Review

Preoperative recombinant human erythropoietin in anemic surgical patients

Terri G Monk

Professor, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, USA

Correspondence: Terri G. Monk, Terri.Monk@duke.edu

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Abstract

Preoperative anemia in a surgical patient predisposes to poor outcomes and allogeneic blood transfusions. As an alternative to transfusions, pharmacologic management of preoperative anemia with recombinant human erythropoietin (rHuEPO) has been well studied in many different types of surgery. rHuEPO, when used alone or in combination with preoperative autologous blood donation before elective surgery, stimulates erythropoiesis and helps to avoid or reduce the need for allogeneic blood transfusions. The clinical evidence on preoperative use of rHuEPO in orthopedic, cardiac, and cancer surgery, as well as in bloodless surgery, is reviewed.

Keywords allogeneic blood transfusions, anemia, recombinant human erythropoietin, surgical patients

Anemia, which can be defined as hemoglobin less than 13 g/dl or hematocrit less than 36%, is a relatively common preoperative finding. Approximately one third of patients are anemic before they undergo joint arthroplasty, with baseline hemoglobin levels between 10 and 13 g/dl [1]. In veterans undergoing noncardiac surgery, the incidence of preoperative anemia (hematocrit <36%) was 34% [2], and in surgical patients who refused transfusions because of religious reasons, 28% had preoperative hemoglobin levels less than 12 g/dl [3]. The incidence of anemia also increases with age [4]. In a recent study of 296 elderly patients with hip fractures, the mean hemoglobin on hospital admission was 12.1 ± 1.7 g/dl [5]. Anemia is especially prevalent in patients with cancer, and treatment plans often include surgery. A low initial hemoglobin level measured at disease presentation is a risk factor for further development of anemia throughout the course of treatment. In patients with colorectal cancer the incidence of preoperative anemia was 46% [3]. Following radical mastectomy for breast cancer, 38% of women were anemic (hemoglobin <12 g/dl) before their first chemotherapy cycle, and 59% became anemic after surgery and chemotherapy [6].

Ensuring adequate tissue oxygenation in the surgical setting frequently involves the administration of blood transfusions. Patients with preoperative hemoglobin levels between 10 and 13 g/dl may be three or more times as likely to receive allogeneic blood than those with baseline hemoglobin greater than 14 g/dl [7]. Although it has been documented that patients prefer to receive autologous blood [8], those who are anemic before surgery are not candidates for preoperative autologous donation (PAD). Patients with coronary artery disease have impaired hemodynamic and nonhemodynamic responses to hypoxia, and autologous blood donation is not feasible because the hemodilution that ensues may not be tolerated [9]. Endogenous erythropoietin normally stimulates the bone marrow to increase red blood cell (RBC) mass under hypoxic conditions, but if this nonhemodynamic response to hypoxia is impaired then hemoglobin levels do not rebound sufficiently. If hemoglobin levels fall even further during surgery due to blood losses, as commonly occurs, the likelihood of receiving an allogeneic blood transfusion increases [10]. RBC transfusions are associated with an increased risk for postoperative infections [11] and tumor recurrence [12], as well as with a variety of immunologic complications [13] that may adversely affect surgical patients. Longer hospital stays and higher health care costs have also been linked to blood transfusions [14].

PAD = preoperative autologous donation; RBC = red blood cell; rHuEPO = recombinant human erythropoietin.

Although allogeneic blood is now reportedly safer than ever [15], safety issues with the blood supply still exist [16]. Furthermore, blood is a scarce resource that is becoming even more so. As the 'baby boomer' population ages, two factors are converging that will limit blood availability and drive up its cost. First, the eligible donor pool is shrinking and, second, surgery in these patients, whether elective or otherwise, is on the increase. Because of these quality-of-care and economic factors, the decision to transfuse should be carefully weighed by all members of the surgical team, and transfusion alternatives considered.

The importance of correcting preoperative anemia cannot be overemphasized because this condition is known to be associated with poor outcomes after surgery. Coronary artery disease patients with anemia exhibit higher mortality rates and experience more cardiac, abdominal, and renal complications after cardiac or noncardiac surgery than do patients with normal hemoglobin levels [9]. Myocardial ischemia is one of the major complications that occur in anemic patients without overt cardiac disease. In elderly men undergoing radical prostatectomy, ST-segment changes and postoperative ischemic episodes were seen more frequently in those with lower hematocrit [17]. In another study of noncardiac surgical patients of various types comprising a large Veterans Administration database, perioperative anemia and blood transfusions were associated with an increased risk for infection, higher mortality rates, and substantial consumption of health care resources [2]. Dunne and coworkers [18] recently documented a relationship between preoperative anemia and stage of colorectal cancer at diagnosis, and a study of 198 patients with rectal cancer [19] showed that low preoperative hemoglobin levels were an independent risk factor for mortality ($P < 0.0001$). Taken together, these reports indicate that preoperative anemia is prevalent, that anemia and blood transfusions are associated with risks and poor outcomes, and that anemia should be treated, preferably with strategies that exclude allogeneic blood.

