Université de Montréal

Évaluation pharmacodynamique et sécurité d'emploi de l'Époétine alfa chez les patients aux soins intensifs

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Ce mémoire intitulé :

Évaluation pharmacodynamique et sécurité d'emploi de l'Époétine alfa chez les patients aux soins intensifs

présenté par :

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a été évalué par un jury composé des personnes suivantes :

Résumé

Objectif : L'objectif primaire était de comparer la réponse érythropoïétique de deux doses d'érythropoïétine humaine recombinante (EPO) exprimée par la variation moyenne des réticulocytes et de l'hémoglobine durant le séjour aux soins intensifs. **Devis** : étude prospective, ouverte, multicentrique. **Patients** : 58 patients hospitalisés aux unités de soins intensifs chirurgicaux et/ou médicaux de trois centres hospitaliers de soins généraux spécialisés et ultraspécialisés québécois entre juillet 2003 et décembre 2004. **Intervention** : les patients inclus dans l'étude recevaient soit EPO 40 000 unités sous-cutanée 1 fois par semaine (groupe A) ou EPO 40 000 unités sous-cutané 2 fois par semaine (groupe B), pour 4 doses maximum durant le séjour aux soins intensifs. Les patients ont été recrutés successivement : les 30 premiers patients correspondant au groupe A, les patients suivants correspondant au groupe B. Si la condition clinique du patient le requérait, une transfusion pouvait être administrée si l'hémoglobine était inférieure à 70 g/L ou si l'hémoglobine était inférieure à 90 g/L en présence de syndrome coronarien aigu. Aucune transfusion ne devait être administrée uniquement sur une valeur d'hémoglobine. **Résultats :** 30 patients ont été recrutés dans le groupe A et 28 patients dans le groupe B. Aucune différence statistiquement significative entre les deux groupes ne fut observée au niveau de la variation quotidienne des réticulocytes ou de l'hémoglobine. **Conclusion** : une dose d'EPO supérieure à 40 000 unités par semaine ne permet pas d'obtenir une stimulation des réticulocytes ou une production d'hémoglobine plus rapide, plus élevée ou plus soutenue chez les patients hospitalisés aux soins intensifs.

Mots-clés : érythropoïétine humaine recombinante, réticulocytes, hémoglobine, anémie, transfusion sanguine, soins intensifs, pratique transfusionnelle.

Abstract

Objective: The primary objective was to compare response of erythropoiesis of 2 doses of recombinant human erythropoietin (EPO) expressed by the average variation of reticulocytes count and hemoglobin during the stay in intensive care. **Desing** : prospective, multiple center, open study. **Patients**: 58 patients hospitalized in the multidisciplinary intensive care units (ICU) of 3 hospitals in Québec, between July 2003 and December 2004. **Intervention**: the patients included in the study received 40 000 units of EPO weekly by subcutaneous injection (group A) or 40 000 units of EPO twice a week (group B), for a maximum of 4 doses during the stay in the ICU. The patients were recruited successively: the first 30 patients corresponding to the group A, the following patients corresponding to the group B. If the clinical condition of the patient required it, a transfusion could be administered with hemoglobin < 70 g/L or hemoglobin < 90 g/L in the presence of acute coronary syndrome. No transfusion based only on a single value of hemoglobin. **Results**: 30 patients were enrolled in the group A and 28 patients in the group B. No statistically significant difference between the two groups was observed for the daily variation of réticulocytes or hemoglobin. **Conclusion**: a dose of EPO > 40 000 units weekly does not provide a higher or a more sustained stimulation of reticulocytes or hemoglobin production in ICU patients.

Key words : recombinant human erythropoietin, reticulocytes, hemoglobin, anemia, blood transfusion, critical illness, transfusion practice.

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Abréviation	*Définition*
APACHE	Acute Physiology And Chronic Health Evaluation
BFU-E	Burst-Forming Units-Erythroid
CFU-E	Colony-Forming Units-Erythroid
FID	Functional Iron Deficiency
EPO	Epoetin alfa
Hb	Hemoglobin
ICU	Intensive Care Unit
IL-1	Interleukin-1
IL-6	Interleukin-6
IV	Intravenous
MODS	Multiple Organ Dysfunction Syndrome
PRCA	Pure Red Cell Aplasia
rHuEPO	recombinant Human Erythropoietin (epoetin alfa)
TNF	Tumor Necrosis Factor
TRALI	Transfusion Related Acute Lung Injury
TRICC	Transfusion Requirement In Critical Care

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- *Mme Sandra Demers*

INTRODUCTION

Depuis quelques années, une attention particulière est portée afin de diminuer le nombre de transfusions chez les patients aux soins intensifs.[1] Les équipes traitantes ont été sensibilisées aux effets délétères pouvant survenir à la suite d'une transfusion de globules rouges.[1,2] Traditionnellement, l'administration de culots globulaires chez les patients aux soins intensifs était courante afin de maintenir une concentration d'hémoglobine au-dessus de 100 g/L.[3] Une étude importante menée au Canada et publiée en 1999 amena toutefois les équipes traitantes à repenser leur pratique transfusionnelle.[1] En effet, cette étude démontrait qu'une approche transfusionnelle libérale n'était pas plus efficace qu'une stratégie transfusionnelle restrictive, voire même néfaste chez les patients moins âgés et les patients moins sévèrement malades.[1,4] La transfusion de globules rouges est théoriquement administrée afin d'augmenter les concentrations d'hémoglobine dans le sang et ainsi optimiser la livraison d'oxygène aux tissus. Toutefois, il semble que l'hémoglobine provenant du sang transfusé ne soit pas aussi performante que l'hémoglobine formée par les patients.[5] La livraison tissulaire en oxygène augmente effectivement suite à la transfusion mais la captation tissulaire en oxygène serait altérée, diminuant ainsi le but ultime de la transfusion.[5] À cela s'ajoutent les complications reliées à la transfusion telles que la formation de microthromboses, la fièvre et l'émergence de problèmes respiratoires ou TRALI (Transfusion Related Acute Lung Injury).[2]

Les réserves de sang sont limitées et coûteuses. Afin d'assurer une utilisation judicieuse des produits sanguins, des programmes de conservation du sang doivent être instaurés dans les centres hospitaliers par l'intermédiaire d'un comité de médecine transfusionnelle. Les stratégies développées pour restreindre la transfusion de globules rouges devraient d'abord s'intégrer à une pratique transfusionnelle restrictive basée sur l'état clinique des patients et non pas seulement sur une valeur d'hémoglobine. Diminuer le volume des tubes de

prélèvement et restreindre les analyses de laboratoires font partie des stratégies pour diminuer les besoins transfusionnels. L'utilisation d'érythropoïétine humaine recombinante (EPO) afin de stimuler l'érythropoïèse pourrait également être une alternative à la transfusion qui favoriserait la production d'hémoglobine performante sans les effets néfastes de la transfusion.

Normalement, les concentrations d'EPO endogène augmentent rapidement en présence d'anémie. Toutefois, une réponse anormale est souvent observée lors d'états inflammatoires. Les médiateurs de l'inflammation inhiberaient la production d'EPO, favoriseraient la dégradation des globules rouges et augmenteraient la séquestration du fer nécessaire à l'érythropoïèse. Bien que les pertes sanguines soient souvent importantes aux soins intensifs, l'anémie observée chez ces patients serait principalement de nature inflammatoire. Plusieurs patients ne présentant pas de saignements auront une baisse d'hémoglobine constante durant le séjour aux soins intensifs. L'utilisation de l'EPO précocément chez ces patients pourrait permettre la stimulation de l'érythropoïèse malgré l'inflammation.

Pajoumand et coll. proposaient récemment des recommandations pour l'utilisation de l'EPO chez les patients aux soins intensifs.[6] À la lumière des études publiées, les auteurs concluaient que 40 000 unités d'EPO une fois par semaine pouvaient être utilisées comme alternative à la transfusion mais que la dose optimale n'était pas clairement établie.[6] Toutefois, étant donné le coût élevé de l'EPO, nous croyons qu'elle devrait être utilisée conjointement avec une approche transfusionnelle restrictive telle que celle proposée dans l'étude TRICC[1] (Transfusion Requirement in Critical Care). Il ne serait pas judicieux d'ajouter une thérapie coûteuse visant à diminuer les transfusions tout en transfusant de façon libérale **[VOIR ARTICLE I]**.

