The Predictive Power of Baseline Hemoglobin for Transfusion Risk in Surgery Patients

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ABSTRACT

Preoperative hemoglobin concentration may be an important predictor of transfusion risk in surgical procedures with significant expected blood loss. Contemporary studies investigating transfusion risk with regard to the relationship between perioperative administration of Epoetin alfa and baseline hemoglobin provide data to test this hypothesis. The predictive power of seven preoperative variables (hemoglobin concentration, age, erythropoietin level, ferritin concentration, serum iron, total iron-binding capacity, and predicted blood volume) on transfusion risk was examined via retrospective logistic regression analysis of 276 orthopedic surgical patients. In the two studies used to perform the regression analysis, patients were treated daily with either Epoetin alfa or placebo. Based on the retrospective analyses, a prospective study was conducted to validate the hypothesis. Of the seven variables evaluated, baseline hemoglobin concentration and predicted blood volume were significantly predictive of transfusion risk in both Epoetin alfa- and placebo-treated patients. Further, an inverse correlation between hemoglobin concentration and transfusion risk was demonstrated in placebo-treated patients. Placebo-treated patients with hemoglobin > 10 to ≤ 13 g/dL had an approximately twofold greater risk of transfusion than patients with hemoglobin > 13 g/dL. In contrast to placebo treatment, Epoetin alfa significantly reduced transfusion risk in patients with hemoglobin > 10 to ≤ 13 g/dL. Baseline hemoglobin concentration is an excellent predictor of transfusion risk in orthopedic surgical patients. As a result, hemoglobin testing should be considered a part of routine preoperative testing for orthopedic surgical patients.

INTRODUCTION

Preoperative assessment of a patient’s transfusion risk facilitates appropriate application of blood management strategies that can reduce or eliminate exposure to allogeneic blood and allow for prudent allocation of blood bank resources. Baseline hemoglobin (Hb) concentrations that are below normal have been associated with a higher rate of transfusion in patients undergoing major elective surgery.¹ ¹ ¹ Nuttall and colleagues² analyzed the charts of 299 patients undergoing total hip arthroplasty and found that estimated perioperative blood loss and preoperative Hb concentration are significant indicators of allogeneic blood transfusion. Furthermore, although preoperative autologous blood donation is a measure to reduce the need for allogeneic blood, patients who donate preoperatively are likely to have lower hematocrit (HCT) values and are likely to be transfused earlier and more frequently than nondonating patients.³ In the paper entitled “Prediction of red cell transfusion in orthopedic surgery,” presented at the 65th American Academy of
Orthopaedic Surgeons meeting, results from 9482 total joint replacement patients indicate that baseline Hb concentration (e.g., anemia) and lack of autodonated blood are important predictors of allogeneic transfusion. In this study, 9% of patients who autodonated, the majority of whom underwent primary arthroplasty, still required allogeneic blood.7

To identify potential baseline clinical variables predictive of transfusion, retrospective logistic regression analyses were performed using the data from two major, double-blind, placebo-controlled clinical trials conducted by the Canadian Orthopedic Perioperative Erythropoietin Study Group (Canadian study)1 and Faris et al.2 The results of the retrospective analyses were then tested prospectively in a study conducted by de Andrade et al.8 The objectives of the present study were to determine the pretreatment (i.e., baseline) clinical variables that are prognostic for transfusion risk in orthopedic surgical patients, and to confirm which patients are most likely to benefit from recombinant human erythropoietin (Epoetin alfa).

MATERIALS AND METHODS
Study Design. The statistical modeling was performed on data from two randomized, double-blind, placebo-controlled, multicenter clinical trials1-2 that evaluated the risk of exposure to allogeneic blood in patients treated with Epoetin alfa or placebo (Table 1). In these two clinical trials, 276 patients were administered 300 U/kg Epoetin alfa or placebo daily by subcutaneous injection for 14 to 15 days beginning 10 days before surgery.1,2 Lower dosing regimens were used in both the Canadian and Faris studies, but these additional patients were not used in the modeling. The results of these analyses were then prospectively applied to the study design by de Andrade et al (Table 2).8 Patients in all three studies received daily oral iron supplementation and standard anticoagulation therapy.

