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# A Comparative Study for Management of Anemia in Elective Surgery Patients with Combination of IV Iron and Erythropoietin Alpha Vs Hemotransfusion

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**ABSTRACT**

**Title:** A COMPARATIVE STUDY FOR MANAGEMENT OF ANAEMIA IN ELECTIVE SURGERY PATIENTS WITH COMBINATION OF IV IRON AND ERYTHROPOIETIN ALPHA VS HEMOTRANSFUSION

**Background:** Generally defined, anemia is present when the hemoglobin concentration is below a normal value based on the reference population. The mean normal value of hemoglobin is dependent on age, gender, race, and altitude. According to WHO criteria, the lower limit of normal in adults is 13 g/dL in men and 12 g/dL in women. Anaemia is believed to increase the risk of surgery, and it is common practice for non-urgent surgery to be postponed if a patient is anaemic. The level of circulating haemoglobin below which such an effect exists is, however, unknown. Nor is it known whether the risk is real. The justification for considering anaemia as a risk is based on the theoretical concept of oxygen flux (Freeman and Nunn, 1963).

This study is aimed to evaluate the efficacy of the combination therapy of intravenous iron sucrose and subcutaneous human recombinant erythropoietin alpha therapy in reducing the need for blood transfusion and maintenance of hemoglobin level in perioperative management of patients undergoing elective surgery.

**Methods:** A hospital based Prospective Comparative Study was undertaken among pre-operative patients. It is a prospective randomized control trial. A total number of 100 patients (50 in each group) will be enrolled. Group A will be study group and Group B will be control group. Patient will be screened prior to enrollment and eligibility will be assessed by specific inclusion and exclusion criteria.

1. Group A or study group patients will be given erythropoietin 300 iu/kg by subcutaneous injections in three divided doses in first week.
2. Each patient will receive intravenous iron sucrose as per calculated in divided doses for 5 days in first week.

Group B or control group patients will receive blood transfusion 2 days prior to scheduled surgery. On day 16 patients will undergo elective surgery.

**Results:** In group A among 50 patients, 6 patients dropped out of the study. In 44 cases, 18 patients received no blood transfusion, 10 patients received only 1 unit blood transfusion and 16 patients received more than 1 unit blood transfusion. 41% patients achieved target Hb, 22% patients improved significantly and 37% patients did not achieved the target.

In 50 patients of group B all patients required blood transfusion among which 42 patients received more than 1 unit blood transfusion to achieve the target.

The cost of treatment in group A is slightly higher than in group B patients. But it has no blood transfusion related complication and improved outcome in patients after surgery.

More detailed and significant improvement of this therapy can be proved by larger sample size and long standing follow-up study in various surgical facilities which includes patients of Hb level below 9 gm/dl to achieve target level before surgery. So, IV iron & erythropoietin therapy can be used for correction of pre-surgical anemia to reduce the number of transfused blood units.

**Conclusion:**

This study shows a significant rise in hemoglobin level, serum iron & ferritin level in study population after the therapy. 41% patients did not require any transfusion to achieve target hemoglobin and 22% improved partially and received comparatively less blood transfusion than their counterpart in group B. So, IV Iron and Erythropoietin can be used to reduce the demand of blood transfusion and can improve post surgical outcome in patients. Large and multi setup studies are required to achieve further data to support the use of this therapy as an effective blood alternative in future.

**Keywords:** ERYTHROPOETIN ALPHA, INTRAVENOUS IRON SUCROSE, ANAEMIA.

**INTRODUCTION**

Anaemia is believed to increase the risk of surgery, and it is common practice for non-urgent surgery to be postponed if a patient is anaemic. The level of circulating haemoglobin below which such an effect exists is, however, unknown. Nor is it known whether the risk is real. The justification for considering anaemia as a risk is based on the theoretical concept of oxygen flux (Freeman and Nunn, 1963) [4].

