Effects of Recombinant Erythropoietin on Hemoglobin Levels and Blood Transfusion Needs in Patients with Preoperative Anemia Undergoing Cardiac Surgery

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ABSTRACT

Introduction: Preoperative anemia is an important and relatively common problem in patients undergoing cardiac surgery, and its treatment is crucial in improving postoperative outcomes. The use of recombinant erythropoietin is one of the suggested methods in this field. Therefore, in the present study, we sought to evaluate the effects of recombinant erythropoietin on hemoglobin (Hb) levels and blood transfusion needs in cardiac surgery in patients with preoperative anemia.

Methods: This randomized nonblind clinical trial was performed on patients with mild-to-moderate anemia (Hb <12 g/dL in men and Hb <11 g/dL in women) undergoing cardiac surgery at a referral heart hospital (Tehran, Iran). The patients were randomly divided into two groups of 33 patients. In the intervention group, recombinant erythropoietin was administered at a dose of 500 IU/kg one to three days before surgery. Intra- and postoperative Hb levels and the need for blood transfusion were recorded during surgery and for 3 days afterward.

Results: The use of packed red blood cells in the operating room was similar in the intervention and control groups (P = 0.156), but it was significantly lower in the intensive care unit in the intervention group (P = 0.030). The mean Hb, which was initially identical in the two groups (P > 0.05), showed a significantly lower decrease in the intervention group (P = 0.001). No significant differences were observed concerning other variables.

Conclusions: The use of recombinant erythropoietin (500 IU/kg/day) one to three days before cardiac surgery in our anemic patients blunted a reduction in Hb levels and decreased blood transfusion needs.

Keywords: Anemia, cardiac surgery, erythropoietin, postoperative, transfusion

INTRODUCTION

Preoperative anemia is a common problem in cardiac patients and surgery candidates. Prevalence of preoperative anemia is reported to range between 18% and 33%. An increased risk of mortality and complications has been reported in patients suffering from this condition. Recombinant erythropoietin (EPO) is an important drug in the armamentarium of pharmacologic therapies in
human epoetin (recombinant EPO) and its effects on chemotherapy, HIV, and chronic renal failure-induced anemia have been confirmed.\textsuperscript{[12-14]} In the present study, we aimed to investigate the effects of preoperative recombinant EPO on hemoglobin (Hb) levels and blood transfusion needs during and after cardiac surgery.

**METHODS**

This randomized nonblind clinical trial was performed on patients undergoing first-time elective cardiac (coronary artery bypass grafting [CABG] and valve) surgery at a referral heart hospital in Tehran, Iran. Patients were recruited in the study via the convenience sampling method. The inclusion criteria consisted of being scheduled for first-time elective isolated CABG or valve surgery, willingness to participate in the study, age between 18 and 65 years old, and preoperative mild-to-moderate anemia (Hb <12 g/dL in men and Hb <11 g/dL in women). The exclusion criteria comprised the refusal of the patients or their companions to participate in the study, a history of coagulation disorders, preoperative blood transfusion, severe renal or hepatic diseases, and allergies to recombinant EPO or intravenous iron.

The sample volume was calculated based on the following formula ($\alpha = 0.05$, $\beta = 0.2$, $P_1 = 0.93$, and $P_2 = 0.67$) and reference No. 19.

$$N = \frac{P_1 (1 - P_1) + P_2 (1 - P_2) \times (Z_1 - \alpha/2 + Z_1 - \beta)^2}{(P_1 - P_2)^2} \Rightarrow N = \frac{(0.93 \times 0.07) + (0.67 \times 0.33) \times 7.8}{(0.26)^2} \Rightarrow N = 33$$

Ultimately, 66 individuals were allocated to two groups of 33 in the study.

The research proposal was approved by our institutional ethics committee, and informed written consent was obtained from all the patients. The study population was randomly divided into two groups of 33 patients by online random allocation software (https://www.randomizer.org). The intervention group received 500 IU/kg/day of subcutaneous PDpoetin® (Pooyesh Darou Co, Iran; https://pooyeshdarou.com/) between one and three days before surgery. Seven patients in the intervention group and six patients in the control group who had hypochromic microcytic anemia received 500 mg of intravenous iron Ferinject® (ferric carboxymaltose) a day before surgery.