Transfusion Guidelines. In the Canadian study,1 a surgical transfusion trigger was established at a blood loss level > 15% of the total predicted blood volume (PBV) or at a Hb concentration < 8 g/dL. In the Faris study,2 final blood management decisions were left to the discretion of the investigators. In the de Andrade study,8 transfusion was discouraged for asymptomatic patients whose Hb was > 9 g/dL; however, final blood management decisions were left to the discretion of the clinicians.
Integrated Statistical Analysis. Statistical regression analyses were performed on data from 276 patients who underwent total joint arthroplasty. Seven preoperative variables thought to be important for assessing the likelihood of transfusion were analyzed, including age, ferritin concentration, serum iron, total iron-binding capacity, endogenous serum erythropoietin concentration, Hb concentration, and PBV. PBV was calculated from patient gender, height, and weight. In both studies, all variables were measured at baseline before Epoetin alfa therapy or placebo (10 days before surgery) and were treated in statistical analyses as continuous measurement variables.

Logistic regression analyses using all seven variables identified Hb concentration and PBV as the two most important predictors of transfusion risk, regardless of the patient’s treatment assignment. For each of the two studies, statistical logistic models for predicting the likelihood of transfusion based on a patient’s Hb and PBV were developed separately for patients treated with placebo and 300 U/kg Epoetin alfa. For both studies, regardless of treatment, as baseline Hb decreased, transfusion likelihood increased. The same pattern essentially held true for PBV; that is, the lower a patient’s PBV, the higher the likelihood of transfusion. By examining relative odds ratios for transfusion likelihood for Epoetin alfa-treated patients versus placebo-treated patients, predictive regions of Hb and PBV values were identified. These were regions where Epoetin alfa-treated patients were relatively less likely to be transfused than placebo-treated patients.

RESULTS
Patient Demographics and Baseline Characteristics. A summary of demographic and baseline characteristics for the intent-to-treat populations in the Faris and Canadian studies is presented in Table 3. Statistical analysis of these variables indicates there were no significant differences between treatment groups in baseline Hb concentration, HCT, and endogenous erythropoietin concentration, and demographic and baseline characteristics were comparable between the two studies. Generally, the estimated surgical blood loss was similar between treatment groups in each study. Intraoperatively, estimated blood loss in the Canadian study exceeded estimated blood loss in the Faris study because of the types of surgery (i.e., hip only versus hip and knee) and the application of blood salvaging techniques in the more contemporary Faris study. The primary rationale for transfusing patients in both studies was intraoperative blood loss, and hypotension in the recovery room was the secondary rationale for transfusion.

Transfusion Risk. In both studies, the proportion of placebo-treated patients requiring transfusion was significantly greater than the proportion of Epoetin alfa-treated patients requiring transfusion (Fig 1). Overall, 27 of 131 (21%) Epoetin alfa-treated patients required transfusion, compared with 70 of 145 (48%) placebo-treated patients. This represents approximately a twofold greater transfusion risk for patients receiving placebo.

Figure 2 illustrates the results, based on logistic regression analyses, of the probability of transfusion-free surgery in relation to baseline Hb concentration. In both treatment groups, baseline Hb was inversely related to
Fig 1: Percentage of evaluable patients transfused from the Canadian (left) and Faris (right) studies. Patients stratified by baseline hemoglobin (Hb) concentration were treated daily for 14 or 15 days, beginning 10 days before surgery with 300 U/kg Epoetin alfa (closed bars) or placebo (open bars). Shown in the inset is the percentage of patients transfused from all hemoglobin stratifications combined. Between-treatment P values are indicated. *Indicates significant difference from placebo treatment.