Clearly, the presence of anaemia increases the risk of depletion of available oxygen. Thus some anaesthetists have hitherto tended to set an arbitrary level of haemoglobin below which they regard the risks of elective surgical anaesthesia as unjustifiable. It may be, therefore, that either surgery is occasionally postponed unnecessarily because of anaemia or that surgery is occasionally undertaken in patients who should first have had treatment for anaemia.

Generally defined, anemia is present when the hemoglobin concentration is below a normal value based on the reference population. The mean normal value of hemoglobin is dependent on age, gender, race, and altitude. According to WHO criteria, the lower limit of normal in adults is 13 g/dL in men and 12 g/dL in women. The blood hemoglobin concentration is believed to reflect more accurately the total red cell mass or status of the erythron (erythroid precursors of the marrow and circulating mature red cells) compared with the hematocrit[1].

Tissue oxygen delivery is also the major controlling factor of erythropoiesis through the synthesis and release of erythropoietin (EPO) by the proximal tubular cells or the peritubular interstitial cells in the

kidney. EPO synthesis is governed by the activation of hypoxia inducible factor-1 (HIF-1), which controls the metabolic responses of multiple gene products to hypoxia. HIF-1 binds and activates the hypoxia-responsive transcriptional enhancer in the erythropoietin gene regulatory region that upregulates EPO expression. EPO stimulates erythroid precursor cells (CFU-E [colony-forming units—erythroid]), leading to increased proliferation and shortening of their maturation time. The marrow responds to increased EPO maximally in 4 to 7 days if enough iron is available. Erythropoiesis can be increased by as much as a factor of 8. Typical of an endocrine loop feedback mechanism, there is an inverse relation between the hemoglobin and EPO levels measured in the blood. Although this relation holds true in simple iron deficiency, it is somewhat distorted in the anemia associated with inflammation or chronic disease, in which there may be a blunted EPO response. This has made prediction of the hemoglobin response to treatment with exogenous EPO unpredictable, except in limited circumstances [2].

Iron deficiency is one of the most common causes of anemia in the India and worldwide. The three stages of iron deficiency are iron depletion (reduced stores), early iron deficiency anemia (depleted stores, normal MCV, and red cell morphology), and advanced iron deficiency anemia. Bleeding is the most common cause, typically GI bleeding or menstruation, although other causes of blood loss (e.g., pulmonary, urinary, and even factitious) occasionally present themselves [5]. Malabsorption of iron may result from achlorhydria (e.g., that seen in vitamin B12 deficiency), gastric bypass surgery, and celiac disease. Gastric resection alone would not be expected to cause iron deficiency unless the upper duodenum, the major site of iron absorption, was also removed or bypassed. About 50% of patients who have undergone a subtotal gastric resection will have impaired food iron absorption, but will still absorb exogenous iron. Inflammatory bowel disease involving the upper jejunum and duodenum may also cause malabsorption of iron. It has been estimated that approximately two thirds of patients with iron deficiency anemia have GI lesions that can be detected by endoscopy, and 10% to 15% have a GI malignancy.

Chronic disease anemia (CDA), or the anemia of inflammation, is a mild to moderate anemia accompanying infectious, inflammatory, or neoplastic disease that is characterized by abundant reticuloendothelial iron unavailable to bone marrow erythroid precursors [6]. Other mechanisms in CDA that limit erythropoiesis include inappropriately low EPO secretion and diminished EPO responsiveness. This same pattern of iron diversion and altered response to EPO can be seen in acutely ill patients in the intensive care unit with multiorgan dysfunction or sepsis. Although typically found in inflammatory conditions or malignancy, CDA is also associated with noninflammatory disorders, such as congestive heart failure, COPD, alcoholic liver disease, and chronic kidney disease. In diabetics, for example, the EPO response to anemia is blunted, even in those patients without renal insufficiency [7]. In anemic COPD patients, moderately elevated erythropoietin levels have been described, suggesting relative EPO resistance. Anemia develops 1 to 2 months after the onset of illness, does not progress, and parallels the severity of the underlying condition. Iron therapy is ineffective because of limited iron absorption and trapping of iron in macrophage storage sites.