The patients were thoroughly monitored for heart rate, invasive blood pressure, central venous pressure, $SpO_2$, temperature, capnography, and electrocardiography upon arrival at the operating room. During surgery and 3 days afterward, the amount of blood needed for transfusion, the units of transfused packed red blood cells (RBCs), the amount of chest tube drainage, and the level of Hb were recorded. According to our institutional protocol, packed RBCs were transfused when the Hb level was below 8g/dL for low-risk and hemodynamically stable patients and when the Hb level was below 9 g/dL for high-risk patients (i.e., age >70 years, and neurological and ischemic condition) and those with unstable hemodynamics. The Hb level was maintained at a minimum of 10 g/dL in critically ill patients. The activated clotting time (ACT) during surgery was assessed with the ACT Plus® System (Medtronic), and the basic ACT was checked before cardiopulmonary bypass: all the values were within the normal range (70–120 sec). Routinely, heparin-coated bypass circuits were used. For isolated CABG and single-valve surgery, tranexamic acid was not administered based on the institutional protocol.

**Statistical analysis**

Qualitative variables were presented as frequencies and percentages of frequencies, and quantitative variables were expressed as the mean ± the standard deviation. The Kolmogorov–Smirnov test was used to check whether the variables were normally distributed. The independent samples $t$, Mann–Whitney, Fisher’s exact, and $\chi^2$ tests were employed to compare the two groups. Additionally, the repeated measures ANOVA was utilized to evaluate intragroup changes in the quantitative variables in time trends. The data were analyzed by SPSS software, version 25, and a $P$ value of 0.05 or less was considered statistically significant.

**Ethical considerations**

The purpose of the study was fully explained to all the study patients, and informed written consent was obtained from them. The information of the entire study population was kept confidential by the project manager. All the stages of the research were conducted in keeping with the Helsinki declaration, as a statement of ethical principles, and the ethical statements of research committees at Iran University of Medical Sciences. The study was carried out after it was approved by the Research Council of the Medical School and received the code of ethics (IR.IUMS.FMD.REC.1398.172) and the letter of introduction.

**RESULTS**

Out of 243 adult candidates for CABG or valve surgery, 66 patients (24 male and 42 female) with mild-to-moderate...
anemia were enrolled and divided into an intervention group (n = 33) and a control group (n = 33). The frequencies of the variables of age, sex, body mass index, cigarette smoking, diabetes mellitus, hypertension, and a history of surgery, as well as intra- and postoperative parameters, did not show statistically significant differences between the two groups (P > 0.05) [Table 1].

The amount of chest tube drainage at 6 hours after admission to the intensive care unit (ICU) was determined in the intervention and control groups (157.6 ± 146.4 mL vs. 115.2 ± 26.5 mL; P = 0.557). The amount of chest tube drainage in the two groups was also recorded at 12, 24, 48, and 72 hours after admission to the ICU. The trend of change in the average amount of chest tube drainage in the control and intervention groups was evaluated by the repeated measures ANOVA. At the five abovementioned time points, the mean intragroup trend of change in the amount of drainage was statistically significant in both groups (P < 0.001), whereas the difference regarding this trend between the two groups failed to constitute statistical significance (P > 0.05). Figure 1 shows the trend of change in the average amount of chest tube drainage at the five time points. Table 2 presents the laboratory tests of the prothrombin time (PT), the partial thromboplastin time (PTT), the international normalized ratio (INR), and the platelet count before surgery, at ICU admission, and 48 hours later in both groups. The results showed that with respect to these variables, the intervention and control groups were not statistically significantly different (P > 0.05). The mean trend of change in PT, PTT, INR, and the platelet count of the control and intervention groups was evaluated by the repeated measures ANOVA, and the intragroup trend exhibited statistically significant changes at the three aforementioned time points (P < 0.001).

In the preoperative period, the mean Hb level was 10.8 ± 0.4 g/dL in the intervention group and 10.6 ± 0.7 g/dL in the control group (P = 0.203). At the time of admission to the ICU, the mean Hb level in the intervention group was higher than that in the control group (10.4 ± 0.7 g/dL vs. 9.9 ± 0.8 g/dL; P = 0.028). Additionally, at 12, 24, 48, and 72 hours after admission to the ICU, the mean Hb level was significantly higher in the intervention group than in the control group (P < 0.01) [Figure 2]. The mean trend of change of the Hb level was evaluated in the two groups by the repeated measures ANOVA, and the results revealed that the within-group trend of change of this variable was statistically significant at the five abovementioned time points in both groups (P < 0.05).

