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ORIGINAL RESEARCH INTENSIVE CARE

Erythropoietin as a prophylactic measure against anemia in critically ill patients: A combined prospective and retrospective study

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Abstract

Background & Objective: Critically sick patients often develop moderate to severe anemia, due to various factors. We tested the hypothesis that administering prophylactic recombinant human erythropoietin (rHuEPO) together with early identification and correction of iron deficiency anemia in traumatic brain injury patients would have a positive effect on the incidence of RBCs transfusions.

Methodology*:* One hundred and seventeen head-trauma patients were enrolled. They received 40,000 units of prophylactic rHuEPO, starting on day three after admission and continuing at weekly intervals for 6 weeks, with follow-up of iron biomarkers. Any patient developing iron deficiency anemia was prescribed oral or intravenous iron supplement. The incidence of RBCs transfusion was recorded.

Results: The number of RBCs transfusion was significantly less in the prospective group (27.35%) than the retrospective group (42.86%). Hemoglobin and hematocrit levels were significantly less in the first and second weeks after admission and then began to rise. Serum iron, transferrin saturation, and ferritin were at their lowest levels in the fourth week. Meanwhile, total iron binding capacity was higher in the fourth week and lower in the sixth.

Conclusion: The administration of prophylactic rHuEPO with early discovery and correction of iron deficiency anemia resulted in a significant reduction in the incidence of RBCs transfusion in the head-trauma patients.

Abbreviations: rHuEPO: recombinant human erythropoietin, RBC: red blood cell, ICU: intensive care unit, TBI: traumatic brain injury, GCS: Glasgow Coma Scale, APACHE: Acute Physiology and Chronic Health Evaluation

Key words: Erythropoietin; Iron deficiency; Anemia; Critically ill

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1. Introduction

Anemia and the need of red blood cell (RBC) transfusions are frequently encountered issues in patients admitted to any intensive care unit (ICU).[1] Multiple factors have been proposed to contribute to the etiology of anemia, including sepsis, very frequent blood sampling, reduced production of endogenous

erythropoietin, and immune-associated functional iron deficiency.[2]

Over the decades, great efforts have been devoted to the management of such issues particularly in patients with traumatic brain injury (TBI), where the decline in the oxygen-carrying capacity and in turn the oxygen delivery to the brain tissue, is correlated with the fall in serum hemoglobin, and it may worsen outcomes and increase the mortality.[3]

Erythropoietin is a glycoprotein that attracted much attention in TBI, not only as an antianemia, but also as a neuroprotective agent.[4] Previous researches advocated the use of prophylactic recombinant human erythropoietin (rHuEPO) in adults,[5] and pediatric critically ill patients,[6] to overcome the blunted erythropoietic response to anemia with a resultant decrease in the incidence of RBC transfusions. Nevertheless, the depletion of iron stores along with the limited resources for iron supplementation, altered iron metabolism, and the nutritional deficiencies of folic acid, vitamin B12, and iron may be considered potential threats for the development of concomitant iron deficiency anemia in ICU patients receiving erythropoietin therapy.[7,8]

We tested the hypothesis that administering prophylactic erythropoietin together with early identification and correction of iron deficiency anemia to TBI patients receiving enteral feeding formulae would influence the incidence of RBC transfusion as a primary outcome.

2. Methodology

This study was conducted in the intensive care units during the period from March 2018 to May 2020 after being approved by the local research ethics committee No 32173/03/18) and a written informed consent was obtained from the patients' legal guardians. The retrospective data was obtained from the medical sheets of patients admitted to the ICU in the period from March 2017 to January 2018.

All moderate-to-severe head-trauma patients were enrolled, with Glasgow Coma Scale (GCS) 12−3 (moderate: GCS 9−12; severe: GCS 3−8), of either gender, aged above 18 and who could tolerate full caloric intake of enteral feeding formulae within 48 h of admission to ICU and remained in the ICU for at least 120 days during the study period.