The human recombinant form of endogenous erythropoietin (rHuEPO; epoetin alfa) is indicated for the treatment of anemic patients who are scheduled to undergo elective surgery (noncardiac and nonvascular) to reduce the need for allogeneic blood transfusions [20]. Multiple clinical studies involving many different surgical types have shown that preoperative rHuEPO is safe and effective. Patients with initial hematocrits between 33% and 39% and who stand to lose up to 3000 ml blood during surgery are among those who can benefit the most [21–23]. Less benefit can be expected in patients with relatively normal preoperative hemoglobin levels [24].

The positive impact of rHuEPO is readily apparent in patients undergoing orthopedic surgery, which is often elective and associated with substantial blood losses [25]. Oral iron supplementation and treatment with rHuEPO should be considered in any anemic patient (hemoglobin >10 and ≤13 g/dl) whose risk for transfusion is estimated to exceed 10% [7]. Patients undergoing major orthopedic surgery who received rHuEPO 300 units/kg per day for 10 days preoperatively, on the day of surgery, and 4 days postoperatively had a nearly six-fold reduction in allogeneic transfusion risk as compared with patients who received placebo [1,26]. In another study that compared rHuEPO administered daily (300 units/kg per day) with rHuEPO administered weekly (600 units/kg per week) for four doses beginning 21 days before surgery [27], transfusion requirements were comparable, indicating that the weekly rHuEPO regimen also reduces transfusion requirements while improving patient convenience. Importantly, weekly dosing can result in cost savings of approximately 43%. rHuEPO has also been demonstrated to reduce transfusion requirements in elderly patients undergoing major hip or knee reconstruction [28], in more heterogeneous populations of patients needing total joint arthroplasty or major hip or knee surgery [29,30], and even in children requiring craniosynostosis repair [31].

In cardiac surgery, all of seven randomized studies included in a meta-analysis [32] provided evidence that rHuEPO, with or without PAD, produced significant decreases in the proportion of patients transfused with allogeneic blood. In another single-blind, randomized study of patients undergoing coronary artery bypass graft surgery [33], patients treated with low dose (100 units/kg) rHuEPO for 4 days before surgery received less than half the amount of autologous blood ($P < 0.01$) as compared with the control group.

Surgery in cancer patients represents a particular challenge because these patients may suffer severe anemia caused by their cancer or its treatment. In patients with a hemoglobin under 8.5 g/dl and with colorectal cancer, 300 IU/kg rHuEPO on day 4 before surgery followed by 150 IU/kg for the next 7 days thereafter stimulated erythropoiesis and reduced transfusion requirements compared with placebo [34]. Transfusion requirements were reduced and hemoglobin levels were improved with preoperative rHuEPO treatment in patients with gastrointestinal tract cancer [35] and in those with rectal cancer undergoing surgery [36]. Epoetin beta has shown similar effects in patients with colon cancer [37]. Other patient groups for whom surgery is indicated and in whom preoperative rHuEPO exerts beneficial effects include those with prostate cancer [38], head and neck cancer [39], and women undergoing gynecologic surgery for benign conditions [40].

When surgical blood losses are anticipated to exceed 3000 ml, rHuEPO is effectively used in conjunction with PAD [41]. In patients who were to undergo total hip replacement, rHuEPO facilitated dose-dependent increases in PAD amounting to 4.3 units (300 IU/kg), 3.4 units (150 IU/kg), and 3.0 units (75 IU/kg), as compared with 2.1 units with placebo, and it minimized reductions in hematocrit associated with repeated phlebotomy [42]. Treatment with rHuEPO resulted

in rapid increases in RBC production (3.5 days) in nonanemic (hematocrit >39%) patients who were participating in an aggressive program for autologous blood donation [43,44]. This treatment allowed for higher RBC volumes to be donated compared with placebo-treated patients. Even in anemic gastrointestinal cancer patients, rHuEPO facilitated PAD compared with patients who were supplemented with iron alone [45]. Other examples of the utility of rHuEPO in PAD before gynecologic surgery [46] and orthopedic surgery [32,47] can be found.

Although a field of medicine unto itself, the practice of bloodless surgery is gaining attention and therefore deserves brief mention [48]. Jehovah's Witnesses refuse transfusions on the basis of religious convictions, but are known to survive trauma and surgery with remarkably low hemoglobin levels. In many cases, these patients do so with the pharmacological support of erythropoietic agents [49–51]. In a case study involving 48 Jehovah's Witness patients, rHuEPO was successfully used to avoid transfusions completely during and after elective coronary and heart valve surgery [52]. When used in combination with products that can substitute for blood [53] (e.g. the hemoglobin-based oxygen carriers, also known as HBOCs), there may be complementary effects. Thus, patients wishing to avoid transfusions may have even more options in the future.

In conclusion, preoperative anemia can be effectively managed with minimal exposure to allogeneic transfusions in virtually all surgical specialties. rHuEPO reduces transfusion requirements, facilitates collection of preoperative autologous blood, and is effective alone or with other blood conservation strategies in severe anemia. Surgeons should enthusiastically adopt available therapies that help to avoid transfusions and their accompanying risks, conserve blood, and treat preoperative anemia, with the goal of improving surgical outcomes.

Competing interests

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