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INTRAVENOUS IRON FOR TREATMENT OF POSTOPERATIVE ANEMIA IN ORTHOPEDIC AND SURGERY PATIENTS

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ABSTRACT

Background and Objectives: Postoperative anemia remains a critical concern due to its association with adverse surgical outcomes. To address this issue, our study aimed to investigate the efficacy of intravenous iron therapy in promptly correcting anemia following surgery.

Materials and Methods: Our study involved the prospective enrollment of patients undergoing elective orthopedic and general surgery, who were then randomized into two distinct groups: the Control group receiving placebo, and the Iron Group receiving intravenous iron therapy. Blood tests were conducted preoperatively as baseline measurements and on several postoperative days (PODs) - specifically PODs 1, 3, and 7.

Results: Throughout the postoperative period, both groups exhibited significantly lower hemoglobin (Hb) concentrations compared to their respective baselines, with no statistically significant differences in postoperative Hb levels observed between the groups. Moreover, both groups demonstrated elevated serum erythropoietin, ferritin, and vitamin B12 levels, along with an increased reticulocyte count surpassing normal ranges. A considerable decline in serum iron levels was observed in both groups postoperatively. No substantial inter-group variances in hepcidin levels were identified.

Conclusion: Our study indicated an absence of significant efficacy in correcting postoperative anemia among orthopedic and surgery patients, despite inducing higher reticulocyte counts within the initial week following the surgical procedure. Also, we discourage the practice of Vitamin B12 administration during the early postoperative period.

Key words: Reticulocyte Count, Vitamin B 12, Anemia, Ferritin, Haemoglobin.

INTRODUCTION

Postoperative anemia, a prevalent complication following major surgeries, poses a significant risk to surgical outcomes. Addressing this concern has garnered increased attention in recent times. The etiology of postoperative anemia primarily stems from perioperative blood loss, encompassing surgical bleeding, coagulopathies, phlebotomies, and inflammation-induced suppressed erythropoiesis [1]. Emerging evidence suggests that postoperative anemia bears a closer resemblance to anemia of chronic disease (ACD) rather than iron deficiency anemia [2]. In the management of postoperative anemia, therapeutic options extend beyond red blood cell (RBC) transfusion, encompassing dietary iron supplementation, intravenous (IV) iron therapy, and recombinant human erythropoietin therapy. While dietary iron replacement shows limited effectiveness at best, the latter two approaches have demonstrated promise in managing anemia types with pathophysiological features akin to postoperative anemia, such as anemia of chronic diseases [3, 4]. Notably, a standardized treatment approach specifically tailored to postoperative anemia is currently lacking. The precise impact of IV iron therapy on early postoperative anemia recovery remains uncertain [5–8].

In light of these uncertainties, our study sought to assess the efficacy of IV iron therapy in the prompt correction of postoperative anemia following orthopedic and general surgery. The study aimed to enhance our comprehension of the intricate interplay between erythropoietin, iron metabolism, and erythropoiesis in the context of postoperative anemia.

MATERIAL & METHODS

Patients undergoing elective orthopedic and general surgery were prospectively assessed. The inclusion criteria encompassed individuals aged ≥ 18 years, while the exclusion criteria consisted of hemodynamic instability necessitating rescue therapy, the use of anticoagulants (e.g., aspirin, clopidogrel, warfarin), preoperative anemia (baseline hemoglobin levels < 12 g/dL), a history of chronic inflammatory disease, evidence of postoperative infection or hemolysis, the requirement for autologous or allogeneic blood transfusion, and refusal to participate in the study. The participants were randomly assigned to one of two groups. Iron Group received iron therapy (200 mg IV iron sucrose), and the Control group was administered 200 mL of normal saline (placebo). The assigned therapies were administered three times in total on postoperative days (POD) 1, 3, and 7, and the iron sucrose was diluted in 200 mL of normal saline and delivered over 1 hour. Patients remained blinded to the administered IV solutions, and treatment adherence and side effects were closely monitored.

Blood tests were conducted on the day before surgery (baseline) and on PODs 1, 3, and 7. Hemoglobin (Hb) concentration and reticulocyte count were determined using the Hematology Analyzer. Serum erythropoietin, folate, and vitamin B12 levels were assessed using the chemiluminescent assay. Iron metabolism was analyzed, encompassing serum iron level, transferrin level, transferrin saturation (TSAT) (calculated from serum iron and transferrin concentration), and ferritin level. Serum hepcidin was measured using ELISA.