Exclusion criteria included pregnancy, uncontrolled hypertension, renal or hepatic dysfunction, recent thromboembolic events (within 6 months), active bleeding, hemoglobin (Hb) level > 12 g/dl at the time of admittance, hematologic diseases, previous intake of rHuEPO in the preceding 30 days, iron deficiency (serum transferrin saturation < 15% with serum ferritin < 100 ng/mL) or iron overload (serum ferritin ≥ 1,000 ng/mL or serum transferrin saturation ≥ 50%) at the time of ICU admission, and intolerance of or allergy to iron. Those who received recent cytotoxic or immunosuppressive remedy (within one month) were also excluded.

TBI patients were managed according to the guidelines for management of severe traumatic brain injury that have been published by the Brain Trauma Foundation. Once effectively resuscitated, all patients received early enteral nutrition according to their caloric need detected by indirect calorimetry. Enteral feeding was supplied in the form of high caloric enteral formula (Fresubin ®Fresenius KABI, 1.5 kcal/ml, 19.5 mg iron/1500 ml) as the only source of iron via a nasogastric tube for no more than 8 weeks and through a jejunostomy tube if beyond 8 weeks. Administering 40,000 units of prophylactic rHuEPO via the subcutaneous route was initiated on day three (day of trial commencement) and continued at weekly intervals for 6 weeks as long as the Hb level remained ≤ 12 g/dl. In case of rising Hb concentrations above that level, rHuEPO therapy was briefly discontinued and restarted when Hb declined to ≤ 12 g/dl again.

All patients were on prophylactic measures for deep vein thrombosis (DVT) in the form of low molecular weight heparin (enoxaparin 40 mg SC daily) with application of graduated compression stockings. Serial assessment of serum Hb, hematocrit, iron indicators, including serum Fe, total iron-binding capacity (TIBC), serum transferrin saturation, and serum ferritin was accomplished at the time of admission and weekly for 120 days.

Patients who developed iron deficiency anemia were prescribed oral iron (ferrous sulphate 150 mg) once daily. If they demonstrated gastrointestinal symptoms (vomiting or constipation) suggesting intolerance to oral iron preparations, intravenous iron (200 mg iron sucrose twice weekly) was given instead. However, patients who showed manifestations of intolerance to enteral feeding in general (abdominal distention, vomiting, and high gastric residual volume) which necessitated shifting to total parenteral nutrition were excluded.

RBC transfusions were carried out according to guidelines of the British Committee for Standards in Haematology (BCSH) which recommended that in patients with traumatic brain injury, the target Hb concentration should be > 9 g/dl in case of evidence of cerebral ischemia; otherwise, it should be 7–9 g/dl. To avoid risk of cerebral ischemia, Hb levels were kept above 9g/dl throughout the study.

The percentage of patients receiving RBCs transfusions in both the prospective and retrospective groups was recorded. Moreover, the incidence of adverse effects in