REVUE DE LITTÉRATURE

Utilisation de l'EPO aux soins intensifs

Quelques études ont démontré qu'il était possible d'obtenir une stimulation rapide de l'érythropoïèse chez les patients aux soins intensifs en administrant de hautes doses d'EPO.[7-10] Une revue systématique de la littérature publiée entre 1990 et 2001 recensait quatre études évaluant l'administration d'EPO dans ce contexte **[VOIR ARTICLE II]**.[11] Parmi elles, une seule étude (EPO-1) mesurait l'impact clinique de l'EPO sur les besoins transfusionnels.[10] L'étude EPO-1, effectuée chez 160 patients, démontrait une diminution d'environ 50% des besoins transfusionnels cumulatifs chez les patients recevant l'EPO par rapport au groupe placebo. Les doses d'EPO correspondaient alors à environ 100 000 unités pour les 5 premiers jours, suivies de 60 000 unités par semaine pour un patient de 70 kg. Toutefois, les nombreux critères d'exclusion de cette étude limitaient l'utilisation d'EPO dans un contexte de soins intensifs. D'autres études étaient donc nécessaires avant d'utiliser l'EPO chez les patients aux soins intensifs **[VOIR ARTICLE II-CONCLUSION]**. En 2002, une étude de grande envergure (EPO-2) fut publiée.[12]

L'étude EPO-2 était une étude prospective, à double-insu et contrôlée par placebo avec répartition aléatoire des sujets, mesurant l'impact de l'administration d'EPO sur les besoins transfusionnels des patients aux soins intensifs.[12] Elle fut menée dans 65 unités de soins intensifs médicaux et/ou chirurgicaux. Les patients étaient inclus lors du troisième jour d'hospitalisation aux soins intensifs s'ils étaient âgés de plus de 18 ans en présence d'une valeur d'hématocrite inférieure à 38 %. Les patients étaient exclus s'ils présentaient des antécédants de convulsions, un saignement gastro-intestinal actif, une hypertension non contrôlée, un syndrome coronarien aigu, s'ils étaient dialysés chroniquement ou déjà sous EPO. L'objectif principal était de comparer le pourcentage de patients dans chaque groupe ayant reçu au moins une

transfusion de globules rouges du jour 1 au jour 28 de l'étude. Le nombre cumulatif de transfusions pour chaque groupe ainsi que le taux de mortalité à 28 jours furent également mesurés.

Durant le séjour aux soins intensifs, les patients recevaient 40 000 unités d'EPO ou un placebo sous-cutané une fois par semaine pour un maximum de quatre doses. L'administration de la médication était interrompue temporairement lorsque l'hématocrite excédait 38 %. Tous les patients recevaient également un supplément de fer oral ou parentéral correspondant à au moins 150 mg de fer élémentaire par jour.

Au total, 1302 patients ont été inclus dans l'étude soit 650 patients dans le groupe recevant l'EPO et 652 patients dans le groupe placebo. Les caractéristiques des deux groupes au moment de la répartition aléatoire étaient comparables au niveau de l'âge, de l'hémoglobine, du taux d'érythrocytes et au niveau de la sévérité de la maladie.

Plus de la moitié des patients du groupe placebo (60,4%) ont reçu au moins une transfusion entre le jour 1 et le jour 28 comparativement à 50,5% des patients recevant l'EPO (394 patients vs 328 patients; respectivement, $p < 0.001$). Une réduction de 19% du nombre cumulatif de culots de globules rouges transfusés dans le groupe recevant l'EPO a également été observée comparativement au groupe placebo (1590 culots vs 1963 culots; respectivement). Par contre, aucune différence statistiquement significative ne fut observée entre les deux groupes au niveau de la mortalité, de la durée de séjour aux soins intensifs ou des besoins en ventilation mécanique. L'incidence d'effets indésirables pouvant être attribuables à l'EPO était comparable dans les deux groupes.

L'étude EPO-1 ne précisait pas de critères transfusionnels, la décision de transfuser étant laissée à la discrétion de l'équipe traitante. Cette faiblesse fut corrigée dans l'étude EPO-2, pour laquelle un seuil transfusionnel était établi :

aucune transfusion en présence d'une hémoglobine supérieure à 90 g/L ou d'une valeur d'hématocrite supérieure à 27%, à moins d'une condition aiguë le requérant. À partir de ce seuil transfusionnel, les patients étaient transfusés à la discrétion de l'équipe traitante.

Étant donné les risques et les limites associés à la transfusion de globules rouges, il apparaît particulièrement important de réduire les besoins transfusionnels durant le séjour aux soins intensifs. Par conséquent, il aurait été intéressant de connaître l'impact sur les besoins transfusionnels non seulement à 28 jours mais également durant le séjour aux soins intensifs. Les bénéfices observés dans l'étude EPO-2 sont modestes par rapport à ceux observés dans l'étude EPO-1. Cette différence pourrait en partie s'expliquer par la dose beaucoup plus faible utilisée dans l'étude EPO-2. Le régime thérapeutique optimal d'EPO reste donc à déterminer.

Métabolisme du fer chez les patients aux soins intensifs

L'augmentation de l'érythropoïèse induite par l'administration d'EPO augmente les besoins en fer.[13] Il est donc essentiel d'administrer un supplément de fer aux patients qui reçoivent de l'EPO afin d'optimiser la réponse et de prévenir une carence fonctionnelle en fer. L'administration de fer dans le contexte des soins intensifs représente toutefois un véritable défi. Les suppléments de fer peuvent être administrés par voie orale, intramusculaire ou intraveineuse. L'administration de fer par voie intramusculaire n'apparaît pas idéale étant donné la grande variabilité de sa biodisponibilité et la proportion non négligeable de malades anticoagulés à risque d'hématome. L'administration de fer intraveineux est discutable chez cette population de patients puisqu'il existe un risque théorique de promouvoir la croissance bactérienne lorsque le fer est administré par cette voie.[14] La voie orale semble donc être à privilégier dans ce contexte. Toutefois, l'utilisation du fer par voie orale aux soins intensifs, est généralement limitée par sa faible biodisponibilité et les conditions médicales

qui rendent le tube digestif non fonctionnel. La dose de fer adéquate est également difficile à déterminer puisque le contexte inflammatoire modifie considérablement le métabolisme du fer, ne permettant pas un suivi approprié des paramètres habituels.[15] [**VOIR ARTICLE III**].

OBJECTIFS

Notre étude a été élaborée pour évaluer si l'administration d'une dose d'EPO supérieure à 40 000 unités par semaine, conjointement avec un seuil transfusionnel restrictif, stimule d'avantage l'érythropoïèse des patients aux soins intensifs. L'objectif principal était de comparer la stimulation de l'érythropoïèse de deux doses d'EPO chez les patients sévèrement malades aux soins intensifs. Les paramètres de l'érythropoïèse mesurés étaient la variation moyenne de l'hémoglobine et des réticulocytes durant le séjour aux soins intensifs. Cette étude visait à évaluer si une augmentation des doses d'EPO permettait une stimulation accrue de l'érythropoïèse spécifiquement durant le séjour aux soins intensifs.

MÉTHODOLOGIE

Cette étude ouverte et prospective a été menée dans les unités de soins intensifs de la Cité de la Santé de Laval, de l'Hôpital du Sacré-Coeur de Montréal et de l'Institut de Cardiologie de Montréal entre juillet 2003 et décembre 2004. L'étude était de nature exploratoire, la taille des échantillons ayant été déterminée par des considérations économiques et de faisabilité. Les 30 premiers patients (groupe A) inclus à l'étude selon les critères d'inclusion et d'exclusion recevaient 40 000 unités d'EPO une fois par semaine pour un maximum de 4 doses. Les 30 patients suivants (groupe B) devaient recevoir 40 000 unités d'EPO deux fois par semaine pour un maximum de 4 doses. Les critères transfusionnels utilisés étaient : aucune transfusion basée uniquement sur une valeur d'hémoglobine. Si la condition clinique du patient le requérait, il

pouvait être transfusé si l'hémoglobine < 70 g/L ou hémoglobine < 90 g/L en présence de syndrome coronarien aigu. [**Voir l'ARTICLE IV pour une description détaillée de la méthodologie**].

RÉSULTATS

Au total, 58 patients ont été inclus à l'étude dont 30 dans le groupe A et 28 dans le groupe B. Les caractéristiques de base des patients étaient généralement comparables entre les deux groupes. Le score APACHE II moyen était environ de 21 pour les deux groupes. Au moment de l'inclusion à l'étude, près de la moitié des patients recevaient un vasopresseur et la majorité des patients étaient ventilés mécaniquement. La ferritine élevée et la saturation de la transferrine abaissée dans les deux groupes étaient caractéristiques d'un état inflammatoire.

