Int J Clin Exp Med 2021;14(9):2259-2270
www.ijcem.com /ISSN:1940-5901/IJCEM0130006

Review Article

Meta analysis of the effect of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia

Xiaolong Ye[1], Yubo Ma[2]

[1]*Mudanjiang Medical University, Mudanjiang, China;* [2]*Department II of Orthopedics, Hongqi Hospital Affiliated to Mudanjiang Medical University, Mudanjiang, China*

Received January 12, 2021; Accepted July 7, 2021; Epub September 15, 2021; Published September 30, 2021

Abstract: Background: Objective to systematically evaluate the effect of recombinant human erythropoietin combined with iron in the treatment of elderly hip fracture patients with perioperative hemorrhagic anemia. Material and methods: Our objective was to search the clinical research literature of recombinant human erythropoietin combined with iron in the treatment of elderly hip fracture perioperative hemorrhagic anemia, through strict inclusion and exclusion criteria; where the quality of the selected literature was evaluated, binary and continuous variables were expressed by odds ratio (or) and a 95% CI interval. Randomized controlled trials (RCTs) were collected and meta-analysis was performed by Cochrane systematic review and revmen 5.3 software. Results: A total of 943 elderly patients with hip fracture were treated. The results showed that compared with the blank control group and the control group using iron alone, the perioperative blood transfusion rate of recombinant human erythropoietin combined with iron in the treatment of elderly hip fracture with hemorrhagic anemia was lower than that in the control group [Compared with blank control: OR=0.34, 95% CI (0.18, 0.64), Z=3.31, P=0.0009; Compared with iron alone: OR=0.24, 95% CI (0.08, 0.78), Z=2.38, P=0.02], and the total effective rate of being non anemic was better than that of the control group [Total effective rate: OR=4.14, 95% CI (1.73, 9.93), Z=3.18, P=0.001]. The hemoglobin in the seven day treatment group was better than that in the blank control group [hemoglobin: OR=12.93, 95% CI (10.61, 15.25), Z=10.93, P<0.00001]. The postoperative complications were lower than those in the control group [Postoperative complications: OR=0.23, 95% CI (0.06, 0.84), Z=2.23, P=0.03], and the difference was statistically significant. Conclusions: Recombinant human erythropoietin combined with iron has certain curative effect on the treatment of perioperative hemorrhagic anemia in elderly hip fractures, but iron alone can improve the perioperative blood transfusion rate and the incidence of postoperative complications, and recombinant human erythropoietin combined with iron compared with the blank control group, the results of postoperative complications need to be further explored.

Keywords: Recombinant human erythropoietin, iron agent, perioperative management of hip fracture, anemia, randomized controlled, meta-analysis

Introduction

Hip fractures include “femoral neck fracture”, “intertrochanteric fracture”, “acetabular fracture” and “subtrochanteric fracture”. More than 95% of the cases occur in the elderly. With the aggravation of the aging population in China, the number of patients with hip fracture is also increasing [1]. At present, surgical treatment is the first choice for hip fracture in the elderly. For hip fracture, it is generally accepted that selective surgery rather than emergency surgery should be adopted as far as possible, which is helpful to improve the preoperative examination of elderly patients and promote their postoperative recovery [2]. In general, patients after surgery have less blood loss, but hidden blood loss is often large, which easily causes anemia, and will seriously affect the recovery of patients. Hamid et al. [3] retrospectively analyzed 204 cases of hip fracture patients aged 60 and above. The results showed that the incidence of hip fracture death was 24%, and the mortality increased significantly with the increase of age. Studies have shown [4] that after hip fracture, 30%-45% of patients have hemoglobin concentration lower than the standard of normal people, and about 10% of patients have severe anemia. According to statistics [5], about one-third to half of hip fracture patients need red blood cell infusion. Recent studies have shown [6] that anemia is associated with poor prognosis in the frail and elderly. Iron deficiency anemia (IDA) is the most common and treatable anemia in the world. On the premise of hemorrhagic anemia, oral or intravenous administration of iron can effectively improve the symptoms of anemia, thus further shortening the length of hospital stay and reducing the probability of postoperative complications [7]. Recombinant human erythropoietin (rhEPO) is a new genetic engineering drug developed on the basis of erythropoietin (EPO) [8]. A large number of clinical trials have proved that it has a significant effect on the treatment of renal anemia [9]. However, the efficacy of recombinant human erythropoietin (rhEPO) combined with iron in the treatment of elderly hip fracture perioperative hemorrhagic anemia is still controversial. The purpose of this study is to evaluate the efficacy of recombinant human erythropoietin (rhEPO) combined with iron in the treatment of elderly hip fracture with perioperative hemorrhagic anemia by meta-analysis of all randomized controlled trials. At the same time, the combined use of rhEPO and iron in the treatment of elderly hip fracture was compared with the iron alone control group and the blank control group objective to investigate the clinical effect of perioperative hemorrhagic anemia.

Materials and methods

Inclusion criteria

(1) The main intervention measures were clinical randomized controlled analysis of recombinant human erythropoietin (rhEPO) combined with iron, recombinant human erythropoietin (rhEPO) alone and iron alone in patients with hip fracture during perioperative period; (2) There are clear and recognized clinical diagnostic criteria for anemia improvement; (3) There was a good balance and comparability between groups; (4) The sample size of each group was more than 20.

Exclusion criteria

(1) There were no case reports in the control group; (2) The patients in the treatment group were treated with other drugs or other operations; (3) There was no narrative study of statistical analysis in the literature retrieval.

The literature retrieval time was from 2012-2020, and the retrieval language was Chinese and English. English was searched from PubMed, emcase, Cochrane Library and other databases. The key words were: [Recombinant human erythropoietin combined with iron or Erythropoietin combined with iron or Recombinant human erythropoietin combined with iron or Recombinant human erythropoietin combined with sucrose iron or Erythropoietin combined with sucrose iron or Recombinant human erythropoietin combined with sucrose iron or Recombinant human erythropoietin combined with sucrose iron or Recombinant human erythropoietin or iron or Sucrose iron and (hip fracture or intertrochanteric fracture or subtrochanteric fracture or femoral neck fracture or acetabular fracture or intertrochanteric fracture) and random and perioperative and anemia]. The Chinese database was based on [recombinant human erythropoietin combined with iron, Erythropoietin combined with iron or recombinant human erythropoietin combined with iron or recombinant human erythropoietin combined with sucrose iron or erythropoietin combined with sucrose iron or recombinant human erythropoietin combined with sucrose iron or recombinant human erythropoietin or erythropoietin or iron or sucrose iron, or subtrochanteric fracture or femoral neck fracture or acetabular fracture or intertrochanteric fracture and random and perioperative and anemia]. Chinese journal database retrieval, included CNKI and Wanfang database.

