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Original Article

Perioperative administration of erythropoietin combined with iron sucrose in gynecological tumor patients: a retrospective study

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Abstract: Our goal was to explore the effects of recombinant human erythropoietin (rhEPO) combined with iron sucrose on red blood cell (RBC) mobilization and on the rate of blood transfusion in anemic patients undergoing gynecological tumor surgery. In this retrospective study, a total of 97 patients were divided into three groups. Thirty gynecological tumor patients received rhEPO (10000 IU sc.) plus iron sucrose (100 mg iv. drip) every day for a period from 4 days before surgery to 5 days after surgery (group A). Thirty-five patients received iron sucrose alone every day (group B) and thirty-two patients received neither agent (group C). Differences in characteristics among the three groups were tested by one-way analysis of variance (one-way ANOVA). Differences between any two groups were tested by independent Student's t-test. By the sixth postoperative day, patients in group A showed a significant increase in hematologic indices (hemoglobin, red blood cell, hematocrit and reticulocyte percentage) as compared to those in groups B and C. In addition, patients in group A received fewer blood transfusions during the perioperative period. No complications were observed due to administration of rhEPO combined with iron sucrose. Our results indicate that gynecological tumor patients with anemia benefited from perioperative administration of rhEPO combined with iron sucrose through RBC mobilization and a reduction in the need for blood transfusions.

Keywords: Erythropoietin, iron sucrose, anemia, blood transfusion, gynecological tumor

Introduction

Gynecological diseases are almost always associated with anemia, which not only makes patients weak, but also affects surgical outcomes. Allogenic blood transfusion is currently the main method to correct anemia in the perioperative period. However, blood transfusion is associated with high cost, a risk of transmitting infections, and negative immunological responses [1, 2]. In some situations, scarcity of blood is also a limiting factor. Together, these issues mean that surgeons sometimes do not proceed with allogenic blood transfusion unless the patient presents with hemoglobin (Hb) lower than 70.0 g/L, or with Hb higher than 70.0 g/L but is in poor health. In light of these issues, several alternative methods to correct perioperative anemia have been used, including autologous blood transfusion, administration of intravenous (IV) iron, and administration of recombinant human erythropoietin (rhEPO) [3, 4].

As a hematopoietic cytokine, EPO can stimulate medullary hematopoiesis in a short period of time [5]. Several trials support a short perioperative course of rhEPO to reduce the need for perioperative blood transfusion and improve Hb level, especially in orthopaedic and gastrointestinal cancer patients [3, 6-10]. However, there are few papers that examine this issue in gynecological diseases, and particularly in gynecological tumor surgery. To explore whether rhEPO can increase Hb levels and decrease the need for blood transfusions within the perioperative period in patients with either benign or malignant gynecological tumors, we performed a retrospective study.

Table 1. Characteristics of patients at admission (Mean ± SD values)

	Group A n=30	Group B n=35	Group C n=32	P
Age (years)	45.57±3.89	44.69±6.58	43.81±7.36	0.54
Hb (g/L)	85.37±7.35	85.17±9.04	89.63±6.55	0.038
RBC ($\times 10^9$/L)	3.80±0.41	3.77±0.55	3.69±0.33	0.57
HCT (%)	28.66±2.10	28.37±2.69	29.45±2.07	0.15
RET (%)	1.91±0.50	1.80±0.68	1.68±0.57	0.70
Ferritin (ng/ml)	118.48±57.11	116.65±68.43	114.76±51.83	0.97

Table 2. Disease diagnoses

	Group A	Group B	Group C
Uterine leiomyoma	18 (60.0%)	22 (62.8%)	18 (56.2%)
Ovarian benign tumor	3 (10.0%)	3 (8.6%)	5 (15.6%)
CIN II-III	0 (0.0%)	2 (5.7%)	3 (9.4%)
Ovarian carcinoma	3 (10.0%)	2 (5.7%)	5 (15.6%)
Cervical carcinoma	6 (20.0%)	7 (20.0%)	3 (9.4%)
Endometrial cancer	4 (13.3%)	2 (5.7%)	2 (6.2%)
Endometrial sarcoma	0 (0.0%)	1 (2.8%)	0 (0.0%)
Total patients	30	35	32

Note: Since some patients presented with two gynecological diseases, the patient numbers and percentages add up to more than 100%.

Subjects and methods

Samples

Data from patients with gynecological tumors, who were treated in the Department of Gynecology of the First Affiliated Hospital of Xi'an Jiaotong University between May 2014 and November 2014, were retrospectively collected in this study. The inclusion criteria were a diagnosis of gynecological tumors (uterine leiomyoma, ovarian benign tumor, cervical intraepithelial neoplasia II-III [CIN II-III], ovarian carcinoma, cervical carcinoma, endometrial malignancy or vulvar cancer) with anemia (Hb 70.0-100.0 g/L), and perioperative administration of rhEPO with iron sucrose, iron sucrose alone, or neither agent, according to the conditions described below. Patients whose pathological examination after surgery indicated a diagnosis of endometrial cysts or adenomyosis were excluded from this study.