Aucune différence statistiquement significative entre les deux groupes ne fut observée au niveau des réticulocytes. Une augmentation significative des réticulocytes a été observée dans chacun des groupes par rapport aux valeurs de base. Aucune différence significative ne fut observée entre les deux groupes au niveau de la variation quotidienne des concentrations d'hémoglobine durant le séjour aux soins intensifs. Les seuils transfusionnels ont globalement été respectés : l'hémoglobine moyenne pré-transfusion était de 72 ± 9 g/L dans le groupe A et de 67 ± 6 g/L dans le groupe B. **[Une description plus détaillée des résultats est présentée dans l'article IV]**.

DISCUSSION

Notre étude démontre qu'il n'y a pas d'avantage à utiliser une dose d'EPO supérieure à 40 000 unités par semaine au niveau de la production des réticulocytes. Dans une étude précédante, Corwin et coll. avaient utilisé une dose beaucoup plus élevée et démontré une réduction de près 50% des

besoins transfusionnels chez les patients recevant l'EPO comparativement au placebo.[10] Les résultats plus modestes observés dans la seconde étude[4], imposaient d'étudier si un effet maximal était atteint avec une dose de 40 000 unités d'EPO une fois par semaine.

Dans notre étude, aucune différence ne fut observée entre les deux groupes au niveau de la variation quotidienne de l'hémoglobine durant le séjour aux soins intensifs. Notre étude est la première à évaluer l'effet de l'EPO conjointement avec une approche transfusionnelle restrictive telle qu'utilisée dans l'étude TRICC[1]. La valeur moyenne de l'hémoglobine pré-transfusion observée dans l'étude de Corwin et coll. Était de 86 g/L. Nos critères transfusionnels plus restrictifs ont permis d'obtenir une hémoglobine moyenne pré-transfusion de 72 g/L pour le groupe A et de 67 g/L pour le groupe B. On observe dans notre étude une stabilisation des concentrations d'hémoglobine durant 28 jours aux soins intensifs. Bien qu'un seuil transfusionnel moyen à 72 g/L ait été appliqué pour le groupe A, la concentration moyenne de l'hémoglobine durant le séjour aux soins intensifs se situait près de 90 g/L. Cette augmentation pourrait être secondaire à l'administration d'EPO. **[Voir l'article IV pour une discussion plus détaillée]**.

L'utilisation de l'EPO à hautes doses dans le contexte des soins intensifs était peu étudiée et requérait un suivi des effets indésirables. Les effets secondaires de l'EPO ont principalement été rapportés chez les patients insuffisants rénaux ambulatoires. Parmi ces effets secondaires, l'hypertension (rapporté chez 24% des patients insuffisants rénaux) et les troubles thromboemboliques (0,04 événements par patient-année) étaient les plus préoccupants. Le faible nombre de patients dans notre étude ne permettait certainement pas de faire émerger de façon claire ces effets secondaires. Toutefois, un comité de surveillance indépendant avait été mis en place dans le cas où le contexte des soins intensifs aurait fortement augmenté l'incidence de ces événements. **[Les effets**

secondaires pouvant être attribuables à l'EPO sont rapportés dans l'ARTILE IV].

CONCLUSION

Une dose d'EPO supérieure à 40 000 unités par semaine ne permet pas d'obtenir une stimulation des réticulocytes ou une production d'hémoglobine plus rapide, plus élevée ou plus soutenue chez les patients hospitalisés aux soins intensifs.

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To the Editor :

The recommendations provided by Pajoumand et al in their article recently published in ***The Annals*** [1] are interesting. However, these recommendations on the use of EPO in critically ill patients should be integrated to a blood conservation strategy. As reported in the ABC study[2], the amount of blood loss through blood sampling in the ICU is considerable, averaging 41 mL per day. Therefore, sparing mechanisms to reduce blood draws should be developed in the ICU before widespread utilisation of EPO. Non pharmacological alternatives such as limiting blood collection, using smaller collecting tubes and restrictive transfusion thresholds are among the strategies.

Indeed, we strongly believe that a restrictive transfusion approach is an important step to implement a blood conservation strategy in critically ill patients. The use of EPO without a restrictive transfusion approach would not be efficient. In our ICU, the transfusion medicine committee developed a tool to ensure an appropriate use of red blood cells transfusions. The tool is a prescription with printed recommendations for blood products administration. Among others, these recommendations specify that the prescription of red blood cells transfusion should be based on the clinical condition of the patient rather

than on a single hematocrit or hemoglobin value. We simply ask to the medical team to prescribe blood products on that tool and to justify the reason of transfusion. We assume that this exercice will educate, change transfusion practice and avoid unnecessary blood transfusion.

A review of the litterature concerning the role of EPO in critically ill patients was also published two years ago in ***The Annals*** [3]. When we revised this topic, the EPO-2 study conducted by Dr Corwin and colleagues[4] had not been published yet. We support Dr Pajoumand et al. conclusion that optimal EPO dosage remains to be determined. It seems that higher doses of EPO could provide a higher erythropoiesis response during the ICU stay. More important, additional studies combining the use of EPO with a restrictive transfusion approach such as proposed in the TRICC trial [5] are needed.

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ARTICLE II :Recombinant Human Erythropoietin Use in Intensive Care. Ann Pharmacother 2002; 36 :1068-74.
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ABSTRACT

OBJECTIVE: To review the literature concerning the role of recombinant human erythropoietin (rHuEPO) in reducing the need for transfusion in intensive care patients.

DATA SOURCES: Articles were obtained through searches of MEDLINE database (1990 to June 2001) using the key words erythropoietin, epoetin alfa, anemia, reticulocytes, hemoglobin, critical care, intensive care, critical illness and blood transfusion. Additional references were found in the bibliographies of the articles cited. The Cochrane library was also consulted.

STUDY SELECTION AND DATA EXTRACTION: Controlled, prospective, randomized studies on the use of rHuEPO in critically ill adults were selected.

DATA SYNTHESIS: Anemia is a common complication in intensive care patients. It is caused, in part, by abnormally low levels of endogenous erythropoietin and is seen mainly in patients with sepsis and multiple organ dysfunction syndrome, in whom inflammation mediator levels are often elevated. High doses of rHuEPO produce a rapid response in these patients, despite elevated cytokine levels. There have been three studies on rHuEPO administration in intensive care and one study in acutely burned patients. Only two of these studies looked at the impact of rHuEPO administration on the need for transfusion.

CONCLUSION: In summary, few randomized controlled trials explore the role of rHuEPO in the intensive care. Only one was a large randomized clinical trial but presents many limitations. Future outcome and safety studies comparing

rHuEPO vs placebo must include clinical end points such as end organ morbidity, mortality, transfusion requirements and pharmacoeconomic analysis. rHuEPO appears to provide an erythropoietic response. Optimal dosage and the real impact of rHuEPO on the need for transfusion in intensive care remain to be determined. So far, rHuEPO cannot be recommended to reduce red blood cell transfusions in anemic critically ill patients.

Introduction

Anemia is a common complication in intensive care patients.[1-8] Many of these patients receive multiple transfusions, despite the absence of active bleeding.[4] In 1990, it was estimated that 85% of patients hospitalized in intensive care for more than one week received at least one red blood cell unit and that, on average, patients received two to three units per week.[4] More recently, it was reported that approximately 31% of intensive care patients received transfusions.[9] Transfusion practices in intensive care also vary considerably; some intensivists use a hemoglobin concentration of 10 g/dL as the transfusion threshold while others use a much more restrictive approach.[10]

Although red blood cell transfusion is a common practice in intensive care,[5] the actual benefits of increasing hemoglobin levels through transfusion have not been clearly established. Red blood cell transfusion may increase the delivery of oxygen to the tissues, but it is not known whether cellular oxygen consumption actually increases.[5,7,11] Transfused blood is low in 2,3-diphosphoglycerate thereby reducing the ability of the red blood cells to unload oxygen to the tissues.[12] Moreover, anemia may be a factor interfering with a patient's ability to wean from mechanical ventilation.[11] Nor is there a consensus on the advantages of using a high transfusion threshold (Hb 10 g/dL) versus a restrictive one (Hb 7 g/dL) for accelerating the point at which intubated patients can be taken off mechanical ventilation.[11]

Transfusions also entail the risk of adverse reactions and virus transmission.[13] Moreover, patients in intensive care may be more susceptible to the complications associated with immunosuppression, immunomodulation, and microthrombosis secondary to red blood cell transfusion.[1,5,6,13] Immunomodulation increases the risk of nosocomial infection and potentially a recurrence of neoplasia.[13] Patients receiving blood that had been stored for more than 15 days develop evidence of splanchnic ischemia attributable to the poor deformability of the transfused red blood cells.[12] Consequently, there is growing evidence to suggest that red blood cell transfusion is not necessarily beneficial and, in some cases, may even be harmful.[12-14]

Given the limitations and risks of blood transfusion in intensive care patients, a review of transfusion practices that takes into account restrictive transfusion strategy and transfusion alternatives, such as recombinant human erythropoietin (rHuEPO), is in order. The purpose of this article is to review the literature concerning the role of rHuEPO in reducing the need for transfusion in intensive care patients.