Literature quality evaluation

Five authors independently evaluated all the detected literature. Data extraction was completed through preliminary screening and secondary screening. The quality of the literature was evaluated from five aspects: randomization method, concealment of randomization method, blindness or not, balance between groups, and follow-up. Then we cross compared the evaluation results of 5 people, if the evaluation results of 5 people were consistent, then used the results; if the evaluation results of 5 people were inconsistent, then we discussed the results with 5 people together until a consistent conclusion was reached. The quality of the included RCTs was evaluated according to

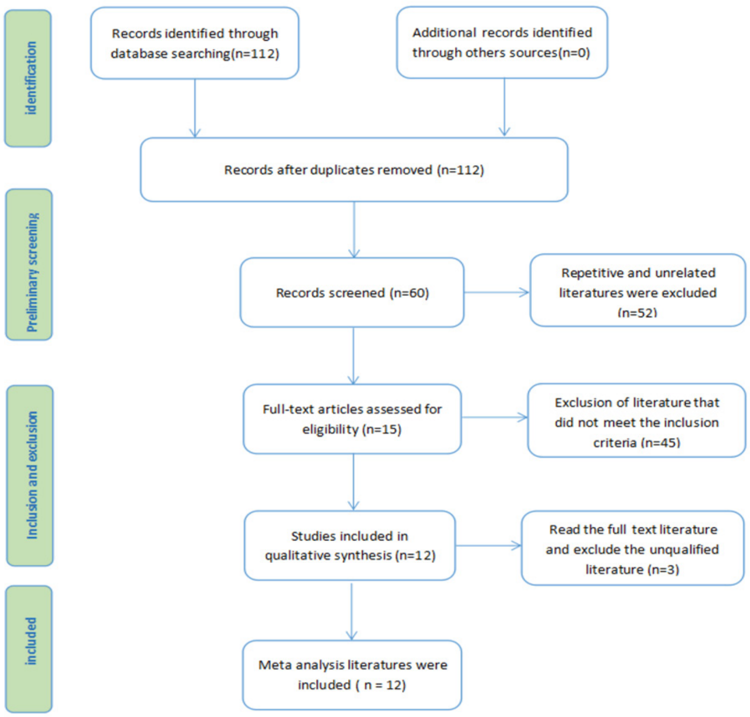

Figure 1. Flow chart of literature selection.

the modified Jadad scale, and the risk of bias was assessed by using Cochrane risk bias assessment tool.

Efficacy index

The total effective rate, perioperative blood transfusion rate, hemoglobin (HB) and postoperative complications were observed.

Statistical analysis

Binary and continuous variables were expressed by odds ratio (OR) and 95% CI interval. Meta-analysis was performed by revmen 5.3 software. Statistical results showed homogeneity (P>0.10, I^2≤50%). Fixed effect model was used for meta-analysis; if the results showed heterogeneity (P≤0.10, I^2>50%), the random effect model was used for combined analysis. Descriptive analysis was used when meta-analysis was not available. P<0.05 was statistically significant.

Results

Search results

A total of 112 studies were retrieved from the database, according to inclusion criteria and exclusion criteria. Finally, a total of 12 articles [10-21] were included, all of which were Chinese journal articles. All of them have been published within the most recent five years, for a total of 943 elderly patients with hip fractures that were included in this study, the flow chart of literature selection is shown in **Figure 1**.

Basic information of literature

Among the 12 included articles, there were 6 articles in the treatment group using recombinant human erythropoietin (rhEPO) combined with iron or sucrose iron in the treatment of elderly hip fracture perioperative hemorrhagic anemia [10-12, 15-17]. Two papers [13, 14] used tranexamic acid combined with recombinant human erythropoietin (rhEPO) and iron or sucrose iron in the treatment of elderly hip fracture perioperative hemorrhagic anemia. There were two reports on the treatment of elderly hip fracture patients with perioperative hemorrhagic anemia with recombinant human erythropoietin (rhEPO) alone [20, 21]. There were two reports [18, 19] on the treatment of elderly hip fracture with perioperative hemorrhagic anemia by iron or sucrose iron alone. In the control group [17-21], 0.9% sodium chloride solution was injected as the control. Three studies [10, 12, 16] simply gave iron or sucrose iron as control. The remaining seven articles [11, 13-15, 18-20] have no special explanation.

Quality evaluation and risk assessment

All the 12 included articles mentioned random allocation, of which 11 articles used computer-generated random sequence pairing [10, 15, 19, 21] and a random number table method [11-12, 14, 16-18, 20], one article [21] did not mention the specific random allocation method, and one article [14] had patient withdrawal. A study [21] achieved the goal of distribution hiding by computer method. In the selected studies, the baseline similarity between groups

Table 1. Methodological quality evaluation of included studies

Included literature	Random method	Allocation hidden	Blind method	baseline	sign out, Lost visit	jadad
Xu HY, 2019	P	NR	NR	agreement	0	4
Long Y, 2019	RCT	NR	NR	agreement	0	3
Xie B, 2015	RCT	NR	NR	agreement	0	3
Huang L, 2020	NR	NR	NR	agreement	0	2
Hu S, 2018	RCT	NR	NR	agreement	4/7	3
Wang BS, 2019	P	NR	NR	agreement	0	3
Yang HZ, 2020	RCT	NR	NR	agreement	0	3
Zhao HS, 2019	RCT	NR	NR	agreement	0	3
Wang F, 2018	RCT	NR	NR	agreement	0	3
Lin JX, 2017	P	NA	NA	agreement	0	2
An S, 2017	RCT	NR	NR	agreement	0	3
Wang SC, 2017	P	CM	NR	agreement	0	5

RCT: Randomized controlled trial, P: Pairing method, NR: Notreported, NA: Not adopted, CM: Computer methods.