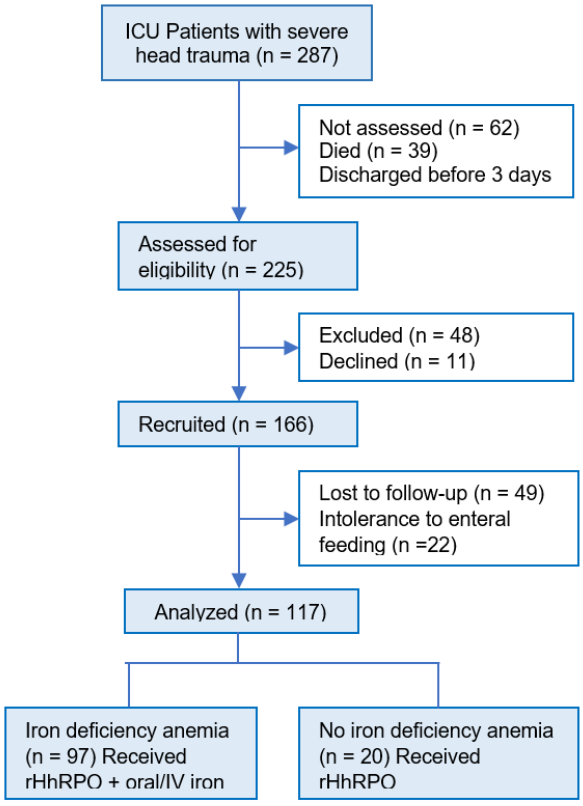

Figure 1: Study flow diagram

the prospective group (DVT, pulmonary embolism, myocardial infarction, and stroke) was also noted.

Statistical Analysis

Data were analyzed using Minitab® 16 Statistical Software (Minitab, Inc., LLC, State College, Pennsylvania). The Kolmogorov-Smirnov test was used to assess the normality of data. For continuous variables, the data were expressed as mean ± standard deviation or as median and interquartile range and were compared using Student's t-test or the Mann–Whitney U test as appropriate, whereas the nominal variables were shown with numbers and percentages and analyzed using the chi-square or Fisher exact test. Within the prospective group, data at different time intervals were compared using repeated measures analysis of variance for numerical variables, while the nonparametric variables were analyzed utilizing the Wilcoxon signed-rank test. $P < 0.05$ was considered significant.

3. Results

A total of 287 patients with moderate-to-severe head trauma were admitted to the ICU over the study period. Sixty-two of these patients either died or were discharged before day 3 in ICU and were therefore excluded from screening. Of the remaining, 48 patients were excluded based on the listed study criteria and 11 patients were excluded as their guardians refused to participate in the study, so 166 patients had received prophylactic rHuEPO. Twenty-two patients developed intolerance to enteral feeding and 27 patients died during the study period. At last, 117 patients remained for 120 days in ICU and were therefore included in the data analysis (Figure 1).

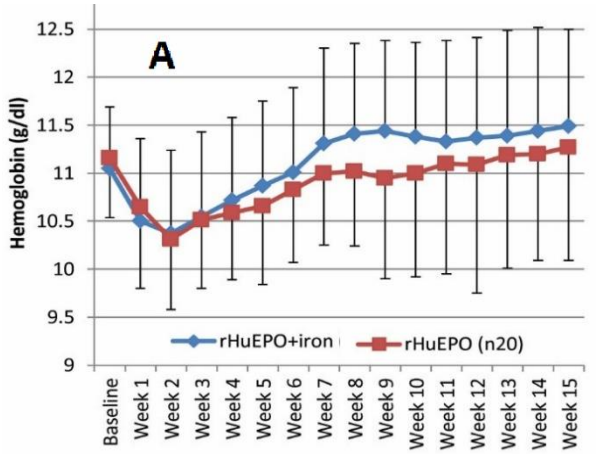

Figure 2-A: Comparative hemoglobin levels in two groups

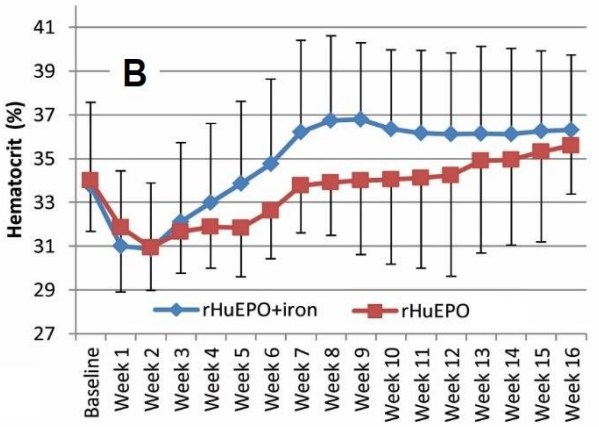

Figure 2-B: Comparative hematocrit% levels in two groups

There were no significant differences between both the prospective and retrospective groups regarding age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and the injury severity score (ISS) (Table 1).