Data collection

Patients were retrospectively divided into 3 groups: group A (study group) received rhEPO (Epiao, 3SBio Inc.) 10000 IU sc. plus iron sucrose (iron sucrose injection, Shanxi Pude Pharmaceutical Inc.) 100 mg iv. drip every day; group B (control group) received iron sucrose 100mg iv. drip every day; and group C (blank control group) did not receive either rhEPO or iron sucrose. RhEPO and/or iron sucrose were administered for 4 days before surgery up to 5 days after surgery.

In accordance with our study, the following data were collected: (a) Hb, hematocrit (HCT), and reticulocyte percentage (RET) on the day before administration of reagents (designated as "baseline"), 1 day before surgery (-1) and 1, 3, and 6 days after surgery (+1, +3, +6); (b) ferritin at baseline; (c) alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin (DBIL), indirect bilirubin (IBIL), creatinine (CRE), and blood urea nitrogen (BUN) at baseline and at the sixth postoperative day; (d) daily blood pressure; (e) volume of transfused blood during hospitalization; (f) blood loss during surgery; (g) side effects observed (headache, mild fever, myalgia, allergy, thrombosis, and gastrointestinal reaction); (h) postoperative complications; and (i) length of hospitalization.

Ethics statement

The Institutional Review Board (IRB) of Xi'an Jiaotong University confirmed that ethical approval was not required for this study, and also waived the need to obtain written informed consent from the patients. All patient information was anonymised and de-identified prior to analysis.

Data analysis

Data were analyzed using SPSS 22.0 (IBM) and GraphPad Prism 5 software and are presented as the means ± standard deviations (SD). Differences among the 3 groups were tested by one-way analysis of variance (one-way ANOVA). Differences between any 2 groups were tested by independent Student's t-test. Statistical significance was considered when $P<0.05$.

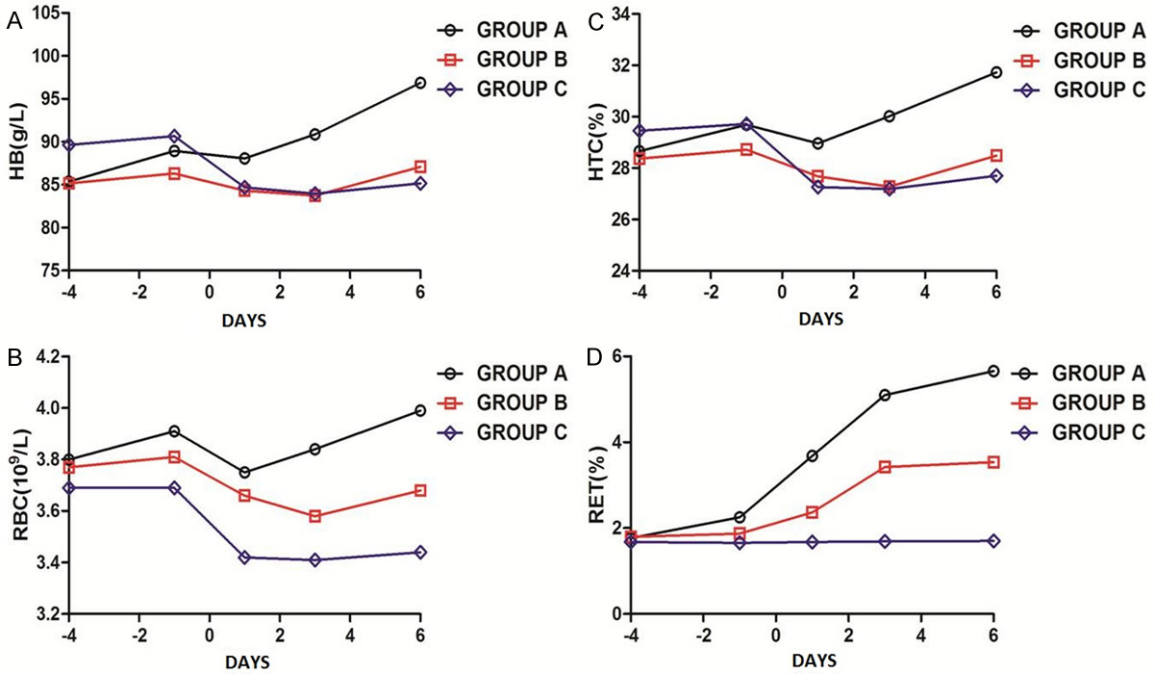

Figure 1. Changes in hematologic indices in different groups. (A) Hemoglobin levels, (B) Red blood cell levels, (C) Hematocrit, and (D) Reticulocyte percentage. Day 0: day of surgery.