Table 2. Characteristics of included studies

Study	Study Design (methods)	No. of patients		Mean age (years)		Sex (M/F)		Research objects (months)	Fracture type/ASA score/ Harris	Jadad
		EX	CO	EX	CO	EX	CO			
Xu HY, 2019	P	32	32	71.4	71.4	12/20	13/19	26	Garden/Evans, II-IV/II-V	4
Long Y, 2019	RCT	31	40	84.1	81.5	13/18	14/26	18	AO/ASA, A1-A3/II-IV	3
Xie B, 2015	RCT	52	67	71.4	70.9	12/40	16/51	35	Evans/ASA, I-III/III-VI	3
Huang L, 2020	NR	51	50	66.4	65.5	25/26	24/26	17	Harris, EX/CO	2
Hu S, 2018	RCT	40	40	56.1	60.6	13/27	18/22	9	Harris, EX/CO	3
Wang BS, 2019	P	54	54	73.4	71.8	26/28	29/25	48	Garden, III-IV	3
Yang HZ, 2020	RCT	20	20	62.5	62.5	12/8	13/7	13	NR	3
Zhao HS, 2019	RCT	38	37	65.7	65.2	15/23	17/20	24	NR	3
Wang F, 2018	RCT	38	38	76.5	79.4	10/28	11/27	23	NR	3
Lin JX, 2017	P	41	40	78.2	79.4	9/32	10/30	15	NR	2
An S, 2017	RCT	40	40	79.3	80.2	21/19	23/17	13	Evans/ASA, I-IV/I-IV	3
Wang SC, 2017	P	24	24	62.9	64.1	NR	NR	28	NR	5

RCT: Randomized controlled trial, P: Pairing method, NR: Not reported, EX: Experimental, CO: Control.

was consistent, and the blind method was not mentioned. There was no withdrawal or loss of follow-up. The basic characteristics and quality evaluation of the included studies are shown in **Table 1**, and the research characteristics of the included studies are shown in **Table 2**. Two papers with a score of less than 3 were considered to be of low quality. Two papers with an improved Jadad score of more than 3 were considered to be of high quality. The other eight papers with an improved Jadad score of 3 were considered to be of average quality. Through the evaluation of Cochrane risk bias assessment tool, the results show that the risk of included literature mainly comes from allocation concealment, blinding of participants and researchers, and outcome blinding (**Figure 2**).

Efficacy evaluation index

The diagnostic criteria was mentioned in two [10, 16] studies with the comparison of the total effective rate of postoperative anti-anemia treatment, nine [10-12, 14-19] studies showed the comparison of perioperative blood transfusion rate, seven [11, 13, 14, 18-21] studies had the comparison of hemoglobin (Hb), and seven [11, 12, 15-19] studies had the comparison of postoperative complications. All literature had analyses related to perioperative blood transfusion rate, perioperative blood

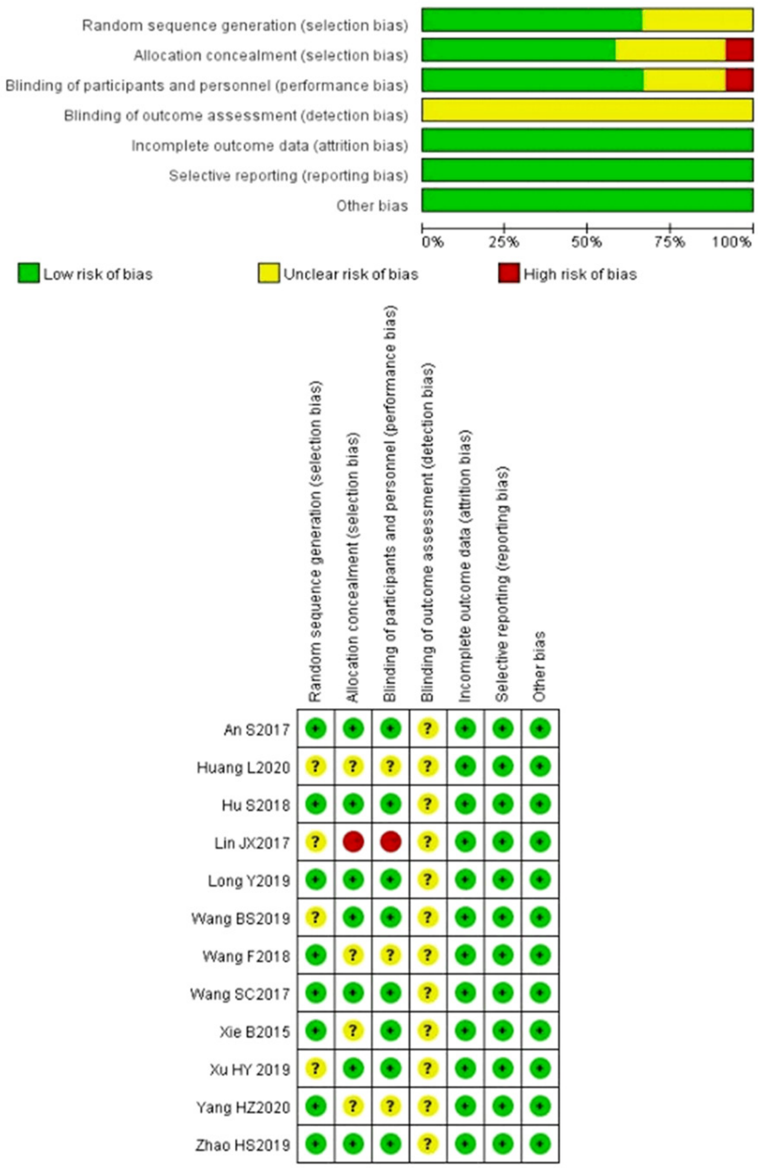

Figure 2. The results of literature quality evaluation of Cochrane risk bias assessment tool.

loss, postoperative complications and the number of adverse drug reactions (**Table 3**).

Meta analysis of the effect of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia

Meta-analysis of the total effective rate of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture during the perioperative period compared with iron alone

The results of **Figure 3** show that the total sample size was 104 cases, and the binary variables are used. Among them, there were 52 cases in the recombinant human erythropoietin combined with iron treatment group, 42 cases were effective in anti-anemia; there were 104 cases in the control group, 26 cases were effective in anti-anemia.

Heterogeneity test results, I^2=0%, P=0.32, using a fixed effects model. OR=4.41, 95% CI (1.73, 9.93), Z=3.18, P=0.001, the treatment group was more effective than the control group in the perioperative period of anti-anemia.

Meta-analysis of blood transfusion rate of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia

The meta-analysis of the postoperative blood transfusion rate of perioperative anemia in elderly hip fractures treated with iron alone compared with the blank control group: It is shown in **Figure 4**.