The upper threshold for which baseline Hb defined a responsive Epoetin alfa subpopulation relative to placebo varied across analyses from approximately 13 to 16 g/dL. While the choice of the threshold is somewhat arbitrary and depends on the desired degree of relative assurance of avoiding transfusion, 13 g/dL was chosen as the upper threshold for further evaluation. The proportion of patients requiring transfusions in the two studies was stratified retrospectively by baseline Hb, patients with Hb > 10 to ≤ 13 g/dL had a greater transfusion risk than patients with Hb > 13 g/dL. Within the placebo-treated groups in both studies, the risk of receiving a blood transfusion was twofold greater for patients with a Hb > 10 to ≤ 13 g/dL (51% received transfusions) than for patients with a Hb > 13 g/dL (26% received transfusions). However, treatment with Epoetin alfa reduced this risk. For patients with Hb > 10 to ≤ 13 g/dL, transfusion frequency in placebo-treated patients was 74% in the Canadian study and 78% in the Faris study, but in Epoetin alfa-treated patients, the transfusion frequency was 32% in the Canadian study and 14% in the Faris study. These findings provided the rationale for a prospective study of the subgroup of patients with Hb > 10 to ≤ 13 g/dL, which was conducted by de Andrade et al.

Prospective Hypothesis Testing. The patient population in the de Andrade study was similar to the patient populations studied in the Canadian and Faris studies (Table 4). Among treatment groups, hematologic parameters, percent of red blood cell salvaging, and perioperative blood loss were also similar. In the de Andrade study, the most common reason for transfusion was postoperative anemia (i.e., Hb < 9 g/dL), followed by high intraoperative blood loss.

In the Hb > 13 g/dL stratum, only a modest benefit was observed in the percentage of Epoetin alfa-treated patients transfused (9%) compared with placebo (13%). In direct contrast to the Hb > 13 g/dL stratum, surgery patients in the Hb > 10 to ≤ 13 g/dL stratum significantly benefited from perioperative Epoetin alfa: only 16% of Epoetin alfa-treated patients received allogeneic blood, compared with 45% of placebo-treated patients.

The relationship between the probability of transfusion and baseline Hb concentration was similar between treatment groups for all Hb values evaluated in the study. In addition, the logistic regression analysis showed that Epoetin alfa-treated patients were less likely to be transfused than placebo-treated patients (Fig 3). The association between baseline Hb concentration and probability of transfusion in the de Andrade study was consistent with the analyses in the Canadian and Faris studies.

**DISCUSSION**

Transfusion risk assessment facilitates rational preoperative planning and the cost-effective use of surgical blood management strategies. Two recent studies have developed mathematical models based on estimated...
blood loss and preoperative Hb concentration or HCT to predict transfusion risk and to apply those predictions to rational blood management. Cohen and Brecher developed a nomogram for calculating the volume of blood loss that can be tolerated by patients with different baseline HCT levels before transfusion is required. The model was used to determine which patients were the best candidates for preoperative autologous donation (PAD) by evaluating the projected blood needs of individual patients before surgery.

Nuttall and colleagues developed a surgical blood ordering equation for total joint arthroplasty, based on evaluation of preoperative Hb concentration and estimated perioperative blood loss, that can be used to determine the number of blood units a particular patient may require and whether PAD might be an appropriate option. Their analysis showed that patients with preoperative Hb > 15 g/dL had 0% probability of transfusion, compared with patients with preoperative Hb ≤ 11 g/dL who had nearly 100% probability of transfusion. Other significant predictors of transfusion in this study included PBV, weight, age, and aspirin use. Many of these blood management equations were designed to be used in conjunction with PAD, and the utility of PAD is limited in patients who are unable to predonate in the presence of anemia. Results from the present study show a significant negative relationship between baseline Hb concentration and transfusion risk. Several other studies also have demonstrated that lower baseline Hb concentration is associated with greater transfusion risk. Studies examining the effects of anemia on surgical outcomes have even suggested that surgical outcome is inversely correlated with preoperative Hb levels.