Table 1: Demographic and Clinical Variables of the two Groups

| Variable                  | Intervention Group | Control Group | P    |
|---------------------------|--------------------|---------------|------|
| Age (y)                   | 59.4±8.9           | 61.4±9.3      | 0.385|
| Gender                    | Male: 13 (39.4%)   | 11 (33.3%)    | 0.609|
|                           | Female: 20 (60.6%) | 22 (66.7%)    |      |
| BMI                       | Normal: 19 (56.7%) | 12 (36.4%)    | 0.171|
|                           | Overweight: 11 (33.3%) | 14 (42.4%) |      |
|                           | Obese: 3 (9.1%)    | 7 (21.2%)     |      |
| Cigarette smoking         | 7 (21.2%)          | 5 (15.2%)     | 0.523|
| Diabetes mellitus         | 11 (33.3%)         | 9 (27.3%)     | 0.592|
| Hypertension              | 20 (60.6%)         | 22 (66.7%)    | 0.609|
| History of surgery        | 14 (42.4%)         | 9 (27.3%)     | 0.196|
| Operation type (CABG/valve)| 21/12              | 23/10         | 1.000|
| Cardiopulmonary bypass time (min) | 92.1±40.2 | 89.9±39.8 | 0.492|
| Aortic cross‑clamp time (min) | 55.7±29.9 | 51.3±23.4 | 0.637|
| Duration of surgery (hours) | 4.2±1.4          | 3.9±1.6       | 0.509|
| Mechanical ventilation time (hours) | 17.2±11.8 | 17.4±11.8 | 0.806|
| Duration of ICU stay (days) | 3.6±1.4          | 3.5±1.4       | 0.731|

BMI: Body mass index; CABG: Coronary artery bypass grafting; ICU: Intensive care unit

Table 2: Laboratory Tests of Coagulation in the two Study Groups

| Variable                    | Intervention Group | Control Group | P    |
|-----------------------------|--------------------|---------------|------|
| Preoperative PT (sec)        | 15.9±1.9           | 15.9±1.4      | 0.926|
| PT at ICU admission (sec)    | 18.5±2.1           | 17.8±1.4      | 0.217|
| PT 48 hours later (sec)      | 17±2.2             | 16.6±1.2      | 0.515|
| Preoperative PTT (sec)       | 34.3±6.3           | 35.8±6.9      | 0.245|
| PTT at ICU admission (sec)   | 42.3±18.1          | 43.3±19.8     | 0.63 |
| PTT 48 hours later (sec)     | 43.4±8.9           | 42.7±9.2      | 0.649|
| INR before surgery           | 1.2±0.1            | 1.2±0.1       | 0.667|
| INR at ICU admission         | 1.3±0.2            | 1.3±0.2       | 0.156|
| INR 48 hours later           | 1.2±0.2            | 1.2±0.1       | 0.362|
| Platelet count before        | 234±97             | 264±104       | 0.305|
| surgery ('1000/mL)           |                    |               |      |
| Platelet count at ICU        | 206±72             | 188±38        | 0.594|
| admission ('1000/mL)         |                    |               |      |
| Platelet count 48 hours      | 234±86             | 221±69        | 0.575|
| later ('1000/mL)             |                    |               |      |

PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; ICU: Intensive care unit
Table 3 summarizes the units of packed RBCs and the amounts of fresh frozen plasma (FFP) and platelet concentrates transfused in the operating room and the ICU. The transfusion amount of packed RBCs in the operating room was similar in both groups, whereas it was lower in the intervention group in the ICU. There were no statistically significant differences between the two groups regarding FFP and platelet transfusion ($P > 0.05$).

Our findings showed that 24 patients (72.7%) in the intervention group and 26 patients (78.8%) in the control group did not use any packed RBCs in the operating room. Eight patients (24.2%) in the intervention group and seven patients (21.2%) in the control group used one unit of packed RBCs, and one patient in the intervention group used two units of packed RBCs ($P = 0.156$). No major complications, including massive bleeding, thrombotic events, re-exploration, and death, were reported in the study population.