The results of **Figure 4** show that the total sample size is 157 cases, using binary variables, including 79 cases in the treatment group treated with iron alone and 78 cases in the control group. Heterogeneity test results, I^2=0%, P=0.53, using a fixed effects model. OR=0.71, 95% CI (0.38, 1.35), Z=1.05, P=0.30. The results showed that the blood transfusion rate of the treatment group was lower than that of the control group. Since P>0.05, after excluding the bias of the literature itself, this indicates that there may be publication bias, the results still need to include more RCT literature data to support.

Meta-analysis of the blood transfusion rate of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia compared with the control group using iron alone: It is shown in **Figure 4**.

Table 3. Outcomes of included studies

Study	Perioperative blood transfusion rate (%)		Blood loss (ml)		Postoperative complications							
					Delirium		Infected		Venous thrombosis		ADR	
	EX	CO	EX	CO	EX	CO	EX	CO	EX	CO	EX	CO
Xu HY, 2019	1 (3.13)	7 (21.88)	844.59±175.81	787.97±161.18	NR	NR	NR	NR	NR	NR	4	1
Long Y, 2019	8 (25.8)	22 (55.0)	NR	NR	0	0	8	14	6	8	0	0
Xie B, 2015	35 (48.1)	46 (68.7)	NR	NR	0	0	2	6	3	3	2	0
Huang L, 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hu S, 2018	4 (10.0)	7 (17.5)	293.75±240.16	333.33±190.26	0	0	0	0	2	0	2	0
Wang BS, 2019	2 (3.7)	9 (16.7)	NR	NR	0	0	0	0	0	0	2	3
Yang HZ, 2020	0 (0.00)	6 (30.0)	NR	NR	0	0	0	0	0	3	0	0
Zhao HS, 2019	3 (7.90)	6 (16.2)	NR	NR	0	0	0	0	0	0	0	0
Wang F, 2018	12 (31.6)	17 (44.7)	NR	NR	4	4	2	1	1	2	0	0
Lin JX, 2017	20 (48.8)	21 (52.5)	NR	NR	9	10	3	3	1	1	0	0
An S, 2017	15 (37.5)	21 (52.5)	179.82±30.54	323.69±57.62	NR	NR	NR	NR	NR	NR	NR	NR
Wang SC, 2017	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR: Not reported, EX: Experimental, CO: Control, ADR: Adverse drug reactions.

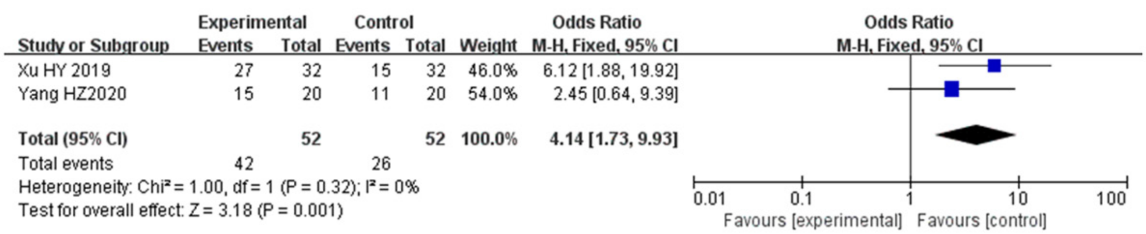

Figure 3. Forest map of meta-analysis results. The total effective rate of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture during perioperative period was higher than that of iron alone.

The results of **Figure 4** show that the total sample size is 223 cases, using binary variables, including 104 cases in the single recombinant human erythropoietin combined with iron treatment group; 119 cases in the control group were treated with iron alone. Heterogeneity test results, I^2=31%, P=0.24, using fixed effect model. OR=0.24, 95% CI (0.08, 0.78), Z=2.38, P=0.02. The results showed that the blood transfusion rate of the treatment group was lower than that of the control group.

A meta-analysis of the blood transfusion rate of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia compared with the blank control group: It is shown in **Figure 4**.

The results of **Figure 4** show that the total sample size is 334 cases, using binary variables, 163 cases in the single recombinant human erythropoietin combined with iron treatment group and 171 cases in the blank control group. Heterogeneity test results, I^2=0%, P=0.76, using fixed effect model. OR=0.34, 95% CI (0.18, 0.64), Z=3.31, P=0.0009. The results showed that the blood transfusion rate of the treatment group was lower than that of the control group.

Meta-analysis of hemoglobin (Hb) 3 days after operation in elderly hip fracture patients with perioperative anemia treated with recombinant human erythropoietin alone versus iron alone

Compared with the blank control group, the treatment group with iron alone for senile hip fracture patients with perioperative anemia has a meta-analysis of hemoglobin 3 days after operation: It is as shown in **Figure 5**.

The total sample size was 157 cases, using continuous variables, including 79 cases in the iron treatment group and 78 cases in the