***Diagonosis of CDA and Iron Deficiency Anaemia:***

| Parameter | Chronic Disease Anemia | Iron Deficiency |
|---|---|---|
| **Iron level** | **↓ to N** | **↓** |
| **Transferrin level** | **↓ to N** | **↑** |
| **Transferrin saturation** | **↓ to N** | **↓** |
| **Ferritin level** | **N to ↑** | **↓** |
| **TFR level** | **N** | **↑** |
| **TFR/log ferritin** | **Low (<1)** | **High (>4)** |

**TFR, transferrin receptor**

Iron requirements are increased during rHuEPO therapy. If there is no increase in the hemoglobin level or a patient stops responding during therapy, iron deficiency should be excluded, because it will limit the erythropoietic response [8]. Recommendations for iron replacement, however, are variable, and there is some debate as to the optimal route, dose, and indication for initiating iron supplements in patients receiving rHuEPO. Iron dextran preparations have a low but significant incidence of serious adverse effects, including anaphylactic reactions. Newer nondextran iron preparations, such as ferric sodium gluconate and iron sucrose, are associated with a lower incidence of immediate toxicities [9].

**MATERIALS AND METHODS**

**METHODOLOGY OF THE STUDY:** An enrolled patient will pass through the following phases mentioned as below here:

**A] SCREENING AND ENROLLMENT:** The participant is examined and evaluated based on the inclusion and exclusion criteria. If the patient is considered eligible and willing only then will enter the study. First laboratory assessment will be done on first day of schedule.

**B] TREATMENT PLAN:**

1. Group A or study group patients will be given erythropoietin 300 iu/kg by subcutaneous injections in three divided doses in first week.
2. Each patient will receive intravenous iron sucrose as per calculated in divided doses for 5 days in first week.

**Individual dose calculation for iv iron sucrose:**

TOTAL DOSE OF IV IRON (IN mg): WEIGHT IN Kg *(TARGET HEMOGLOBIN gm/ dl -BLOOD HEMOGLOBIN gm/ dl)*2.4. [Administration at one time should not exceed 500 mg].

3. Patient who fail to achieve target hemoglobin will receive blood transfusion to achieve target hemoglobin 2 days prior to elective surgery.
4. Group B or control group patients will receive blood transfusion 2 days prior to scheduled surgery.

**C] STUDY OUTCOME:**

**1. PRIMARY OUTCOME:** The number of units required for transfusion in each patient.

The change in hemoglobin percentage after treatment**.**

**2. SECONDARY OUTCOME:** The proportion of patient achieving target hemoglobin level. Changes in serum iron profile level. Adverse reaction if any. To study laboratory parameters for adverse reaction.

***STUDY SETTNG AND STUDY DESIGN:*** It is a prospective randomized control trial. A total number of 100 patients (50 in each group) will be enrolled. Group A will be study group and Group B will be control group. Patient will be screened prior to enrollment and eligibility will be assessed by specific inclusion and exclusion criteria.

***STUDY AREA:*** In patient department in the department of general surgery at IPGMER AND SSKM hospital, Kolkata.

***STUDY POPULATION:*** Indoor patients admitted for elective operations in the department of general surgery. In IPGMER and SSKM HOSPITAL, Kolkata.

***PERIOD OF STUDY:*** From February 2012 to August 2013.

***SAMPLE SIZE AND DESIGN:*** We studied 50 cases of each arm; i.e. 50 preoperative patients in treatment group and 50 in control group.

***SUBJECT ELIGIBILITY:***

***Inclusion criteria:***

1. Male or female patients more than 18 years of age.
2. Patients scheduled to undergo elective surgery 16 days after the date of enrollment.
3. Patients diagnosed to have iron deficiency anemia with hemoglobin range from 9 to 12 gm/ dl in male and 9to11 gm/ dl in female confirmed by serum ferritin less than 100 mcg/ li or 100 to 300 mcg/ li and transferring saturation less than 20%.
4. Patients who have not received erythropoietin or iv iron therapy or any blood transfusion within 3 months.
5. Patients willing to give written informed consent and willing to comply with trial protocol.