Table 3. Changes in hematologic indices (Mean ± SD values)

	1 day after surgery (+1)-baseline				6 days after surgery (+6)-baseline			
	Hb (g/L)	RBC (10^9/L)	HCT (%)	RET (%)	Hb (g/L)	RBC (10^9/L)	HCT (%)	RET (%)
Group A	2.70±8.72	(-0.05)±0.30	0.30±2.96	1.91±0.82	11.5±7.64	0.19±0.25	3.07±2.46	3.89±1.41
Group B	(-0.86)±14.57	(-0.12)±0.51	(-0.69)±4.38	0.57±0.66	1.91±8.60	(-0.10)±0.34	0.12±2.60	1.62±0.67
Group C	(-4.94)±8.99	(-0.27)±0.34	(-2.19)±3.14	0.00±0.19	(-4.47)±5.84	(-0.25)±0.22	(-1.76)±2.10	0.02±0.16
P_{AB}	0.25	0.56	0.29	<0.001	<0.001	<0.001	<0.001	<0.001
P_{AC}	0.001	0.01	0.001	<0.001	<0.001	<0.001	<0.001	<0.001
P_{BC}	0.18	0.15	0.12	<0.001	0.001	0.035	0.002	<0.001

Note: "Baseline" means the day administration begins and "+1" means 1 day after surgery (described in method). There are 4 days for administration before the surgery day. "+1-baseline" means that the data of 1 day after surgery minus the data of baseline.

Results

Patient characteristics

During the 6-month study period, a total of 97 patients meeting the inclusion criteria were distributed into 3 groups: 30 (30.9%) into group A (rhEPO and iron sucrose), 35 (36.1%) into group B (iron sucrose alone) and 32 (33.0%) into group C (neither). No significant differences were found in age, RBC, HCT, RET, or ferritin at admission among the 3 groups, but there was a significant difference in Hb levels, with group C having a higher mean level at admission (**Table 1**). The percentage of patients diagnosed with each of the gynecological tumors was similar in all 3 groups (**Table 2**).

Administration of rhEPO combined with iron sucrose improved hematologic indices

The postoperative changes in hematologic indices are shown in **Figure 1** and **Table 3**. A prominent increase in Hb was observed between the initiation of treatment and the sixth postoperative day (P<0.001) in group A. Similar results were seen for the other hematologic indices, including RBC (P<0.001), HCT (P<0.001) and RET (P<0.001). At the third (P=0.004, P=0.006) and sixth postoperative day (P<0.001, P<0.001), Hb levels for group A were higher than for groups B and C , whereas there was no statistical difference in Hb levels between group B and group C at these time points (**Figure 1A**). Similar improvements were

Table 4. Patients that received blood transfusions

	Baseline Hb (g/L)	Blood loss (ml)	Blood transfusion	
			Suspended RBC (IU)	Plasma (ml)
Group A n=3 (10.0%)	71	200	2 (preoperative)	0
	70	80	1 (preoperative)	0
	88	200	2 (preoperative)	0
Group B n=8 (22.8%)	74	700	4 (intraoperative)	0
	78	300	2 (postoperative)	0
	75	1800	10 (pre-, intra-, postoperative)	200
	73	500	6 (pre-, postoperative)	0
	71	100	4 (pre-, postoperative)	0
	98	200	4 (postoperative)	0
	80	1000	3 (intraoperative)	0
	80	300	2 (intraoperative)	0
Group C n=7 (21.9%)	77	400	3 (postoperative)	0
	98	800	4 (postoperative)	400
	95	700	4 (intra-, postoperative)	0
	89	600	2 (postoperative)	0
	87	600	4 (intra-, postoperative)	0
	80	300	3 (postoperative)	0
	93	400	3 (postoperative)	0

t-test for suspended RBC: P_{AB} = 0.037, P_{AC} = 0.047, P_{BC} = 0.54.

seen in RBC and HCT in group A as well (**Figure 1B**, **1C**). The RBC level of group B, at the sixth postoperative day, was higher than that of group C (P=0.018) (**Figure 1C**). Hb, RBC and HCT on the first postoperative day, measured as differences from baseline, were higher in group A than those in either groups B and C. These differences increased at the sixth postoperative day (**Table 3**).