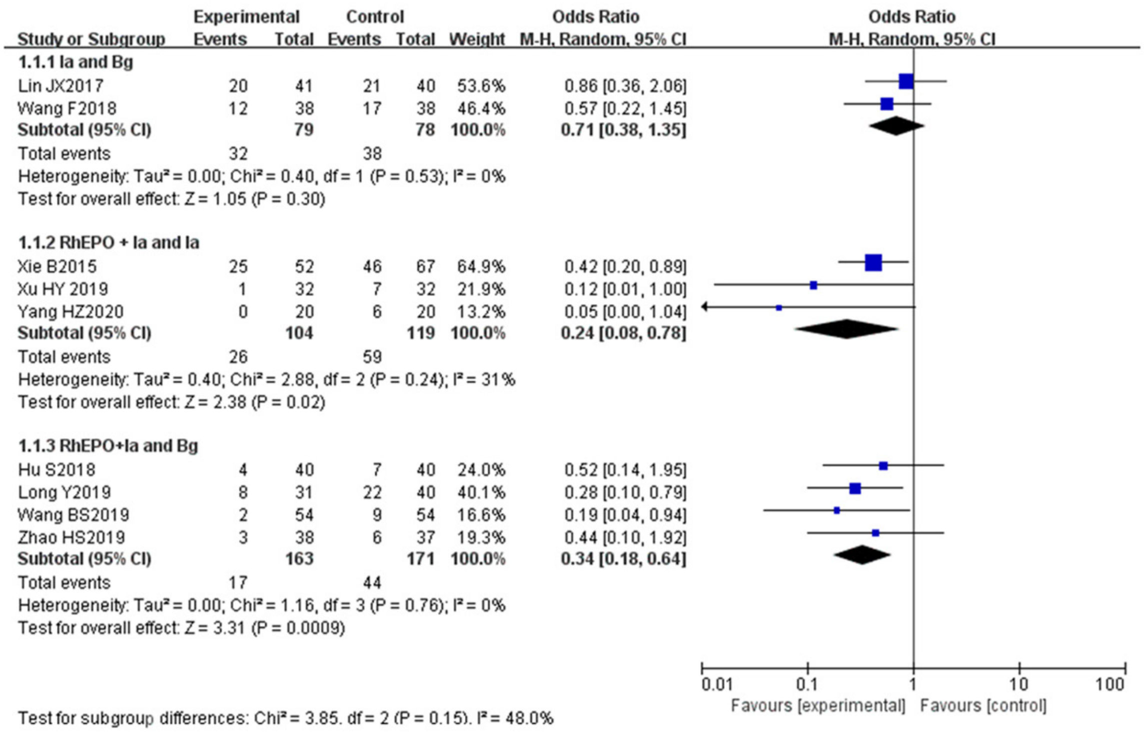

Figure 4. Comparison of recombinant human erythropoietin combined with iron with blank control group and iron alone in the treatment of senile hip fracture with perioperative anemia. RhEPO = Recombinant human erythropoietin; Ia = Iron agent; Bg = Blank control group.

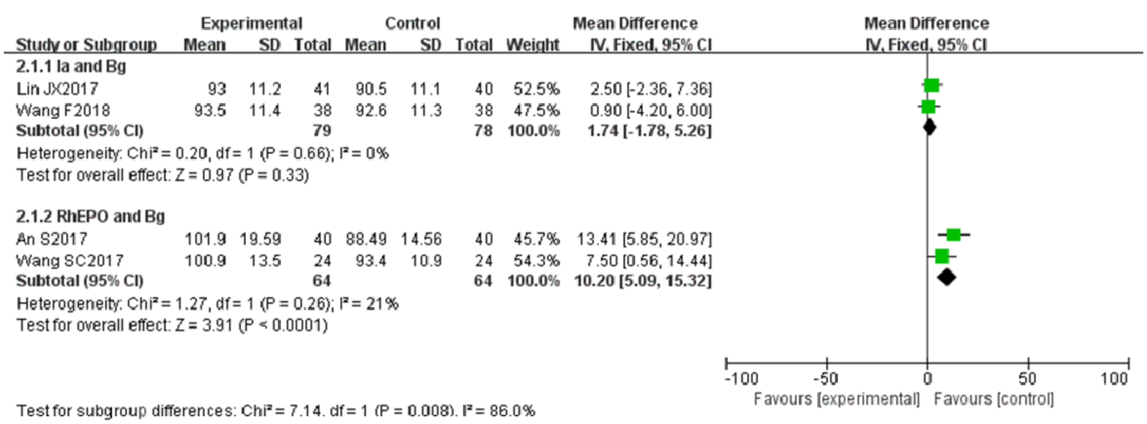

Figure 5. Meta-analysis of hemoglobin (Hb) 3 days after operation in elderly hip fracture patients with perioperative anemia treated with recombinant human erythropoietin and iron alone. RhEPO = Recombinant human erythropoietin; Ia = Iron agent; Bg = Blank control group.

blank control group. Heterogeneity test results, I^2=0%, *P*=0.66, using fixed effect model. *OR*= 1.74, 95% *CI* (-1.78, 5.26), *Z*=0.97, *P*=0.33. This shows that the treatment group is more effective than the control group in hemoglobin (Hb) 3 days after operation. As P>0.05, after excluding the bias of the literature itself, this indicates that there may be publication bias, the results still need to include more literature data to support.

Meta-analysis of hemoglobin (Hb) in 3 days after operation in elderly patients with hip fracture treated with recombinant human erythropoietin alone compared with blank control group: It is shown in **Figure 5**.

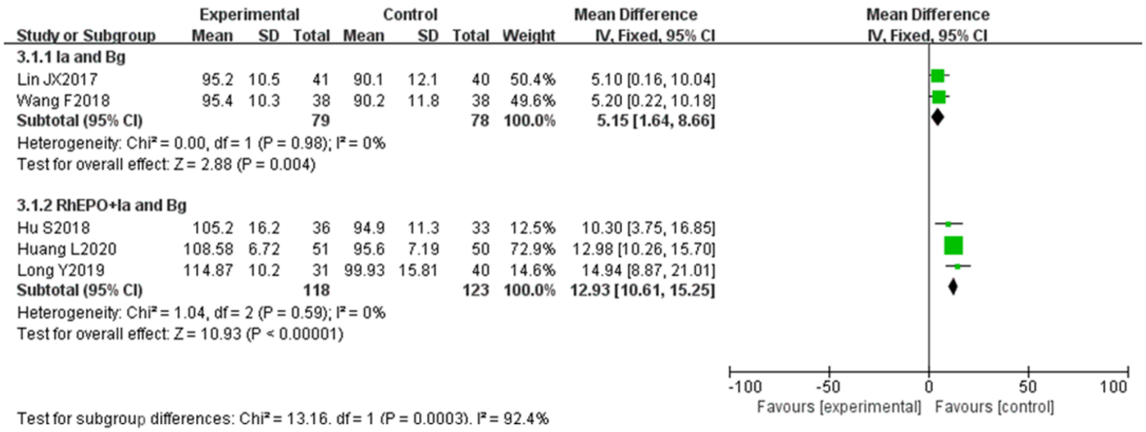

Figure 6. Recombinant human erythropoietin combined with iron compared with iron alone in the treatment of perioperative anemia of hip fractures in the elderly. Meta-analysis results of hemoglobin (Hb) at 7 days after surgery. RhEPO = Recombinant human erythropoietin; Ia = Iron agent; Bg = Blank control group.

The total sample size was 128 cases, using continuous variables, including 64 cases in the recombinant human erythropoietin treatment group and 64 cases in the blank control group. Heterogeneity test results, I^2=21%, P=0.26, using fixed effect model. OR=10.20, 95% CI (5.09, 15.32), Z=3.91, P<0.0001. This shows that the treatment group is more effective than the control group in the comparison of hemoglobin (Hb) 3 days after operation.