Data Sources

A MEDLINE literature search (1990 to June 2001) was performed to identify all controlled, prospective, randomized studies on the use of rHuEPO in critically ill adults. The following search terms were used : erythropoietin, epoetin alfa, anemia, reticulocytes, hemoglobin, critical care, intensive care, critical illness and blood transfusion. The bibliographies of retrieved publications were reviewed for additional references that may have been missed by computerized search. Background information concerning anemia of the critical illness and blood transfusion was identified through the same MEDLINE search strategy.

Criteria for red blood cell transfusion

For many years, a hemoglobin level of 10 g/dL[4,5,14] and a hematocrit of 30%[4,14] were the transfusion thresholds, particularly in the context of surgery.[4,14] However, In a multicenter, randomized, controlled clinical trial involving 838 critically ill patients, Hébert et al recently showed that a restrictive transfusion strategy was just as effective as, and possibly more effective than, a liberal strategy.[6] The hemoglobin concentrations of patients assigned to the restrictive strategy of transfusion were maintained in the range of 7 to 9 g/dL, with a transfusion given when the hemoglobin concentration fell below 7 g/dL.[6] Among patient assigned to the liberal strategy of transfusion, the hemoglobin concentrations were maintained in the range of 10 to 12 g/dL, with a threshold for transfusion of 10 g/dL.[6] The primary outcome was 30-day all-cause mortality. Secondary outcomes included other mortality rates and rates of organ failure. Hébert's study has been a major advance in defining appropriate transfusion practice in the critically ill population.[14] They showed that, overall, there was no statistically significant difference between a restrictive approach to transfusion and a liberal one in terms of mortality after 30 days.[6] Moreover, they found that among less critically ill patients (APACHE II score < 20[15]), mortality was distinctly lower in the restrictive group (8.7% vs 16.1%; $p = 0.03$). The same was true of patients under the age of 55 (5.7% vs 13.0%; $p = 0.02$).[6] These findings suggest that a transfusion threshold of 7 g/dL and target hemoglobin level of 7 to 9 g/dL are preferable to a transfusion threshold of 10 g/dL and a target hemoglobin level of 10 to 12 g/dL.[6] Such an approach is safe for most hemodynamically stable coronary patients, with the possible exception of patients suffering from acute coronary syndrome.[9]

Hébert's study clearly demonstrates the limitations of red blood cell transfusion and the importance of a restrictive approach in intensive care.[6] Moreover, any additional strategy capable of reducing the need for transfusion would be desirable. One such strategy could be to optimize endogenous red blood cell

production by acting on the mechanisms and causes of anemia in patients with multiple organ dysfunction syndrome (MODS) or sepsis.[1]

Anemia in Intensive Care

Several factors contribute to anemia in intensive care patients: numerous blood draws, occult gastrointestinal bleeding and blood loss caused by surgical techniques.[1] Deficient erythropoiesis like that seen in chronic inflammatory disease[16] may also explain why patients with sepsis or MODS, in whom inflammation mediator levels are elevated, develop anemia.[1,3,7,8,17,18]

Erythropoietin, a hormone secreted by the kidneys, triggers the production of red blood cells by stimulating the division and differentiation of precursors in the bone marrow.[8,18] Serum erythropoietin levels in normal individuals are in the range of 5-30 IU/L.[19] A decrease in the supply of oxygen to the kidneys is the primary triggering factor responsible for the production of erythropoietin.[18] A sudden drop in hemoglobin usually causes an exponential increase in the amount of erythropoietin circulating in the bloodstream within minutes or hours.[3,8,16,18] However, this response is blunted in anemic patients seen in intensive care and is exacerbated by sepsis.[1-3] Erythropoietin secretion is blunted when the blood contains high levels of cytokines during inflammatory diseases or sepsis.[1,3,16,17] Consequently, endogenous erythropoietin levels in ambulatory patients with anemia are in the order of 845 + 180 IU/L versus 124 + 13 IU/L for anemic patients with sepsis in intensive care.[3] Erythropoiesis blunting may contribute to the gradual decrease in hemoglobin frequently seen in this context.[1-3,7,17] Low erythropoietin levels observed in MODS could be a compensatory mechanism to maintain a good rheology or hemodilution to overcome the hypercoagulable state frequently seen in that context. In these patients, optimal delivery of oxygen to the tissues is critical in order to avoid multiple organ deterioration.[17] In addition, anemia can be a major obstacle to removing the patient from mechanical ventilation.[11] During mechanical

ventilation, the work done by the respiratory muscles increases the amount of oxygen consumed by the tissues, increasing the need for oxygen to the heart, respiratory muscles, and splanchnic circulation.[11]

rHuEPO use in Intensive Care

rHuEPO stimulates erythropoiesis by binding to the receptors on the surface of erythrocyte precursor cells in the bone marrow.[16] A small number of these receptors are found on early burst-forming units-erythroid (BFU-E); however, their numbers increase according to cellular differentiation, reaching their maximum expression on colony-forming units-erythroid (CFU-E) and proerythroblasts.[16] rHuEPO mainly stimulates the differentiation and proliferation of CFU-Es. If endogenous erythropoietin concentrations are abnormally low, rHuEPO administration prevents the destruction of CFU-Es.[16] However, rHuEPO has no impact after red blood cells are released into the bloodstream because there are almost no receptors on the surface of mature red blood cells.[16] Therapy with rHuEPO was first shown to correct the anemia caused by chronic renal failure in patients undergoing dialysis.[19] It is also used in clinical practice for other indications including treatment of anemic chemotherapy patients with nonmyeloid malignancies, prevention of anemia in surgical patients and treatment of anemia induced by zidovudine therapy in HIV-infected patients.[19] rHuEPO should routinely be given subcutaneously to maximize its effects.[16,19] Intravenous administration leads to unphysiologic high peak plasma erythropoietin concentrations followed by subnormal levels.[19] Subcutaneous administration of rHuEPO induces lower plasma erythropoietin concentrations but markedly longer elimination half life.[16,19] For the treatment of anemia in patients with chronic renal failure, the usual initial dosage is 80-120 U/kg thrice weekly. Several larger dosing regimens of rHuEPO have been used in the surgical setting including 300 U/kg daily for 14 days or 600 U/kg weekly for 4 weeks.[20]

Given the precarious condition of patients in intensive care, there would have to be a rapid, significant response to rHuEPO administration for their transfusion needs to change. In 1990, it was estimated that approximately 40% of transfused intensive care patients only received transfusions during their first week of hospitalization.[4] However, those hospitalized for more than a week were transfused consistently every week.[4] Recent studies have shown that rapid stimulation of erythropoiesis is possible in intensive care patients with high doses of rHuEPO (**Table 1**).[2,7,17,21]

In a prospective, randomized, placebo-controlled study, Gabriel et al studied rHuEPO response in 19 patients admitted to intensive care with MODS following major abdominal surgery or major trauma.[17] Erythropoietin levels, cytokines levels and reticulocyte counts were the major outcomes. The patients were randomized to receive either 600 U/kg rHuEPO or a placebo intravenously three times a week for three weeks. All patients also received intravenous iron, folic acid, and vitamin B_{12} supplements. Patients in both groups were transfused to maintain a hematocrit > 30%. Nine patients received rHuEPO and 10 patients received a placebo. Two patients in the rHuEPO group required massive transfusions following episodes of major bleeding. In terms of the severity of their disease (APACHE II score[15]) and the length of stay in intensive care, the groups were comparable. Gabriel's study showed that high doses of rHuEPO stimulated erythropoiesis in patients with MODS, despite elevated cytokine levels.[17] At the end of the third week of treatment, a statistically significant increase in erythrocytes was observed in the patients who had received rHuEPO compared with those who had received the placebo (4.0 % + 0.9 vs 1.9 % + 0.5 respectively; $p < 0.05$). A statistically significant difference was observed between the placebo group and the rHuEPO group in terms of serum erythropoietin at the first week of treatment (30.4 ± 7.7 U/L vs 150.2 ± 27.6 U/L respectively; $p<0.05$) showing a blunted erythropoietin response in MODS. In the absence of major bleeding (< 6 units of packed red blood cells per week), 2 of 7 rHuEPO patients required red cell transfusions during the third week of

treatment compared with 6 of 10 control patients ($p = 0.335$). However, this study was not designed to assess the impact of rHuEPO on the need for transfusion.