Statistical analysis was conducted using SPSS 21.0. The Shapiro-Wilk test was used to assess the normality of the distribution. Continuous variables were compared using the Mann-Whitney U test, and the Spearman rank correlation test was employed to analyze associations between variables. The dynamic association of variables over days after the operation was evaluated using the independent t-test. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

The study included two groups, the Iron Group, and the Control Group, each consisting of 30 patients. Both groups were comparable in terms of age, gender, and type of surgery, with no statistically significant differences observed ($p > 0.05$). Table 1 summarizes the baseline data of both groups. Throughout the study period, no side effects related to intravenous (IV) iron treatment like hypersensitivity reactions, hypertension, increased risk of venous thromboembolism, or stroke, were reported [9].

Table 1: Baseline characteristics of the two groups

Variables	Iron Group (n = 30)	Control Group (n = 30)	p Value
Gender			
Female	19	17	
Male	11	13	
Mean Age (in years)	49.97	51.35	
Mean Hb (gm/dL)	13.9	13.1	0.055
Reticulocyte count (Mean ± SD)	0.057 ± 0.006	0.041 ± 0.004	0.06
Mean C Reactive Protein (mg/L)	3.06	3.28	0.08
Mean Intraoperative blood loss (mL)	630	655	0.07
Mean Postoperative blood loss (mL)	66	60	0.12

Despite receiving treatment, postoperative anemia was observed in all patients, resulting in significantly lower hemoglobin (Hb) concentrations compared to the normal range on POD7. However, no significant intergroup differences in Hb concentrations were observed at any time point (Table 2). Both groups exhibited a rapid increase in reticulocyte count from baseline, with significantly higher reticulocyte counts observed on POD7 (Table 3).

Table 2: Changes in hemoglobin levels (gm/dL)

Groups	Baseline	POD1	POD3	POD7
Iron Group	142.1 ± 4.82	116.3 ± 4.91	114.1 ± 6.14	109.7 ± 5.71
Control Group	131.9 ± 3.92	111.8 ± 5.47	105.5 ± 5.83	109.9 ± 5.91
p value	0.18	0.64	0.28	0.98

Table 3: Changes in Reticulocytes levels (10^{12}/L)

Groups	Baseline	POD1	POD3	POD7
Iron Group	0.059 ± 0.004	0.057 ± 0.004	0.062 ± 0.006	0.079 ± 0.013
Control Group	0.043 ± 0.004	0.049 ± 0.004	0.054 ± 0.003	0.081 ± 0.005
p value	< 0.05	< 0.05	0.14	0.93

On POD7, a significant increase in serum erythropoietin concentrations was observed in all patients (Table 4). Moreover, in the Control Group, there was a significant correlation between the decrease in Hb concentration and the increase in erythropoietin concentration ($r = 0.81$, $p < 0.05$).

Table 4: Variation in serum erythropoietin levels (mIU/mL)

Groups	Baseline	POD1	POD3	POD7
Iron Group	10.99 ± 1.05	16.19 ± 2.83	27.24 ± 6.89	39.98 ± 22.14
Control Group	9.78 ± 1.16	9.65 ± 1.43	30.05 ± 6.12	21.34 ± 2.98
p value	0.57	<0.05	0.61	0.36

Regarding iron metabolism, on POD3, both serum iron and transferrin saturation (TSAT) were significantly lower in the Iron Group compared to the Control Group. Conversely, on POD7, significantly higher ferritin levels were demonstrated in the Iron Group compared to the Control Group. Serum hepcidin levels peaked on POD1 in all patients, significantly higher than the baseline levels. However, no significant inter-group differences in hepcidin levels were observed at any time point. Furthermore, a significant decrease in serum folate concentration from baseline was observed on POD3 and POD7 in the Iron Group. Serum vitamin B12 concentration increased above the normal range in all patients, with a significant increase from baseline observed at all time points in the Iron Group (Table 5).