The incidence of RBCs transfusion was significantly higher in the retrospective group than the prospective group (42.86% vs 27.35%, respectively, P = 0.027*).

In the prospective group, both Hb and hematocrit levels were significantly less in the first and second week after admission than baseline values and then began to elevate by the third week (Figure 2). Ninety-seven patients

developed iron deficiency anemia and received iron supplementation with an incidence of 82.9%. In this subgroup of patients, serum iron, transferrin saturation, and ferritin were at the lowest level on the fourth week and then started to increase in the sixth week, while total iron binding capacity was higher in the fourth week and lower in the sixth up to 16th week. In non-iron-deficient patients (n = 20), iron biomarkers remained within the normal range throughout the study period (Figures 3 and 4).

Table 1: Comparison of age, APACHE, ISS

Variable	Prospective group (n = 117)	Retrospective group (n = 91)	P value
Age	34 (24–43) (18–60)	33 (30–39) (19–59)	0.452
APACHE	23 (16–29) (8–50)	24 (22–28) (12–50)	0.069
ISS	28.13 ± 6.74	27.65 ± 6.68	

*Data presented as mean ± SD or median [interquartile range (range)]. *Denotes statistically significant difference. APACHE, ISS.*

The incidence percentages of adverse effects in the prospective group including DVT, pulmonary embolism, myocardial infarction, and stroke were 4.2%, 2.56%, 0%, and 0.85%, respectively.

4. Discussion

In this study, it was demonstrated that the administration of prophylactic rHuEPO with early discovery and correction of iron deficiency anemia in head-trauma patients resulted in reduction in the incidence of RBCs transfusion (42.86% for the retrospective period vs 27.35% for the prophylactic rHuEPO group). In agreement with the results, Corwin et al. in two different studies recorded a decrease in both the cumulative number of RBC units transfused and the percentage of patients who received RBC transfusion after rHuEPO injection.[9,10]

In the current study, a significant decrease was observed in the Hb level and hematocrit value in the first and second week in ICU. Thomas et al. also reported a high incidence of patients developing anemia after a week in ICU.[11] The reason for this was speculated to be the decreased RBC life span and decreased RBC production.[1] This fact guided researchers to study the effect of prophylactic rHuEPO on incidence of anemia and RBCs transfusions in orthopedic patients, cancer patients under chemotherapy treatment, and preterm infants.[12,13,14] Although prophylactic rHuEPO has been used in many studies, few data exist regarding the incidence of iron deficiency anemia in those patients. Sources of iron include iron recycling via