Meta-analysis of 7-day postoperative hemoglobin of recombinant human erythropoietin combined with iron compared with iron alone in the treatment of perioperative anemia of elderly hip fractures

Meta-analysis of hemoglobin (Hb) 7 days after operation in elderly patients with hip fracture treated with iron alone compared with blank control group: It is shown in **Figure 6**.

The total sample size was 157 cases, using continuous variables, including 79 cases in the iron treatment group and 78 cases in the blank control group. Heterogeneity test results, I^2=0%, P=0.98, using fixed effect model. OR=5.15, 95% CI (1.64, 8.66), Z=2.88, P=0.004. This shows that the treatment group is more effective than the control group in hemoglobin (Hb) 7 days after operation.

Compared with the blank control group, recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia, the meta-analysis of hemoglobin (Hb) 7 days after operation: It is shown in **Figure 6**.

The total sample size was 241 cases, using continuous variables, including 118 cases in the treatment group treated with recombinant human erythropoietin alone and 123 cases in the blank control group. Heterogeneity test results, I^2=0%, P=0.59, using fixed effect model. OR=12.93, 95% CI (10.61, 15.25), Z=10.93, P<0.00001. This shows that the treatment group is more effective than the control group in hemoglobin (Hb) 7 days after operation.

Meta-analysis of the incidence of postoperative complications of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia

A meta-analysis of the incidence of postoperative complications in the treatment of senile hip fracture with perioperative anemia compared with the blank control group: It is shown in **Figure 7**.

The results of **Figure 7** show that the total sample size is 157 cases, using binary variables, including 79 cases in the treatment group treated with iron alone and 78 cases in the control group. Heterogeneity test results, I^2=0%, P=0.89, using fixed effect model. OR=0.81, 95% CI (0.41, 1.62), Z=0.59, P=0.55. The incidence of postoperative complications in the treatment group was lower than that in the control group. Since P>0.05, after excluding the bias of the literature itself, this indicates that there may be publication bias, the results still need to include more RCT literature data to support.

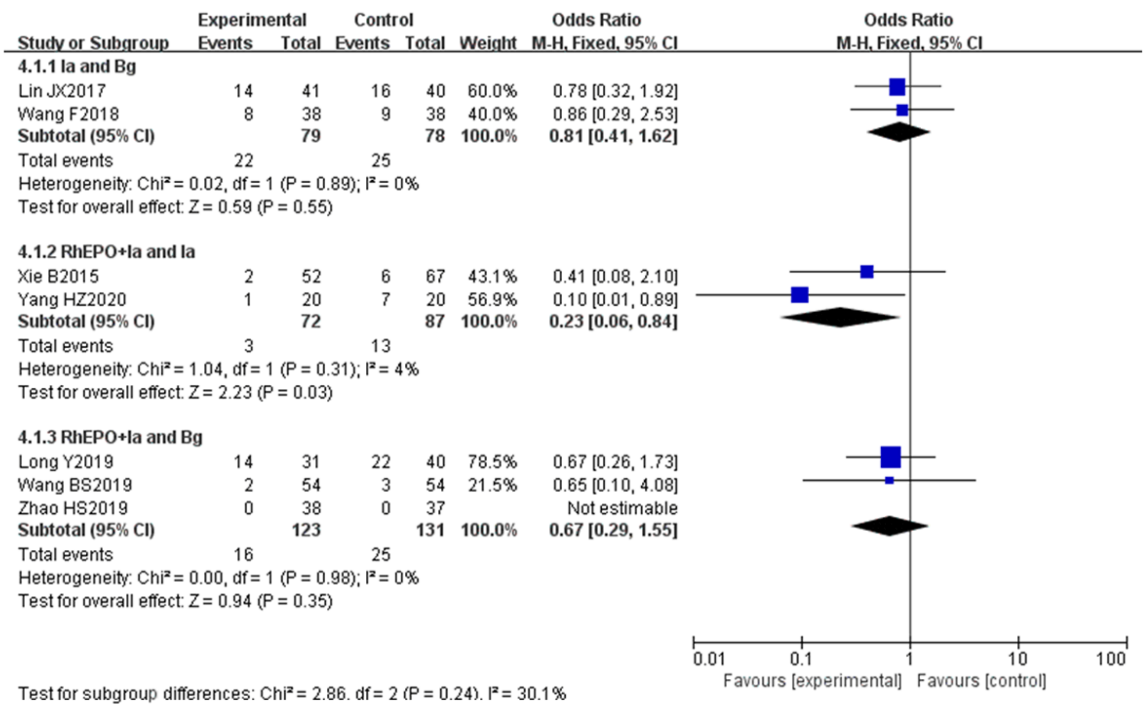

Figure 7. Meta-analysis of the incidence of postoperative complications of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia. RhEPO = Recombinant human erythropoietin; Ia = Iron agent; Bg = Blank control group.

Meta-analysis of the incidence of postoperative complications of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia compared with the control group using iron alone: It is shown in **Figure 7**.

The results in **Figure 7** show that the total sample size is 159 cases, using binary variables, including 72 cases in the single recombinant human erythropoietin combined with iron treatment group; 87 cases in the iron only control group. Heterogeneity test results, I^2=4%, P=0.31, using fixed effect model. OR=0.23, 95% CI (0.06, 0.84), Z=2.23, P=0.03. The results showed that the incidence of postoperative complications in the treatment group was lower than that in the control group.

Meta-analysis of the incidence of postoperative complications of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia compared with the blank control group: It is shown in **Figure 7**.

The results in **Figure 7** show that the total sample size is 254 cases, using binary variables, including 123 cases in the single recombinant human erythropoietin combined with iron treatment group; 131 cases in the blank control group. Heterogeneity test results, I^2=0%, P=0.98, using fixed effect model. OR=0.67, 95% CI (0.29, 1.55), Z=0.94, P=0.35. The results showed that the blood transfusion rate of the treatment group was lower than that of the control group. Since P>0.05, after excluding the bias of the literature itself, this indicates that there may be publication bias, the results still need to include more RCT literature data to support.