***Exclusion criteria:***

1. Patients with known hypersensitivity to study medication or hypersensitivity to human albumin.
2. Pregnant or lactating women.
3. Patients with uncontrolled hypertension [systolic bp more than 160 mm hg and diastolic bp more than 100 mm hg].
4. Patients who are in urgent need of blood transfusion [hb% less than 9 gm /dl].
5. Patients with history of thromboembolic episodes.
6. Patients with iron overload.
7. Patients with poorly controlled associated diseases as: heart disease, thyroid disorder, coagulation and hematological disorders.
8. Patients unwilling to participate.
9. Patients who are in another trial.

***STUDY ASSESMENT:***

**A] PARAMETERS TO BE STUDIED:**

1. Clinical condition of patient to be assessed by pallor.
2. Rise of hemoglobin.
3. Rise of Serum iron and serum ferritin level.
4. Any change in serum potassium and serum creatinine to asses adverse drug effects.
5. Laboratory parameters to be checked on day 0, day 7, day 14.

6. Efficacy based on requirement of blood transfusion shall be measured on 3 point scale:
7. **Markedly improved: no blood transfusion required.**
8. **Improved: one unit blood transfusion required.**
9. **Unchanged: more than one unit blood transfusion required.**

**B] SAFETY VARIABLES:**

1. The nature and severity of adverse effects if any occurs will be recorded in case report forms.
2. If any serious adverse effect occurs will be reported to all concerned as early as possible.

***STUDY MEDICATION:***

**GROUP A or Study Group:**

1. Recombinant Human Erythropoietin alpha [4000IU].
2. Intravenous Iron Sucrose [50mg/ ml].

Target is to achieve hemoglobin level 12 gm/dl on day 14.

**GROUP B or Control Group:**

Patients in this group will receive whole blood transfusion 2 days prior to surgery to achieve target hemoglobin (12gm/dl).

**RESULTS**

The present study was conducted at IPGME&R, Kolkata, West Bengal to compare two methods – Intravenous iron & Erythropoietin therapy verses blood transfusion in treatment of anemia before elective surgery.

All the patients studied, Hb was 9 to 12 gm/dl and target Hb level was fixed 12 gm/dl. Patients whose Hb was below 9 and were in acute crisis received blood transfusion and were not included in the study.

Total number of patients were 100, 50 in each group. One was test group in which patients received iv iron and erythropoietin inj and another is control group in which patients received whole blood transfusion to achieve target heamoglobin.