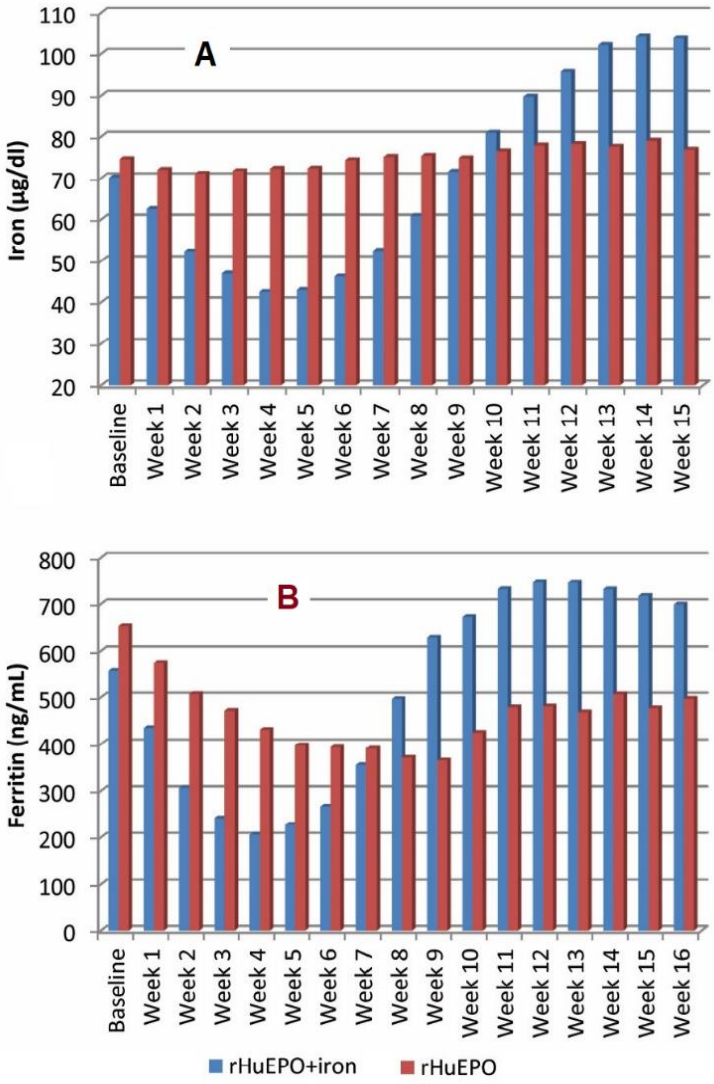

Figure 3: Comparison of (A) Serum iron µg/dl, and (B) Serum ferritin ng/ml follow up

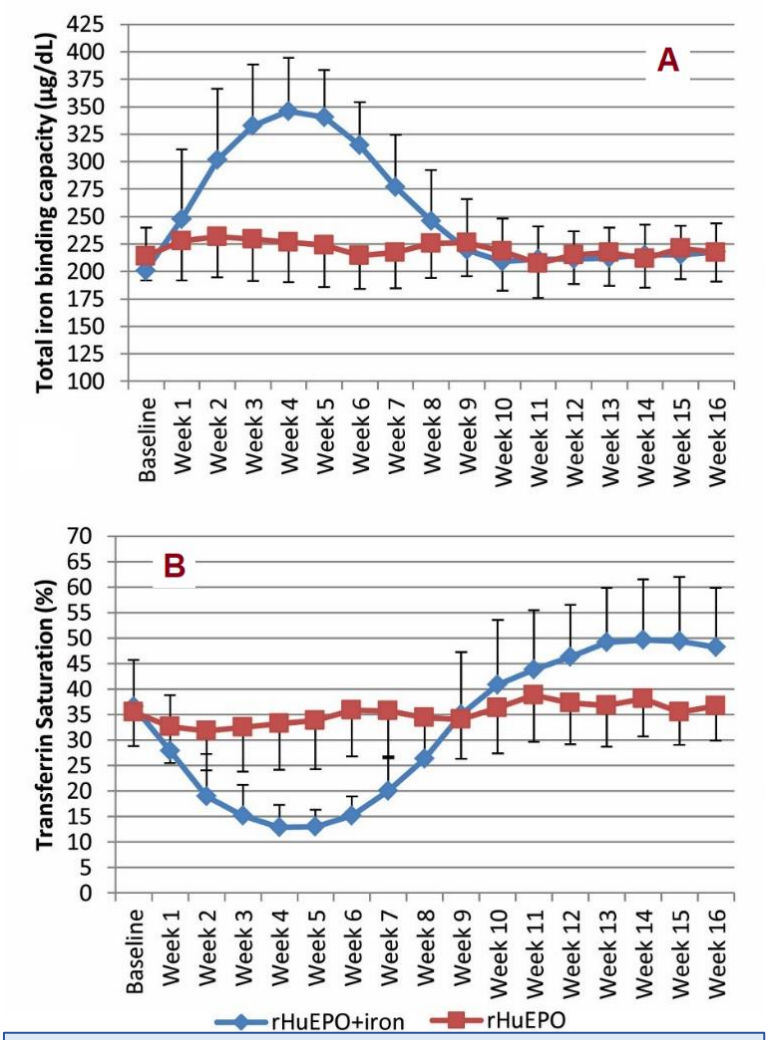

Figure 4: Comparison of (A) total iron binding capacity µg/dl, and (B) transferrin saturation % follow up