In an open, randomized study, van Iperen et al evaluated rHuEPO response in 36 intensive care patients with a hemoglobin count of < 11.2 g/dL (or a hemoglobin of < 12.1 g/dL in coronary patients).[2] The patients were divided into three groups of 12 each and received either 1 mg folic acid daily for 14 days (control group), 1 mg folic acid daily + 20 mg iron iv daily for 14 days (iron group) or 1 mg folic acid daily + 20 mg iron iv daily for 14 days + 300 U/kg rHuEPO subcutaneously every two days for five doses (rHuEPO group). The major outcomes were serum erythropoietin levels and increase in the reticulocyte counts compared with baseline values and compared with the two other groups. The groups were comparable in every regard except length of stay in intensive care, which was longer for the patients in the control group than for the patients in either the iron group or the rHuEPO group (58 ± 31 days vs 29 ± 18 days and 37 ± 20 days respectively; $p < 0.05$). Patients in each of the groups were transfused on the same transfusion threshold : a hemoglobin count of 8.9 g/dL or 9.7 g/dL for coronary patients. The results of this study showed that when rHuEPO was administered, erythropoiesis was rapidly stimulated in intensive care patients. A statistically significant increase in the number of circulating red blood cells was observed after 6 days in the patients who received rHuEPO compared with baseline values and after 8 days compared with the two other groups.[2] Reticulocyte counts increased in the rHuEPO group from $56 \pm 33 \times 10^9$/L to a maximum of $189 \pm 97 \times 10^9$/L on day 13. However, it would have been helpful if the results had been presented in terms of hematocrit instead of reticulocyte count. A statistically significant difference was observed between the placebo group or the iron group in terms of serum erythropoietin after 10 days of treatment compared to the rHuEPO group (19 ± 8 U/L vs 16 ± 5 U/L vs 166 ± 98 U/L respectively; $p<0.05$) showing a blunted response in that mixed population of anemic critically ill patients. However, no differences

between the groups were observed in terms of hemoglobin concentrations during the entire study. On average, 12 ± 14 red blood cell units per patient were transfused over a three-week period in the control group versus 5 ± 7 and 7 ± 7 units for those in the iron group and rHuEPO group, respectively. However, this open study did not measure the impact of rHuEPO administration on the need for transfusion, nor was it designed to.[2]

Corwin et al proposed the use of rHuEPO to reduce the need for transfusion and conducted a prospective, multicenter, double-blind, placebo-controlled, randomized study to measure the impact of rHuEPO administration on the need for transfusion in intensive care.[7] To our knowledge, this is the only study to do so in multidisciplinary intensive care. To qualify for the study, patients had to be over the age of 18 years and have a hematocrit of < 38%. They could not have an iron, vitamin B_{12} or folate deficiency. The many exclusion criteria included patients with active bleeding, neutropenia or thrombocytopenia; patients requiring vasopressive amines other than dopamine administered at a renal dose; patients with unmanaged hypertension, chronically dialyzed patients; and patients with a history of liver failure, cirrhosis, hepatic encephalopathy, seizures during the previous 6 months, recent cerebrovascular accident and recent thromboembolic disease. During their stay in intensive care, patients received either 300 U/kg of rHuEPO or a placebo subcutaneously once a day for five days, followed by a dosing schedule of every two days for a minimum of two weeks, and for a maximum of six weeks. The primary end points was to measure the total number of transfusions per group and the percentage of patients in each group who either received at least one unit of red blood cells or died from day 8 to day 42 of the study. Administration of the medication was discontinued temporarily if the hematocrit exceeded 38%. All patients also received either an oral or a parenteral iron supplement. Whether oral vs parenteral iron use was similar between groups was not mentionned. In all, 160 patients took part in the study: 80 in the rHuEPO group and 80 in the control group. At randomization, the two groups were comparable in terms of age,

hematocrit, erythrocyte count and severity of disease (APACHE II score[15]). There was a clinically and statistically significant decrease in the total number of transfused red blood cell units in the group receiving rHuEPO, compared with the placebo group (166 vs 305 respectively; $p < 0.002$). Forty-five percent of patients in the rHuEPO group either received at least one red blood cell unit or died between day 8 and day 42 of the study compared to 55% for the placebo group (relative risk 0.8; confidence interval 95% from 0.6 to 1.1). No statistically significant difference was observed between the groups in terms of mortality or incidence of side effects attributable to rHuEPO (deep vein thrombosis 4 vs 4, thrombocytopenia 9 vs 3 or thrombocytosis 6 vs 2; rHuEPO vs placebo, respectively).

The results of this study are encouraging; this suggests that rHuEPO is a potential alternative to allogenic blood products in intensive care. We should point out, however, that this study did not use any transfusion criteria; the decision to transfuse was left to the doctor's discretion. The study did not document the hemoglobin value or other criterion for transfusing patients. It would therefore be difficult and premature to conclude that rHuEPO administration in intensive care can reduce the number of transfusions. Nor did the authors indicate the length of stay in intensive care, making it difficult to interpret their results given that transfusion rates vary according to length of stay in intensive care[4].

Moreover, because this study used many exclusion criteria, it cannot easily be generalized or applied to a mixed population of critically ill patients. Many of these exclusion criteria are typical of patients hospitalized in intensive care. Finally, it would have been helpful if the results had been analyzed based on a disease severity score to target patients most likely to benefit from this approach.

Lastly, in a double-blind, multicenter, prospective trial, Still et al studied rHuEPO response in a special population of 40 acutely burned patients[21]. Patients with burns from 25% to 65% total body surface were randomized to receive either 300 U/kg rHuEPO intravenously or a placebo daily for 7 days. The dose was then decreased to 150 U/kg rHuEPO every other day for 23 days. Patients in both groups were transfused to maintain a hemoglobin of 10 g/dL or 8 g/dL after major surgeries. There were no significant differences between groups at enrollment in patient characteristics. After 30 days, there was no statistically significant difference in hemoglobin, hematocrit, blood loss and transfusion requirements.

Validity of trials and analysis

A critical appraisal of randomized controlled trials is summarized in table 2.[2,7,17,21-23] The method of randomization is not described in three studies.[2,17,21] The timing of randomization and concealment of allocation is indicated in table 2. Baseline balance was obtained in three of these trials.[7,17,21]

Only two studies[7,21] presented an intention-to-treat analysis. All patients who were entered into the trial of Corwin et al[7] were accounted for at its conclusion and were followed for a total of 42 days after randomization. In the study of Gabriel et al[17], patients who entered the study but who were treated for less than 3 weeks because of discharge from the intensive care unit or death, were excluded from data analysis. One patient was withdrawn from the study of van Iperen et al[2] because of fulminant bleeding and 15 patients were excluded from data analysis. The reporting of losses is indicated in table 2. Two studies looked at the impact of rHuEPO administration on the need for transfusion[7,21] but only one clearly mentioned that a power analysis was performed before random allocation.[7] The statistical analysis was valid in all trials.

One study was an open trial[2], it is unknown whether the groups were treated equally apart from the experimental therapy. Only two studies were double-blinded[7,21] whereas the blinding was not mentioned in the study of Gabriel et al.[17]

The outcome was considered clinically important only in the study of Corwin et al[7] and in the study of Still et al.[21] The other trials[2,17] reported only end points on laboratory measurements whereas a positive clinical impact on the total number of red blood cell units transfused was demonstrated in Corwin's study[7].