Advances in surgical technique and blood salvage probably account for the modestly lower transfusion rates observed in the placebo-treated patients from the more recent de Andrade study compared with the Faris and Canadian studies. Still, while the overall risk of transfusion in placebo-treated patients has decreased, patients with Hb > 10 to ≤ 13 g/dL who are not treated with Epoetin alfa still receive transfusions in approximately 50% of major orthopedic procedures. These data support the hypothesis that baseline (i.e., pretreatment) Hb concentration is an important variable for predicting transfusion risk.

In the Faris and Canadian studies, baseline Hb and PBV levels were the primary variables for predicting the relative likelihood of transfusion. Because baseline Hb concentration is more readily available and a more meaningful measure than PBV, further statistical analysis considered the pre-
TABLE 4
Summary of demographic and baseline characteristics of patients enrolled in study by de Andrade et al.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Epoetin alfa (n = 112)</th>
<th>Placebo (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.8 ± 12.7</td>
<td>67.8 ± 11.1</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (34%)</td>
<td>40 (39%)</td>
</tr>
<tr>
<td>Female</td>
<td>74 (66%)</td>
<td>63 (61%)</td>
</tr>
<tr>
<td>Perioperative red cell salvaging, %</td>
<td>49.0</td>
<td>45.8</td>
</tr>
<tr>
<td>Estimated intraoperative blood loss per patient, ml (including knees)</td>
<td>451 363</td>
<td>361 328</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.6 ± 1.1</td>
<td>13.5 ± 1.1</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>40.3 ± 3.1</td>
<td>40.1 ± 3.4</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>2.8 ± 0.7</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Serum ferritin, ng/mL</td>
<td>142.8 ± 99.2</td>
<td>123.8 ± 115.0</td>
</tr>
<tr>
<td>Mean serum iron, µg/dL</td>
<td>87.8</td>
<td>84.5</td>
</tr>
<tr>
<td>Mean total iron-binding capacity, µg/dL</td>
<td>316.5</td>
<td>326.8</td>
</tr>
<tr>
<td>Erythropoietin concentration (mU/mL)</td>
<td>32.8 ± 10.7</td>
<td>17.1 ± 8.5</td>
</tr>
<tr>
<td>Predicted blood volume, ml</td>
<td>4704 ± 906</td>
<td>4859 ± 1008</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. SD = Standard deviation.

Fig 3: Logistic regression of the relationship between baseline hemoglobin (Hb) concentration and probability of a transfusion-free surgery in patients treated with 300 U/kg Epoetin alfa (solid line) and placebo (dotted line) in the de Andrade study. The greatest difference in transfusion risk between treatments was observed at hemoglobin concentrations > 10 g/dL and < 13 g/dL.

indicative of Hb concentration alone. Furthermore, the statistical models suggest that baseline Hb concentration by itself is a powerful predictor of transfusion risk. This result established the rationale for the double-blind, placebo-controlled, clinical trial in which total joint arthroplasty patients were prospectively stratified according to baseline Hb levels before randomization to Epoetin alfa or placebo treatment. In the prospectively defined Hb > 10 to ≤ 13 g/dL group, 45% of placebo-treated patients received an allogeneic blood transfusion compared with 16% in the Epoetin alfa (300 U/kg) group. These results support the model’s findings that patients with anemia (i.e., Hb > 10 to ≤ 13 g/dL) are at greatest risk for transfusion and are most likely to benefit from perioperative Epoetin alfa therapy.

CONCLUSION
In conclusion, baseline Hb concentration is an excellent predictor of transfusion in elective orthopedic surgical patients. Baseline Hb concentration, readily measured in the clinic, can be used preoperatively to identify anemic patients at risk for transfusion. Moreover, Hb testing should be considered a part of routine preoperative testing. This paper reviewed the methodology employed in defining the predictive power of baseline Hb for transfusion risk in both a retrospective and prospective fashion.

REFERENCES