hemophagocytosis, which provides 20–25 mg of iron per day (internally recycling), plus dietary iron intake (by duodenal cells) 1–2 mg of iron.[15] Adult patients have 4 to 5 grams of iron in their bodies (~38 mg iron/kg body weight for women and ~50 mg iron/kg body weight for men).[16] Phlebotomy and blood loss associated with trauma can rapidly deplete iron stores and consequently impair erythropoiesis.[2] Von Ahsen et al. observed a median blood loss of 128 mL/day, corresponding to a loss of 64 mg of iron/day.[17]

Hospitalized patients, who get infected, develop anemia of inflammation (AI) with altered iron metabolism.[18] Although development of iron deficiency anemia in ICU is multifactorial, prophylactic iron supplementation is not recommended to avoid potential risk for iron overload, infections, and multiple organ failure.

Iron homeostasis should be maintained while avoiding iron deficiency or overload, as iron deficiency impairs both leukocyte function, B cell function, circulating T cells production, and lymphocyte proliferation, which affect both humoral function and cell-mediated immunity.[19] On the other hand, iron overload is a serious issue as there is no physiological mechanism to excrete iron; chelation therapy is generally required to remove it.

In this study, the iron status was followed up weekly for all head-trauma patients admitted to the ICU during the study period, after giving prophylactic rHuEPO. Patients who developed iron deficiency anemia received oral iron as a first line of treatment. The oral route is physiologically better and it is of low cost and more convenient. Significant changes were observed in iron biomarkers after three weeks in 97 patients, which led to a significant response to oral iron within two to three weeks. Martin et al. mentioned that iron metabolism disorders set in within the first few days of admission. In particular, multiple trauma patients seem to quickly develop hypoferremia secondary to inflammation.[20] Pilar et al. gave oral iron to patients undergoing elective cardiac surgery and found higher serum ferritin levels by day 10.[21] Three studies on different patients populations, e.g., patients under dialysis, patients with rheumatoid arthritis, and patients with Crohn's disease, concluded that iron supplementation clearly improves the response to rHuEPO.[22, 23, 24]

On the other hand, Roman et al. recommended intravenous iron to avoid malabsorption and gastrointestinal side effects with oral iron.[25] The difference between the results of this and the current study might be due to the fact that they selected different populations for their study. Their sample size was small (12 patients) and included preoperative patients over a time span of 3 weeks only.

The percentages of the adverse events reported in our study, DVT, pulmonary embolism, myocardial infarction, and stroke, were 4.2%, 2.56%, 0%, and 0.85%, respectively. In agreement with our results, Corwin et al. mentioned that epoetin alfa was associated with a significant increase in the incidence of thrombotic events.[26]

5. Limitations

One significant limitation of the current study was the relatively large number of study exclusion criteria. The second limitation was that hepcidin was not measured

despite being an important iron-regulatory hormone, due to its non-availability at our hospital.

6. Conclusion

The administration of prophylactic recombinant human erythropoietin (rHuEPO) and early discovery and correction of iron deficiency anemia with oral or intravenous iron resulted in a significant reduction in the incidence of red cells transfusions in head-trauma patients.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

We gratefully acknowledge the great help and assistance by the staff of the Departments of Anesthesia & Intensive Care, Neurosurgery and Trauma to complete this study.

9. Conflict of interest

The study did not receive any external or industry funding. The authors declare no conflict of interest.

10. Authors' contribution

AF, ME: Conduct of study, literature search, statistical analysis and manuscript editing

HI: Concept, conduct of study, statistical analysis and neurosurgical follow up of all cases

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