To determine whether or not stimulation of hematopoiesis accounted for the increases seen in Hb, RBC and HCT, the reticulocyte percentages (RET) at different time points were also analyzed. The mean RET in group A was significantly elevated starting from 1 day before surgery (P=0.025 vs. group B; P<0.001 vs. group C). By the first postoperative day, RET of group B was also raised and was significantly different from group C (P<0.001, **Figure 1D** and **Table 3**).

Administration of rhEPO combined with iron sucrose reduced the rate of blood transfusion

Data from the eighteen (18/96) patients that underwent blood transfusion are depicted in **Table 4**. Fifteen of these patients, all from group B or C, were transfused intraoperatively or postoperatively due to blood loss, and three from group B also received transfusions preoperatively. Three (3/30) patients who were administered rhEPO combined with iron sucrose (group A) were transfused preoperatively, but none required intra- or postoperative transfusion. There was also a significant reduction in the mean blood transfusion volume in transfusion patients in group A compared to those in either group B (P=0.047) or group C (P=0.037).

Administration of rhEPO combined with iron sucrose did not increase the risks of postoperative complications

There were no significant changes observed in mean ALT, AST, DBIL, IBIL, CRE or BUN levels in the 3 groups. However, the ALT levels of one patient in group A and of two patients in group B more than doubled from baseline on the sixth postoperative day. These ALT levels approached the critical value (40 IU/L), but fell back to baseline after 2 weeks without intervention. The blood pressures of all patients remained stable during the treatment period.

Five (5/96) patients suffered postoperative complications. Three of these patients were in group B, and included one patient with infection of the vaginal stump, one patient with incomplete intestinal obstruction, and one patient with poor wound healing combined with incomplete intestinal obstruction. Another two patients were in group C, including one patient with poor wound healing and one patient with deep venous thrombosis. Intriguingly, three of these five patients had received blood transfusions, meaning that 16.7% of the transfused patients (3/18) suffered postoperative complications.

The lengths of hospital stays in the 3 groups were not significantly different (12.40±4.45 days, 12.34±5.70 days and 11.50±5.12 days

for groups A, B and C, respectively; P=0.737). No adverse events associated with the study treatments were observed.

Discussion

Traditionally, blood transfusion has been the principal and fastest method to restore normal hemoglogin levels, which is essential in order to avoid anemia and its associated perioperative complications, and thus to reduce patient mortality [1, 11]. However, more and more surgeons are exploring drugs to replace transfusion, in light of limitations in blood supply and risks associated with transfusion.

EPO regulates the differentiation of erythrocytes in mammals by suppressing apoptosis and promoting the proliferation and maturation of early erythroid precursors in bone marrow [12]. Reticulocyte mobilization has been observed within the first half day after administration of rhEPO [13], and increases in peripheral blood can be seen by the second day [14], consistent with our results (**Figure 1D**). In our study, rhEPO administration subsequently caused elevation of Hb, RBC and HCT levels (**Figure 1A-C**). To obtain the full benefit of rhEPO administration, it is recommended to replenish levels of iron, a necessary component for hematopoiesis, at the same time [15, 16].

Iron sucrose alone can also stimulate erythrocytes. However, by itself, iron takes longer to have an effect, and its effect is weaker than when combined with EPO. There is no generally sufficient time to treat patients for anemia prior to surgery. Thankfully, the combination of rhEPO with iron sucrose has the potential to rapidly correct anemia. Consistent with our study, Francesco Sesti *et al* reported the effect of rhEPO on reducing the need for blood transfusion in patients undergoing gynecologic surgery [17]. Similar results were also found for valvular heart surgery [18], orthopedic surgery [19] and gastrointestinal tract surgery [9]. We speculate that the fundamental reason why rhEPO administration was able to reduce the need for blood transfusion is its ability to quickly mobilize RBC. If it were possible to increase Hb levels prior to surgery, patients with sufficient blood reserves could undergo the operation without complications.

As predicted, in our study of patients with initial Hb levels of <100 g/L, short term administration of rhEPO did not cause any side effects or increase the risk of thrombosis. Whether rhEPO has any effect on gynecologic tumor progression should be investigated further, although the data to date has not shown any evidence that this is the case.

Gynecologists often see patients with anemia, which is almost always caused by abnormal bleeding. Although eliminating the underlying cause is the key to treatment, gynecologists should also try their best to ensure safety during the perioperative period and avoid complications due to blood loss or blood transfusion. This retrospective study demonstrated the potential benefits of administration of rhEPO combined with iron sucrose on RBC mobilization during the perioperative period in gynecological tumor patients. A combination of the two agents was also shown to significantly reduce the rate of blood transfusion without increasing the rate of complications. Prospective studies should be conducted in future to determine the optimal dose and duration of treatment.

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Disclosure of conflict of interest

None.

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