Future Studies

In recent years, there has been increasing interest in restricting red blood cell transfusion. Hébert et al recently proposed a restrictive strategy to transfusion that significantly reduces transfusion in intensive care without affecting mortality.[6] These recent data should be taken into account in any assessment of the impact of rHuEPO administration on the need for transfusion in intensive care. The Hébert study showed that with a restrictive approach to transfusion it is possible to achieve a statistically significant reduction in the mean number of transfused units per patient when compared with a liberal approach (2.6 ± 4.1 vs 5.6 ± 5.3 respectively; $p < 0.01$).[6] In addition, the restrictive approach made it possible to completely avoid transfusion in 33% of patients, whereas all of the patients treated with a liberal approach received at least one transfusion.[6] In future studies on rHuEPO administration in intensive care, a transfusion threshold of 7 g/dL should be used for most critically ill patients. Such studies would have to show that rHuEPO administration combined with a restrictive approach advocated by Hébert results in an additional significant decrease in the need for transfusion, compared with use of the restrictive strategy alone. Other potential benefit to the anemic critically ill patient resulting from rHuEPO can be the possibility to increase oxygen delivery without exposure to the negative effects of transfused blood.[24]

Although there have been no studies on the safety of administering high doses of rHuEPO in intensive care, the incidence of adverse effects does not appear to be higher compared to placebo.[2,7] Corwin et al did not report any statistically significant difference between rHuEPO and placebo in terms of mortality, deep vein thrombosis or thrombocytopenia.[7] No statistically significant differences in the frequency of thrombocytosis have been reported.[2,7] However, an increase in blood pressure is generally observed in patients with renal disease who take rHuEPO chronically,[16] and this increase in blood pressure could also be found in intensive care patients. The level of care provided in an intensive care setting allays these concerns; however, further studies will be necessary to determine the safety of administering high doses of rHuEPO in this context. Moreover, some authors report that elevated endogenous erythropoietin levels, independent of hemoglobin concentrations, are indicative of a poor prognosis in patients in septic shock.[25] Future studies will need to be performed to determine if elevated erythropoietin levels may be harmful to the patient.

The amplification of erythropoiesis that results from the administration of rHuEPO increases the need for iron.[16,19] Consequently, these patients must receive an iron supplement to optimize their response and prevent functional iron deficiency.[16,19] The studies cited in this article describe various types of iron supplementation.[2,7,17,21] In Gabriel's study,[17] patients received 13.5 mg iron intravenously as well as a source of oral iron in their feedings. In van Iperen's study,[2] patients received 20 mg iron iv daily. In Corwin's study,[7] patients received 150 mg of elemental iron orally each day. Parenteral iron was given to patients who were unable to take oral iron (dose not described).[7] In Still's study, oral iron was given at the discretion of the clinician.[21] A patient's need for iron subsequent to rHuEPO administration may exceed the amount that can be provided by oral supplementation, a factor that limits its usefulness.[16] The intramuscular route of administration is often erratic and should be used with precaution in patients on anticoagulation therapy. Consequently, the intravenous route appears to be the route of choice for most critically ill patients.

However, only low doses of intravenous iron are probably appropriate in intensive care because iron can promote the growth of bacteria.[26] Iron supplementation should be administered to all patients except those with increased serum iron and transferrin saturation.[16] The use of serum ferritin as a marker for iron deficiency is limited in MODS since inflammation can result in a false elevation of the ferritin values.[27] Care should be taken in future studies to optimize iron supplementation and evaluate folates and vitamin B_{12} deficiency so that the real efficacy of rHuEPO in intensive care is not underestimated. Moreover, rHuEPO was administered intravenously in two studies[17,21] but should be administered subcutaneously to maximize its effects.[16,19]

Finally, rHuEPO is a very expensive medication and pharmacoeconomic analysis should be performed in future studies. The cost of rHuEPO as used in Corwin's study was on average $ 1,890 per patient.[7] Future economic analysis should take into account the cost of rHuEPO, iron supplement, blood transfusion and the potential savings resulting from the avoidance of adverse reactions related to blood transfusion.

Summary

In summary, few randomized controlled trials explore the role of rHuEPO in the intensive care. Only one was a large randomized clinical trial but presents many limitations. Future outcome and safety studies comparing rHuEPO vs placebo will need to be performed with clinical end points such as end organ morbidity, mortality, transfusion requirements and pharmacoeconomic analysis. rHuEPO appears to improve the erythropoietic response but optimal rHuEPO dosage and the real impact of rHuEPO on the need for transfusion in intensive care remain to be determined. So far, rHuEPO cannot be recommended to reduce red blood cell transfusions in anemic critically ill patients.

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ARTICLE II (Table 1): Randomized studies on the use of rHuEPO with adult patients in intensive care

References	Design	Patients	Medications	Outcomes
Still et al (1995)[21]	Randomized, prospective, multicenter, double-blinded, placebo-controlled	40 acutely burned patients	rHuEPO 300 U/kg iv daily for 7 days, then 150 U/kg every 2 days for 23 days ± oral ferrous sulfate or placebo ± oral ferrous sulfate	▪ No significant differences in hemoglobin, hematocrit, blood loss and transfusion requirements
Gabriel et al (1998)[17]	Randomized, prospective, placebo-controlled	19 patients in intensive care with MODS	rHuEPO 600 U/kg iv 3 times a week for three weeks + iron 13.5 mg iv + folic acid 0.4 mg iv + vitamin B_{12} 5 mg iv daily or placebo + iron 13.5 mg iv + folic acid 0.4 mg iv + vitamin B_{12} 5 mg iv daily	▪ Significant increase in erythrocyte count with rHuEPO vs placebo (4% ± 0.9 vs 1.9% ± 0.5; $p<0.05$) ▪ No significant differences in the need for transfusion
Corwin et al (1999)[7]	Randomized, prospective, multicenter, double-blinded placebo-controlled	160 patients in medical and surgical intensive care	rHuEPO 300 U/kg sc daily for 5 days, then every 2 days for a maximum of 6 weeks + 150 mg of elemental iron orally or placebo + 150 mg of elemental iron orally	▪ rHuEPO significantly reduced transfusions requirements vs placebo (166 vs 305; $p<0.002$). ▪ 45% patients either transfused at least once or died with rHuEPO vs 55% with placebo (NS) ▪ No significant differences in mortality or incidence of side effects

van Iperen et al (2000)[2]	Randomized, open trial	36 patients in medical, surgical, trauma and neurological intensive care	Folic acid 1 mg iv daily for 14 days or folic acid 1 mg iv daily + iron 20 mg iv daily for 14 days or folic acid 1 mg iv daily + iron 20 mg iv daily for 14 days + rHuEPO 300 U/kg sc every 2 days X 5 doses	▪ Reticulocyte count increase with rHuEPO vs baseline values (from 56 ± 33 x 10^9/L to a maximum of 189 ± 97 x 10^9/L on day 13; $p<0.05$) ▪ Significant increase in the number of red blood cell with rHuEPO vs placebo or iron ▪ No significant differences in hemoglobin concentration

rHuEPO: recombinant human erythropoietin ; iv: intravenously ; MODS: multiple organ dysfunction syndrome; sc : subcutaneously ; NS : not statistically significant

ARTICLE II (Table 2): Randomized controlled trials with rHuEPO in the intensive care unit : critical appraisal

(adapted from Doig GS[22])

Study	Still[21]	Gabriel[17]	Corwin[7]	van Iperen[2]
Randomization technique				
Method described	N	N	Y	N
Concealed	Y	N/R	Y	N
Timing	ICU day 3	ICU day 1	ICU day 3	ICU day 1 to discharge
Baseline balance	Y	Y	Y	N
All patients accounted				
Follow-up	Up to 30 d	Up to 21 d	Up to 42 d	Up to 21 d
Reporting of losses	N	Y	Y	Y
All patients analyzed	Y	N	Y	N
Blinding	Y	N/R	Y	N
Equally treated	Y	No clear evidence	Y	No clear evidence
Study outcome				
Clinically important	Y	N	Y	N
Analysis of results				
Valid	Y	Y	Y	Y
Power analysis	N/R	N/R	Y	N/R
Helpful to patients				
Benefit of intervention on outcome	No benefit	No benefit	Y	No benefit
Study level *	II†	II†	Ib‡	II†

N :no ; Y : yes ; N/R : not reported ; ICU : intensive care unit ; d :days ; * Sackett's criteria for the clinical appraisal of evidence[23] ; † small randomized trials with uncertain results; ‡ Large randomized trials

ARTICLE III : Iron metabolism in critically ill patients. Crit Care 2004;8:356-62.*

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ABSTRACT

Critically ill patients frequently develop anemia due to several factors. Iron withholding mechanisms caused by inflammation contribute to this anemia. The iron metabolism imbalances described or reported in all intensive care studies are similar to the values observed in anemia of inflammation. The administration of iron could be useful in the optimization of recombinant human erythropoietin activity however this could be at the expense of bacterial proliferation. Since there is a lack of evidence to support either oral or intravenous iron administration in intensive care patients, further studies are necessary to determine the efficacy and safety of iron supplementation in conjunction with recombinant human erythropoietin in critically ill patients. We review the mechanisms leading to iron sequestration in the presence of inflammation. This article also reviews the literature describing the iron status in critically ill patients and explores the role of iron supplementation in this setting.