**DISCUSSION**

Preoperative anemia is an important and relatively common problem in adult patients undergoing cardiac surgery; accordingly, its treatment is crucial in improving postoperative outcomes. The use of recombinant EPO is one of the proposed methods in this field.$^{19,20}$ We, therefore, performed the current investigation to evaluate the effects of recombinant EPO on Hb levels and blood transfusion needs in cardiac surgery patients with mild-to-moderate preoperative anemia.

Our results demonstrated that the basic Hb level and the units of transfused packed RBCs in the operating room were similar between the intervention and control groups, but the patients who received recombinant EPO one to three days before surgery experienced slower reductions in Hb levels and needed fewer units of packed RBCs after surgery in the ICU. (Additionally, seven patients in the intervention group and six patients in the control group received intravenous iron.)

Various studies have been conducted in this regard. In Japan, Ono et al.$^{21}$ divided 12 patients undergoing heart surgery into six groups with and without recombinant EPO administration and found that blood transfusion needs were significantly lower in the intervention group than in the control group. Also in Japan, Takanashi et al.$^{22}$ divided 47 patients undergoing heart surgery into two groups with and without recombinant EPO administration and reported that blood transfusion needs were significantly lower in the group receiving recombinant EPO (200 IU/kg/day) from 3 weeks prior to surgery to 2 weeks after surgery than in the control group. Additionally, the postoperative Hb level was higher in the intervention group.

In a study by Weltert et al.$^{23}$ in the United States, 600 patients undergoing cardiac surgery presenting with preoperative Hb levels of not more than 14.5 g/dL were divided into two groups of recombinant EPO (800 IU/kg/day) and control. The need for blood transfusion was significantly lower in the intervention group than in the control group (17% vs. 39%). In the first week after surgery, the Hb level was 10.2 g/dL in the intervention group and 8.7 g/dL in the control group, which constituted a statistically significant difference.
In an interventional study by Yoo et al. in South Korea in 2011, 74 patients undergoing preoperative cardiac surgery for anemia were divided into a recombinant EPO group and a control group. In the group receiving recombinant EPO at a dose of 500 IU/kg/day before surgery, the need for blood transfusion was significantly decreased during surgery and for 4 days afterward by comparison with the control group. Transfusion was needed in 32 patients (86%) in the control group and 22 patients (59%) in the recombinant EPO group. The reticulocyte count was found to be significantly greater in the intervention group.

In Spain, Cladellas et al. divided 134 patients with preoperative anemia who underwent cardiac surgery into a recombinant EPO group and a control group, and found that blood transfusion needs were significantly lower in the former group (67% vs. 93%). Morbidity and mortality were also lower in the EPO group.

In a recent (Feb 2021) systematic review, Ebad Ali et al. recommended preoperative EPO for anemic patients; in that preoperative erythropoietin administration conferred a better postoperative outcome, although the risk was equivocal.

Yazıcıoğlu et al. having assessed the effects of administering 100 IU/kg/day of recombinant EPO 4 days before cardiac surgery in nonanemic patients, concluded that EPO induced erythropoiesis rapidly, even when it was administered at a single dose just 4 days before cardiac surgery.

**Limitations**

As a routine in our center, patients are hospitalized between one and three days before cardiac surgery, precluding us from administering recombinant EPO 2–3 weeks before surgery, which is strongly recommended by many authors. Accordingly, while fully cognizant of the limitations, what we aimed to assess in the current investigation was the effect of short-time, high-dose recombinant EPO on erythropoiesis in anemic patients undergoing cardiac surgery. Further, our results would be more robust, had we recorded the estimated blood loss during surgery.

**CONCLUSIONS**

A substantial body of evidence indicates the beneficial effects of recombinant EPO administration from 3 weeks to 1 day before surgery on maintaining better Hb levels and reducing blood transfusion needs in the postoperative period. The use of recombinant EPO at a dose of 500 IU/kg/day, even a few days before surgery, in patients with mild-to-moderate anemia blunts a reduction in Hb levels after cardiac surgery and lessens the need for blood transfusion. In light of the aforementioned information, we also recommend the use of recombinant EPO in anemic patients undergoing cardiac surgery.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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