber EW, Slappendel R, Hemon Y, et al: Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: The European Epoetin Alfa Surgery Trial (EEST). Eur J Anaesthesiol 22:249-257, 2005
9. De Andrade JR, Frei D, Guilfoyle M: Integrated analysis of thrombotic/vascular event occurrence in epoetin alfa-treated patients undergoing major, elective orthopedic surgery. Orthopedics 22:S113-S118, 1999 (suppl)
10. Fuste B, Serradell M, Escolar G, et al: Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. Thromb Haemost 88:678-685, 2002

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Paraplegia Because of Hemostatic Agents in the Costovertebral Space: This Occurs Even in Thoracic Aorta Surgery

To the Editor:

We read with interest the article by John et al[1] reporting a case of delayed paraplegia because of the migration of hemostatic material used to control bleeding at the costovertebral junction that occurred after lung decortication surgery. We fully agree with the authors that, for this potentially reversible complication, a high level of suspicion should be kept in every case of general thoracic surgery complicated by the occurrence of postoperative paraplegia/papaparesis, and this is especially true when hemostasis at the costovertebral angle has been tedious. We would like, however, to stress that as much attention should also be given to this possible cause of paraplegia even when it occurs after thoracic aorta surgery. As we previously described,[2] bleeding problems in the costovertebral angle can occur anytime when a posterolateral thoracotomy is performed; but when the surgical procedure is a vascular one on the thoracic aorta, in case of paraparesis/paraplegia it is much easier to think about a problem related to the replacement of the aorta (ie, an irreversible problem) instead of considering migration of hemostatic sponges, which, in some cases, is reversible.[2] Considering this, theoretically, could avoid some cases of postoperative paraplegia occurring after thoracic aorta surgery.

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