Discussion

The purpose of this study was to search all the Chinese and English literature about the effect of recombinant human erythropoietin combined with iron in the treatment of elderly hip fracture combined with perioperative hemorrhagic anemia within the most recent five years. A total of 12 studies were included in this meta-analysis. A blind study method was not mentioned in the included studies, but the samples were randomized and the baseline was consistent, which will not easily lead to bias, so the risk was low. If the outcome is not evaluated by a blind method, it can cause measurement bias. One article [13] did not specify the study design method. Among them, the fixed effect model was used in the comparison between the simple use of iron [18, 19] and the blank control group. Although there was no obvious heterogeneity, the results of *P* values were greater than 0.05 in the perioperative blood transfusion rate, the amount of change in hemoglobin (Hb) 3 days after operation, and the incidence of postoperative complications, which may be related to the small sample size of data, and the standard of diagnosis and curative effect. Therefore, there is a greater possibility of bias in the data synthesis analysis, which may affect the authenticity of the research results. At the same time, recombinant human erythropoietin combined with iron compared with the simple use of iron control group, had *P* values that were less than 0.05, so compared with the simple use of iron control group, in the perioperative period of anti-anemia efficiency comparison, the overall effect is more significant. In addition, the literature coverage rate of this analysis is low, the sample size is relatively insufficient, various standards are not completely unified, and there may be a certain error rate; moreover, the subgroup analysis literature included in the analysis is less, the published journals are less involved in grade I journals, and the credibility may also have a certain impact. Compared with the blank control group, the *P* value of recombinant human erythropoietin combined with iron was also greater than 0.05. The incidence of postoperative complications or the mechanism of adverse drug reactions caused by recombinant human erythropoietin combined with iron need to be included in more relevant literature data for further consolidation and elucidation. In addition, there were two articles [13, 14]. The treatment group used tranexamic acid intraoperatively, combined with recombinant human erythropoietin and iron after the operation, but in the control group only intraoperative tranexamic acid and tranexamic acid were used. Cyclic acid is used clinically as a hemostatic agent, but there is also literature suggesting that if it is used improperly in clinical practice, it will have side effects, which will affect the recovery of patients [22]. Because both groups have the use of tranexamic acid in the operation, the comparison can still reflect the therapeutic effect of recombinant human erythropoietin combined with iron. In a word, the sample size and outcome indicators included in this study are few, so it is inevitable to be insufficient in providing strong evidence. We need to conduct multi-sample, multi-center, multi-outcome indicators of RCT clinical trials to further verify.

Erythropoietin receptor (EpoR) is a member of cytokine receptor family. At present, studies have shown that rhEPO, due to its unique glycosylation component, can treat anemia in mammals. Only the interaction between recombinant human erythropoietin (rhEPO) and EpoR is an important mechanism of red blood cell production and maturation, leading to the activation of hematopoietic system [23]. Licheng Zhang et al. [24] conducted a follow-up of 1330 patients with hip fracture for at least two years from January 2000 to January 2012, and found that the risk factors of anemia in hospitals varied with the time point of diagnosis. In recent years, studies have confirmed that [25], anemia after surgery diminishes the growth of endogenous EPO, thus delaying erythropoiesis and further aggravating the symptoms of anemia. If we want to improve the hemoglobin content and hematocrit level, quickly correct the number of red blood cells, it is important to use exogenous rhEPO. The use of erythropoietin (rhEPO) in patients with hip fracture during the perioperative period can improve anemia, further shorten the postoperative rehabilitation time of hip joint patients, accelerate the progress of rehabilitation healing, and play an important role in improving the quality of life of patients [26]. In previous studies, red blood cell infusions after hip fracture may not be able to improve the postoperative rehabilitation results and needs further scientific demonstration. In this study, we are committed to explore the effect of recombinant human erythropoietin (rhEPO) combined with iron in improving the postoperative rehabilitation of hip fracture. Although there was bias in the comparison of the iron alone subgroup, the therapeutic effect of iron combined with recombinant human erythropoietin was significantly better than that of iron alone.

Conclusions

Recombinant human erythropoietin (rhEPO) combined with iron [27] may improve the symptoms of perioperative hemorrhagic anemia in elderly patients with hip fracture, which is gradually adopted and promoted in clinical practice [28]. The study reported [29] that 9 cases of hemodialysis patients were treated with rhEPO for two years and followed up. No matter if it was long-term or short-term treatment with rhEPO, it still depends on the ferritin molecules to exert its effect in the process of treatment. Under the premise of sufficient relevant clinical evidence, to ensure the comprehensive use and value based on the advantages and disadvantages of clinical application, still needs further exploration and testing. In order to further popularize its clinical application and open up a safer application prospect with long-term therapeutic effect [30], clinical RCT testing with more detailed indicators is designed to further improve the clinical effect.

Acknowledgements

We thank Professor Ma Yubo for his guidance and help.

Disclosure of conflict of interest

None.

Address correspondence to: Yubo Ma, Department of Orthopedics, Fourth Floor, Surgery Building, Hongqi Hospital Affiliated to Mudanjiang Medical University, 5 Tongxiang Road, Aimin District, Mudanjiang, Heilongjiang, China. Tel: +86-15326652906; E-mail: mybemail999@163.com

References

[1] Buljan M, Nemet D, Golubic-Cepulic B, Bicanic G, Tripkovic B and Delimar D. Two different dosing regimens of human recombinant erythropoietin beta during preoperative autologous blood donation in patients having hip arthroplasty. Int Orthop 2012; 36: 703-709.

[2] Potter LJ, Doleman B and Moppett IK. A systematic review of pre-operative anaemia and blood transfusion in patients with fractured hips. Anaesthesia 2015; 70: 483-500.

[3] Seyedi HR, Mahdian M, Khosravi G, Bidgoli MS, Mousavi SG, Razavizadeh MR, Mahdian S and Mohammadzadeh M. Prediction of mortality in hip fracture patients: role of routine blood tests. J Arch Bone Jt Surg 2015; 3: 51-55.

[4] Rowlands M, Forward DP, Sahota O and Moppett IK. The effect of intravenous iron on postoperative transfusion requirements in hip fracture patients: study protocol for a randomized controlled trial. Trials 2013; 14: 288.

[5] Bernabeu-Wittel M, Aparicio R, Romero M, Murcia-Zaragoza J, Monte-Secades R, Rosso C, Montero A, Ruiz-Cantero A and Melero-Bascones M; PAHFRAC-01 investigators. Ferric carboxymaltose with or without erythropoietin for the prevention of red-cell transfusions in the perioperative period of osteoporotic hip fractures: a randomized contolled trial. The PAHFRAC-01 project. BMC Musculoskelet Disord 2012; 21: 13-27.