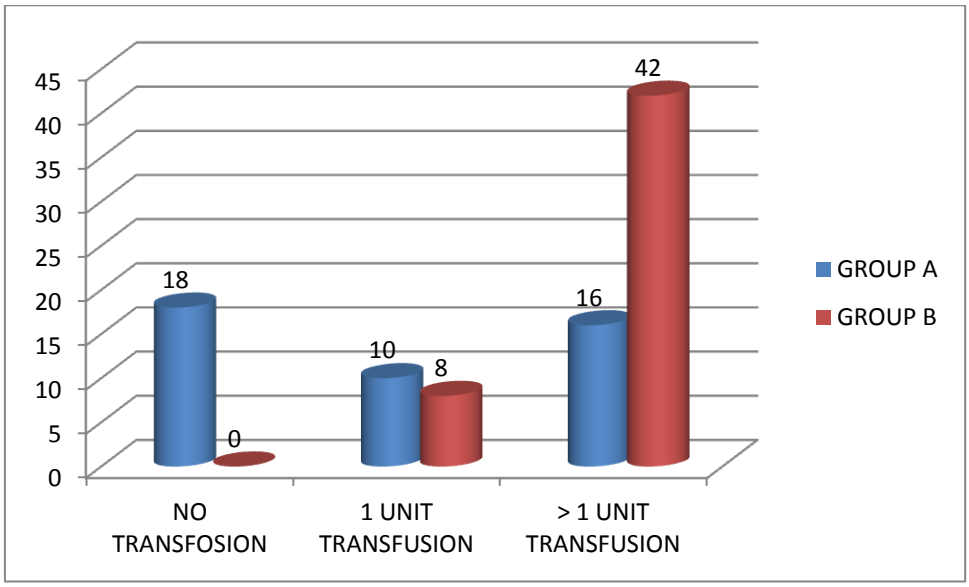
In group A among 50 patients, 6 patients dropped out of the study. In 44 cases, 18 patients received no blood transfusion, 10 patients received only 1 unit blood transfusion and 16 patients received more than 1 unit blood transfusion. 41% patients achieved target Hb, 22% patients improved significantly and 37% patients did not achieved the target. In 50 patients of group B all patients required blood transfusion among which 42 patients received more than 1 unit blood transfusion to achieve the target. In Group A there was no significant complication except in 1 patient and post treatment serum creatinine and serum K+ level did not show any significant changes. In Group A rise of Hemoglobin and serum iron & serum ferritin level has been occurred significantly which was proved by student's paired test, ANOVA Test and Fischer's t test.

The cost of treatment in group A is slightly higher than in group B patients. But it has no blood transfusion related complication and improved outcome in patients after surgery

**COMPARATIVE ANALYSIS BETWEEN GROUP A AND GROUP B**

| GROUP | NO TRANSFUSION | 1 UNIT | > 1 UNIT |
|---|---|---|---|

| | | TRANSFUSION | TRANSFUSION |
|---|---|---|---|
| GROUP A | 18 | 10 | 16 |
| GROUP B | O | 8 | 42 |




**RISE OF HEMOGLOBIN IN AVERAGE:**

| DAY | HEMOGLOBIN(AVG.) g/dl |
|---|---|
| DAY 1 | 9.35 |
| DAY 7 | 10.37 |
| DAY 14 | 11.44 |

**RISE OF SERUM IRON:**

| DAY | SERUM IRON mg/dl |
|---|---|
| DAY 1 | 76.06 |
| DAY 7 | 105.4 |
| DAY 14 | 131.61 |

**RISE OF SERUM FERRITIN:**

| DAY | SERUM FERRITIN ng/ml |
|---|---|
| DAY 1 | 174.76 |
| DAY 7 | 213.73 |
| DAY 14 | 256.18 |

**STATISTICS**

**Software used:**

- Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001]
- GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007]

Statistics of numerical variables done – Test group [n = 44; 6 dropouts excluded**].** Variables are normally distributed by Kolmogorov-Smirnov goodness-of-fit test other than No. of blood units transfused (Blood Unit) variable.

Statistics of numerical variables done – Control group [n = 50].

Comparison of numerical variables between Groups Test (1) and Control (2) – done by Student's unpaired test. Comparison of numerical variables between Groups Test (1) and Control (2) done by – Mann-Whitney U test.

Comparison of numerical variables within Group Control done by – Student's paired test. Comparison of numerical variables within Group Test done by– Student's paired test. Comparison of numerical variables within Group Test – Repeated measures ANOVA followed by Tukey's test if ANOVA returns p value < 0.05.

**Hb**

| **No. of datasets 3 F value 172.46 p value < 0.001** Tukey's Multiple Comparison Test | Mean Diff. | q | P value | 95% CI of diff |
|---|---|---|---|---|
| HbD1 vs HbD7 | -1.0250 | 12.988 | < 0.001 | -1.2918 to -0.75823 |
| HbD1 vs HbD14 | -2.0727 | 26.265 | < 0.001 | -2.3395 to -1.8060 |
| HbD7 vs HbD14 | -1.0477 | 13.276 | < 0.001 | -1.3145 to -0.78096 |

p value <0.001 indicates the difference is significant.