Table 5: Parameters showing Erythropoiesis and Iron metabolism

Parameter	Groups	Baseline	POD1	POD3	POD7
Iron (μmol/L)	Iron Group	21.37 ± 2.04	12.71 ± 2.98	11.96 ± 2.49	14.28 ± 3.68
	Control Group	26.12 ± 3.78	15.98 ± 2.95	14.81 ± 1.97	18.48 ± 2.66
Transferrin Saturation (%)	Iron Group	42.92 ± 4.41	37.88 ± 4.91	29.09 ± 5.29	39.19 ± 9.15
	Control Group	38.34 ± 3.58	29.94 ± 3.13	31.25 ± 2.64	32.88 ± 2.69
Serum Ferritin (ng/ml)	Iron Group	274.7 ± 43.29	348.9 ± 38.77	632.4 ± 58.83	859.6 ± 116.8
	Control Group	301.3 ± 73.21	372.1 ± 96.86	389.5 ± 85.42	340.1 ± 70.29
Serum Hepcidin (pg/ml)	Iron Group	22,049 ± 4012	112,902 ± 24,935	71,905 ± 21,586	53,994 ± 15,520
	Control Group	66,674 ± 15,197	166,112 ± 25,753	107,513 ± 28,669	64,108 ± 21,803
Serum Folate (nmol/L)	Iron Group	12.82 ± 2.56	7.76 ± 1.73	8.27 ± 0.96	10.23 ± 2.12
	Control Group	19.12 ± 2.08	14.48 ± 2.34	13.35 ± 2.78	16.53 ± 1.75
Serum VitaminB12 (pmol/L)	Iron Group	448 ± 130.7	1065 ± 207.1	1198 ± 187.9	1258 ± 214.1
	Control Group	1075 ± 146	906.3 ± 158	1195 ± 153.5	1068 ± 168.3

DISCUSSION

Inflammatory responses triggered by surgical procedures can lead to a state of postoperative anemia characterized by relative deficiencies in iron and erythropoietin, potentially impeding the patient's recovery [10]. This anemic condition is often attributed to perioperative bleeding

and decreased iron availability, alongside normal or near-normal erythropoietin levels, which are the main underlying causes of perioperative anemia [11].

Our study found that while erythropoietin levels remained within the normal range among the control group, IV iron therapy resulted in increased erythropoietin levels beyond the normal range. Transferrin saturation (TSAT) is a significant biomarker for iron availability, with TSAT levels below 20% indicating iron deficiency and levels above 40% suggesting iron overload [12, 13]. Our findings demonstrated a significant decline in serum iron and TSAT levels across all groups on POD3, followed by a significant increase in serum ferritin levels on POD7.

Hepcidin, a 25-amino acid peptide predominantly produced by liver cells, plays a vital role in regulating iron absorption and recycling by inducing the internalization and degradation of ferroproteins [14]. Surgery-induced inflammation leads to an upregulation of hepcidin, which inhibits erythropoiesis by blocking intestinal iron absorption. Intracellular iron therapy has been reported to partially overcome hepcidin blockade, enabling iron export into the plasma and subsequent transportation into the bone marrow as transferrin-bound iron for erythropoiesis [15]. Our study, however, yielded results contradictory to previous studies [16, 17].

Reticulocytes, released into the circulation 18-36 hours before their final maturation into erythrocytes, serve as real-time indicators of erythropoiesis functionality [18]. Our findings of significantly higher reticulocyte levels with combined IV iron and rHuEPO therapy suggest its effectiveness in inducing erythropoiesis during the first week of surgery, but it did not correlate with hemoglobin recovery. This is consistent with findings from similar studies [17, 19], although it contradicts others [20].

Folate, vitamin B12, and iron are critical factors in erythropoiesis. Folate and vitamin B12 are essential for the proliferation of erythroblasts during differentiation. Deficiencies in these vitamins hinder DNA synthesis and cause erythroblast apoptosis, leading to anemia due to ineffective erythropoiesis [21]. Serum folate concentration is considered the most sensitive biochemical indicator of folate deficiency [22]. Folate stores last for three to six months, whereas vitamin B12 stores can last for three to six years. Our study revealed abnormally low serum folate concentrations following IV iron therapy, while control group values remained normal. Thus, we recommend administering folate as a supplement to IV iron therapy within the first week of surgery.

Serum vitamin B12 concentration has been associated with thrombosis-related systemic inflammation [23, 24], and poor prognosis among critically ill patients [25]. Our results indicated increased postoperative serum vitamin B12 levels in all groups compared to baseline; however, this increase was statistically insignificant and likely reflected the natural development of postoperative inflammation. Therefore, we advise against administering vitamin B12 during the early postoperative period.

CONCLUSION

In summary, the findings from our prospective randomized study indicate that early treatment IV iron did not expedite the recovery from newly developed postoperative anemia in orthopedic and surgery patients. However, it did result in higher reticulocyte counts during the first week after surgery. There was no significant improvement observed in the mobilization of storage iron.

Additionally, our study suggests that vitamin B12 supplementation is not necessary during the early postoperative period.

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