[6] Tojo Y, Sekine H, Hirano I, Pan X, Souma T, Tsujita T, Kawaguchi S, Takeda N, Takeda K, Fong GH, Dan T, Ichinose M, Miyata T, Yamamoto M and Suzuki N. Hypoxia signaling cascade for erythropoietin production in hepatocytes. Mol Cell Biol 2015; 35: 58-72.

[7] Elstrott B, Khan L, Olson S, Raghunathan V, DeLoughery T and Shatzel JJ. The role of iron repletion in adult iron deficiency anemia and other diseases. Eur J Haematol 2020; 104: 153-161.

[8] Bedair H, Yang J, Dwyer MK and McCarthy JC. Preoperative erythropoietin alpha reduces postoperative transfusions in THA and TKA but may not be cost-effective. J Clin Orthop Relat Res 2015; 473: 590-596.

[9] Jez J, Castilho A, Grass J, Vorauer-Uhl K, Sterovsky T, Altmann F and Steinkellner H. Expression of functionally active sialylated human erythropoietin in plants. Biotechnol J 2013; 8: 371-382.

[10] Xu HY, Dai ZH, and Huang H. Clinical observation of iron sucrose combined with recombinant human erythropoietin in the treatment of anemia of hip fracture in elderly patients. Zhongguo Gu Shang 2019; 32: 444-447.

[11] Long Y, Wang T, Liu J, Duan X and Xiang Z. Clinical study of recombinant human erythropoietin combined with iron in the treatment of perioperative anemia in elderly patients with intertrochanteric fracture. Zhong guo Xiu Fu Chong Jian Wai Ke Za Zhi 2019; 33: 662-665.

[12] Xie B, Tian J, Yang C, Zhou DP and Xiang LB. Case control study of recombinant human erythropoietin on reducing perioperative blood transfusion in elderly patients with intertrochanteric fracture. Zhongguo Gu Shang 2015; 28: 633-637.

[13] Huang L. Effect of tranexamic acid combined with recombinant human erythropoietin and iron on anemia and hip joint function in patients with tha. Medical Theory and Practice 2020; 33: 1460-1462.

[14] Hu S, Gu MH, Cai LQ, Zhang ZJ, Liao WM and Zhang ZQ. Effect of tranexamic acid combined with iron and recombinant human erythropoietin on early rehabilitation after total hip arthroplasty. J Chinese Journal of Bone and Joint Surgery 2018; 11: 176-181.

[15] Wang BS, Li RZ, Han WF, Liu HL and Zhang JD. Efficacy analysis of recombinant human eryth-

ropoietin combined with iron sucrose in the treatment of anemia during primary total hip arthroplasty. J Journal of Trauma Surgery 2019; 21: 192-200.

[16] Yang HZ, Hu B, Yang YH, Wang XC, Gao ZW, Yang MJ and Yang HL. Clinical effect of iron sucrose combined with recombinant human erythropoietin in the treatment of anemia in middle-aged and elderly patients with hip fracture. J Chinese Contemporary Medicine 2020; 27: 97-99.

[17] Zhao HS, Gao SH, Li YG and Guo LP. Effect of recombinant human erythropoietin combined with iron sucrose injection on anemia after total hip arthroplasty. J Chinese Journal of Gerontology 2019; 39: 4485-4489.

[18] Wang F. clinical effect of intravenous iron sucrose in elderly patients with intertrochanteric fracture. J Henan Medical Research 2018; 27: 3972-3973.

[19] Lin JX, Sun DS, Zheng X, Fu KF, Li Y and Yin DC. Efficacy and safety of intravenous iron sucrose in elderly patients with intertrochanteric fracture. J Journal of Shandong University 2018; 56: 86-89.

[20] An S, Liu LM, He HM and Shen HL. Application of erythropoietin in the treatment of intertrochanteric fractures in the elderly. J Beijing Medical Journal 2017; 39: 351-355.

[21] Wang SC, Sun WP and Wang HB. Effect of erythropoietin on bleeding after hip and knee replacement. J Chinese Journal of Biochemical Pharmacy 2017; 37: 72-74.

[22] Bolam SM, O'Regan-Brown A, Paul Monk A, Musson DS, Cornish J and Munro JT. Toxicity of tranexamic acid (TXA) to intra-articular tissue in orthopaedic surgery: a scoping review. Knee Surg Sports Traumatol Arthrosc 2020: 29: 1862-1871.

[23] Fecková B, Kimáková P, Ilkovičová L, Szentpéteriová E, Debeljak N, Solárová Z, Sačková V, Šemeláková M, Bhide M and Solár P. Far-western blotting as a solution to the non-specificity of the anti-erythropoietin receptor antibody. J Oncol Lett 2016; 12: 1575-1580.

[24] Zhang LC, Yin PB, Lv HC, Long AH, Gao Y, Zhang LH and Tang PF. Anemia on admission is an independent predictor of long-term mortality in hip fracture population. Medicine (Baltimore) 2016; 95: e2469.

[25] LV H, Tan J, Li JS and Jia LS. Application of erythropoietin in total hip arthroplasty. J Chinese Journal of Orthopedics 2001; 8: 1080-1083.

[26] Cenzer IS, Tang V, Boscardin WJ, Smith AK, Ritchie C, Wallhagen MI, Espaldon R and Covinsky KE. One year mortality after hip fracture: development and validation of a prognostic index. J Am Geriatr Soc 2016; 64: 1863-1868.

[27] Torres-Campos A, Floria-Arnal LJ, Muniesa-Herrero MP, Ranera-García M, Osca-Guadalajara M and Castro-Sauras A. Initial hemoglobin value as a predictor of allogeneic blood transfusion in hip fracture. Acta Ortop Mex 2018; 32: 347-353.

[28] McCook O, Georgieff M, Scheuerle A, Möller P, Thiemermann C and Radermacher P. Erythropoietin in the critically ill: do we ask the right questions. Crit Care 2012; 3: 319.

[29] Takasawa K, Tomosugi N, Takaeda C, Maeda T and Ueda N. Regulation of hepcidin-25 by short- and long-acting rhEPO may be dependent on ferritin and predict the response to rhEPO in hemodialysis patients. J Nephron Extra 2014; 4: 55-63.

[30] Rölfing JH, Jensen J, Jensen JN, Greve AS, Lysdahl H, Chen M, Rejnmark L and Bünger C. A single topical dose of erythropoietin applied on a collagen carrier enhances calvarial bone healing in pigs. Acta Orthop 2014; 85: 201-209.