Keywords : iron metabolism, critical illness, erythropoiesis

FID = functional iron deficiency; ICU = intensive care unit; IL-1 = interleukin-1; IL-6 = interleukin-6; IV = intravenous; MODS = multiple organ dysfunction syndrome; rHuEPO = recombinant human erythropoietin; TNF = tumor necrosis factor

INTRODUCTION

Recent observational studies have shown that most patients in the intensive care unit (ICU) become anemic within a few days [1-3]. In Europe,

approximately 37% of patients receive transfusions and close to 70% of those remaining in the ICU for more than seven days are transfused [1]. The CRIT STUDY showed similar results in the United States [2]. A number of factors contribute to this anemia, including the acute inflammatory reaction typical of these patients [5]. Anemia of inflammation has been clearly described in patients with cancer, chronic inflammatory disease and chronic infection [5-10]. This type of anemia is related to the release of mediators that cause a blunted erythropoietic response and activation of red blood cell catabolism by macrophages. The inflammatory state also results in decreased mobilization of iron stores from the reticuloendothelial system, leading to the development and persistence of anemia [5-10].

In recent years, special attention has been paid to limiting the number of transfusions received by ICU patients. Limiting blood collection [1] and restrictive transfusion thresholds [11] are among the strategies that have been adopted for blood conservation. Although the optimal dose of recombinant human erythropoietin (rHuEPO) in the intensive care setting has yet to be determined, its use constitutes another blood conservation strategy [12,13]. Erythropoietin's ability to stimulate erythrocyte production is highly dependent on the availability of iron. Understanding iron metabolism in this patient population is important in order to act on the mechanisms and causes of anemia in critically ill patients. The decrease in iron availability seen in inflammatory diseases may contribute to inadequate erythropoiesis in ICU patients. Is the iron metabolism imbalance seen in chronic inflammatory states similar to that found in ICU patients? To what extent do these disturbances affect erythropoiesis and the patient's response to exogenous erythropoietin? Should iron supplements be administered? The purpose of this article is to review the impact of inflammation on iron status and to review the studies that describe iron metabolism in ICU patients. We also explore the role of iron supplementation in this setting.

IRON WITHHOLDING MECHANISMS IN THE PRESENCE OF INFLAMMATION

Most of the iron available for erythropoiesis comes from the catabolism of senescent red blood cells by the macrophages in the reticuloendothelial system [6-10]. The iron, transported by transferrin, binds to receptors on the surface of the erythroblasts and is used in hemoglobin synthesis [6-10]. The iron also binds to apoferritin to create iron stored in the form of ferritin. Under normal conditions, there is a balance between the iron transport paths and the iron stores [6-10].

Ferritin is an inflammatory protein (acute-phase reactant). The synthesis of ferritin is increased by circulating cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF). When these inflammation mediators are present, iron stored in the form of ferritin tends to increase and the mobilization of iron stored from the reticuloendothelial system tends to decrease. The balance between the amount of iron available for erythropoiesis and the stored iron is disturbed **(Figure 1)** [6-10]. Hypoferremia rapidly sets in due to an increase in the iron-binding capacity of ferritin to the detriment of transferrin. The severity of the hypoferremia depends on the severity of the underlying inflammatory disease [6].

IL-I also stimulates lactoferrin synthesis. Lactoferrin is a circulating protein that binds iron with greater affinity than transferrin [6,7,9]. In the presence of inflammation, iron bound to lactoferrin is captured by the macrophages, then stored in the form of ferritin, thereby withholding iron from the erythroid precursors **(Figure 1)** [6,7,9]. The recent demonstration that a novel protein, hepcidin, is greatly upregulated in response to inflammation via interleukin-6 (IL-6) is yet another potential mechanism of iron sequestration [14]. Hepcidin could be a central mediator of decreased iron absorption through the gut, sequestration of iron in macrophages and has shown homology to naturally

occurring antimicrobial proteins [14]. Changes related to inflammation therefore lead to less iron bound to transferrin and less iron available for erythropoiesis [6-10]. This process has been hypothesized to have evolved as a "tug-of-war" phenomenon resulting in an iron deficient milieu which would lead to compromised microorganism proliferation **(Figure 1)** [7,9].

Overall, these mechanisms result in a decrease in serum iron < 9 μmol/L, a decrease in transferrin levels < 3 g/L and a decrease in the transferrin saturation percentage between 10% and 20%, with normal or elevated ferritin levels > 300 μg/L [8,10]. Elevated ferritin levels in inflammatory states make it difficult to evaluate iron stores. However, a patient presenting with a ferritin concentration > 200 ug/L probably does not have an iron deficiency whereas a value of < 30 μg/L does indicate iron deficiency (ferritin levels between 30 to 200 ug/L in inflammatory conditions) [6,10].

In contrast with these iron deprivation mechanisms, it seems that iron deficiency could impair immune defense. Little evidence is available on iron and its effects on direct immunity. However, in vitro studies suggested that iron deficiency depresses some aspects of cell-mediated immunity [15]. In a review of the literature, Oppenheimer reported deleterious effects of iron deficiency on lymphocyte, neutrophil and macrophage function [15]. Whether these effects depend on the severity of iron deficiency is not known. Not only iron deficiency but iron overload also seems to impair polymorphonuclear leucocyte function, reducing phagocytic function and bacterial killing [16]. Data regarding iron and its effect on immune system are conflicting. More studies are needed to clearly elucidate the role of iron on immunity.

IRON METABOLISM IN ICU PATIENTS

Inflammation is implicated in many critically ill disorders. Indeed, clinical evidence of systemic inflammation is present in almost all patients developing

multiple organ dysfunction syndrome (MODS), a common complication observed in critically ill patients [16]. The severity of the host inflammatory response is highly related to the development of MODS and is frequently seen in patients with sepsis. The anemia of inflammation is a hypoproliferative anemia defined by a low serum or plasma iron concentration in the presence of adequate reticuloendothelial iron stores [5]. It is possible that iron metabolism involved in the anemia of chronic disease is similar to the anemia seen in critically ill patients because of the presence of inflammatory mediators in both conditions. To describe iron metabolism in critically ill patients, a search was performed on MEDLINE database from 1966 to December 2004 for articles describing iron metabolism in adult critically ill patients. The term "critical illness" was combined with the terms "iron", "erythropoiesis" and "anemia". All English language articles describing iron metabolism in the ICU setting were retained. The bibliographies of these articles were reviewed for additional references. Five observational studies described iron metabolism in ICU patients [3,18-21]. One study provided indicators of iron status [22]. All studies described iron metabolism in a population of nonbleeding, acutely ill patients. Studies on iron metabolism mediators are summarized in **Table 1**.

Two studies described iron metabolism throughout the ICU stay [3,18]. The first study described iron status in critically ill surgical patients. In 1989, in a study involving 51 patients, Bobbio-Pallavicini et al. observed a decrease in serum iron and elevated ferritin levels in over 75% of patients on their third day of hospitalization in the surgical intensive care unit [18]. Table 1 shows the variations in iron metabolism indicators during intensive care for all patients. Ferritin values remained abnormally elevated among all patients during their stay in ICU. Patients with sepsis leading to MODS had the highest ferritin values. Indeed, among patients who developed post-operative sepsis, there was a significant drop in hemoglobin (107.3 g/L vs 125.7 g/L; $p < 0.001$), a significant increase in ferritin levels (1585 μg/L vs 641 μg/L; $p< 0.001$) and a significant decrease in transferrin (1.44 g/L vs 1.95 g/L, $p < 0.001$) compared to

their pre-sepsis state. However, sepsis did not significantly affect serum iron levels. When sepsis resolved, the transferrin and hemoglobin values increased. Ferritin decreased dramatically with sepsis resolution (1585 μg/L vs 472 μg/L; $p < 0.001$).

The incidence, severity, characteristics and causes of anemia in 96 patients who had been in a medical ICU for more than three days were assessed in the second study [3]. Fifteen per cent of the patients experienced acute bleeding; 39% of the patients were transfused during their stay in the ICU. While in the ICU, 71 patients (74%) developed anemia (Hb < 110 g/L) which could not be explained by blood loss alone. Elevated ferritin values and decreased transferrin saturation values were observed in these patients (Table 1). During the first 2 weeks of the ICU stay, more than 50% of patients had abnormal serum iron concentrations. These values continued to be observed for over four weeks, as reported in the study performed by Bobbio-Pallavicini et al. [18]. Increased iron sequestration secondary to inflammation could explain the increased ferritin levels and the reduced serum iron concentration and transferrin saturation observed in these studies.