**Comparison of categorical variables between Groups Test (1) and Control (2)**

Fisher's exact test 2-tailed *p* value 0.519

**ETHICAL CONSIDERATIONS**

The Institutional Ethics Committee of IPGME&R, SSKM Hospital, Kolkata are viewed the proposal for ethical consideration and approval was obtained prior to the study.

Written consent was taken from all the respondents prior to enroll in the study. The respondents were explained in detail the full description of the research, confidentiality and voluntary participation. They were assured that all data provided by them would be kept confidential and be used only for research or academic purpose. Every received data were treated carefully. Thus, the three principles which need to be followed in any biomedical research i.e. beneficence (an obligation to do no harm by protecting the participants from physical and psychological harm, and preventing them from exploitation), respect of human dignity (full disclosure of the research project and letting the participants decide whether to participate or not in the study) and justice (study participants have the right to be treated equally and fairly in the selection as well as during the course of the study) was considered throughout this study.

**DISCUSSION**

In Group A there was no significant complication except in 1 patient and post treatment serum creatinine and serum K+ level did not show any significant changes. In Group A rise of Hemoglobin and serum iron & serum ferritin level has been occurred significantly which was proved by student's paired test, ANOVA Test and Fischer's t test.

The cost of treatment in group A is slightly higher than in group B patients. But it has no blood transfusion related complication and improved outcome in patients after surgery.

More detailed and significant improvement of this therapy can be proved by larger sample size and long standing follow-up study in various surgical facilities which includes patients of Hb level below 9 gm/dl to achieve target level before surgery. So, IV iron & erythropoietin therapy can be used for correction of pre-surgical anemia to reduce the number of transfused blood units.

In previous studies, the use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations [10].

A multidisciplinary panel of physicians was convened by Network for Advancement of Transfusion Alternatives to review the evidence on the efficacy and safety of i.v. iron administration to increase haemoglobin levels and reduce blood transfusion in patients undergoing surgery, and to develop a consensus statement on perioperative use of i.v. iron as a transfusion alternative. After conducting a systematic literature search to identify the relevant studies, critical evaluation of the evidence was performed and recommendations formulated using the Grades of Recommendation Assessment, Development and Evaluation Working Group methodology. Two randomized controlled trials (RCTs) and six observational studies in orthopaedic and cardiac surgeries were evaluated. Overall, there was little benefit found for the use of i.v. iron. At best, i.v. iron supplementation was found to reduce the proportion of patients requiring transfusions and the number of transfused units in observational studies in orthopaedic surgery but not in cardiac surgery. The two RCTs had serious limitations and the six observational limited by the selection of the control groups. Thus, the quality of the available evidence is considered moderate to very low. For patients undergoing orthopaedic surgery and expected to develop severe post operative anaemia, the panel suggests i.v. iron administration during the perioperative period (weak recommendation based on moderate/low-quality evidence). For all other types of surgery, no evidence-based recommendation can be made. The panel recommends that large, prospective, RCTs be undertaken to evaluate the efficacy and safety of i.v. iron administration in surgical patients. The implementation of some general good practice points is suggested.

**CONCLUSION**

- The problem of anemia in elective surgery patients occupies a significant health problem in Indian population.
- Until recently only blood transfusion was available to correct this problem.

- Blood transfusion has many complications, Mainly HIV 1 & 2, HBs, HCV infections which are fatal.
- As blood alternatives intra venous iron and erythropoietin therapy has been tried in this study.
- This study shows a significant rise in hemoglobin level, serum iron & ferritin level in study population after the therapy.
- 41% patients did not require any transfusion to achieve target hemoglobin and 22% improved partially and received comparatively less blood transfusion than their counterpart in group B.
- So , IV Iron and Erythropoietin can be used to reduce the demand of blood transfusion and can improve post surgical outcome in patients
- Large and multi setup studies are required to achieve further data to support the use of this therapy as an effective blood alternative in future.
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