Two other studies in critically ill patients reported their observations on iron metabolism on the first few days of admission [19,22]. In the fisrt study, Rodriguez et al. present iron metabolism values for patients with hematocrit < 38% on the second or third day in the ICU [19]. These values come from screening data for a study comparing rHuEPO administration to placebo in surgical and medical ICU patients [23]. Of the 184 patients screened for this study, 16 had transferrin saturation < 15% or ferritin < 50 μg/L and were not included. Eight patients had a vitamin B_{12} deficit or a folate deficit and were also excluded. The remaining 160 patients were included. The admitting diagnoses were pneumonia (24%), respiratory diseases (21%) and trauma (15%). The values for serum iron, ferritin and transferrin saturation for the 160 patients are comparable to values seen in anemia of inflammation and are presented in

Table 1. The mean hemoglobin at the beginning of the study was 103 ± 12 g/L. Although these values were measured at baseline, prior to the administration of the first dose of study medication, this study was not designed to study iron metabolism in consecutive patients.

The second study, conducted by Elliot et al., reported iron metabolism abnormalities in 25 ICU patients with acute failure of at least one organ [22]. Patients with chronic renal failure, coagulopathy or active bleeding were excluded. In the majority of patients in the ICU for more than 12 hours, they found decreased mean serum iron levels (1.0-12.6 μmol/L), increased mean ferritin levels (37-2376 μg/L) and decreased mean transferrin levels (0.57-2.46 g/L). Ferritin values were abnormally elevated (>300 μg/L) in 16 patients and greater than 1000 μg/L in three patients. Iron metabolism imbalances set in fairly quickly after ICU admission, along with the inflammatory process reflected by the raised concentrations of IL-6 and C-reactive protein. The mean hemoglobin at admission was between 80 et 110 g/L. The anemia observed in the Rodriguez and Elliot studies was not secondary to active bleeding or coagulopathy because these etiologies were exclusion criteria [19,22]. However abnormal iron metabolism could have contribute to this disorder. Mean values are not reported in this study and therefore are not presented in **Table 1**. It should be noted that the patients in this observational study received a daily 200 mg supplement of oral ferrous sulfate (or equivalent) that may have affected the results.

Finally, patients admitted to the ICU for multiple trauma also seem to quickly develop hypoferremia secondary to inflammation. Iron metabolism in 23 severely traumatized patients was evaluated by Hobisch-Hagen et al. [20]. On admission to the ICU, they presented with an average hemoglobin level of 100 g/L (68-129 g/L). Twelve hours after admission to the ICU, ferritin levels were markedly elevated (> 300 μg/L). The elevated levels persisted beyond one week. Reduced serum iron concentrations on the second day of hospitalization

were statistically significant, compared to admission, and remained lower for more than a week. Serum transferrin was low and did not change during the ICU stay. Indicators of iron status for this study are presented in Table 1 and compatible with iron parameters usually seen in the presence of inflammation.

In summary, these observational studies all demonstrate that critically ill patients present a decrease in availability of iron along with an elevated ferritin levels. In light of the data presented, iron metabolism in ICU patients seems to behave in the same way as in chronic inflammatory disease. The iron metabolism imbalances described or reported in all of the studies are similar to the values observed in anemia of inflammation. Indeed, elevated ferritin > 300 μg/L, serum iron < 9 μmol/L, transferrin saturation between 10% and 20%, and transferrin levels < 3 g/L are generally observed in critically ill patients **(Table 1)**. Iron metabolism disorders set in within the first few days. Ferritin remained at particularly elevated levels throughout their ICU stay, reflecting the inflammatory condition of these patients. Therefore, iron metabolism disorders probably contribute to the anemia observed in ICU patients.

Functional iron deficiency (FID)

Unlike iron deficiency anemia, patients with inflammation may have normal iron stores but might present a FID. FID refers to the inability to use iron efficiently for erythropoiesis, in spite of adequate iron stores. FID may develop with rHuEPO therapy and might be a cause of poor response. FID is observed in chronic dialysis patients receiving rHuEPO. The increased erythropoiesis activity induced by rHuEPO exceeds the amount of functionally available iron. FID may also occur in inflammatory conditions when the iron is locked away and stored by the reticuloendothelial system, preventing the release of the iron required for erythropoiesis. A decrease in transferrin saturation will occur in spite of normal or elevated ferritin. FID has been defined by the presence of more than 10% of hypochromic red blood cells. An observational study on the

prevalence of FID on admission to the ICU was conducted by Patteril et al. on 51 patients [21]. In this study, a patient was considered to have a FID if more than 10% of the red blood cells were hypochromic. Upon admission to the ICU, 35% of patients (95% CI 22-48%) presented FID. The mean APACHE II scores of patients with and without FID were comparable. Anemia was no more severe among patients with FID than in those without FID (average hemoglobin concentration of 107 g/L vs 108 g/L respectively). The mean length of stay in the ICU was statistically increased among patients with FID (7.6 days vs 3.3 days; $p < 0.0007$). The severity of FID also correlated with the duration of ICU stay. Thus, FID could reflect the severity of the critical illness. However, FID was not associated with APACHE II scores and no difference in the mortality was observed between the two groups. Of course, this could be due to a lack of power and further studies are needed to determine whether FID in critically ill patients is simply a marker of nutritional status or a predictor for outcome. Iron stores are difficult to evaluate in the presence of inflammation because ferritin is frequently increased. The ferritin values of both groups of patients are presented in Table 1.

SHOULD WE SUPPLEMENT CRITICALLY ILL ANEMIC PATIENTS WITH IRON ?

Considering the physiopathology of the anemia of inflammation, it is unlikely that iron supplementation would further stimulate erythropoiesis unless iron deficiency is masked by elevated ferritin levels [6,7]. Only one randomized open-label prospective study evaluated erythropoietic response to the administration of iron supplementation in anemic critically ill patients [24]. In this study, all patients (36 patients) received 1 mg folic acid daily. One-third of the patients received no additional therapy. The iron group (12 patients) received 20 mg intravenous (IV) iron supplementation daily for 14 days. The rHuEPO group (12 patients) received IV iron with 300 U/kg of rHuEPO every two days for 14 days. Compared to the levels in the other two groups, the elevation in

reticulocyte counts was statistically significant only in the rHuEPO group. Reticulocyte counts increased in the rHuEPO group from 56 ± 33 x 10^9/L to a maximum of 189 ± 97 x 10^9/L on day 13. No such increase was seen in the iron group. No significant difference was observed between the three groups in terms of hemoglobin concentration.

Iron supplementation with rHuEPO

Administration of rHuEPO generally makes it possible to alleviate anemia secondary to chronic inflammatory disease. A few studies have shown that rHuEPO administration also stimulates erythropoiesis in ICU patients with acute inflammatory states [12,13]. Recently, a large-scale study demonstrated that rHuEPO together with oral iron supplementation reduced the need for blood transfusions in ICU patients [13]. The amplification of erythropoiesis that results from the administration of rHuEPO increases the need for iron. Consequently, rHuEPO must be used in conjunction with an iron supplement to optimize the eryhropoietic response and prevent FID. Given the high prevalence of FID in ICU patients [21], it would appear essential to provide iron supplementation for critically ill patients receiving rHuEPO.

Oral supplementation such as that used recently in the study by Corwin et al. [13] may not be optimal for all ICU patients because the gastrointestinal tract is not always functional and iron absorption is poor and erratic. Moreover, decreased iron gut absorption by increased hepcidin production and other mechanisms (particularly related to the underlying condition of the patient) may predispose to inadequacy of oral iron therapy. Nevertheless, a significant reduction in transfusion needs was shown in this study [13].

Whether iron supplementation is necessary in these patients or whether the response might have been improved with IV iron remain to be determined. Iron supplementation clearly improves the response to rHuEPO. It has been shown

that IV iron administration with rHuEPO is beneficial for many dialysis patients and has become standard therapy for several patients [25]. Furthermore, administering an IV iron supplement with rHuEPO could make it possible to optimize erythropoietic response in inflammatory states, as demonstrated in patients with rheumatoid arthritis [26] and Crohn disease [27]. However, IV iron supplementation in the ICU setting may prove hazardous, given the hemodynamic adverse effects that are possible with certain formulations of parenteral iron and the risk to promote the growth of bacteria.

Iron supplementation and risk of infection

Iron is an essential component of bacterial growth [9,28]. Iron sequestration during inflammation could represent a defense mechanism [9,28]. However, iron chelation with siderophores allows bacterial proliferation in a reduced-iron environment [9,28]. Therefore iron administration could in theory increase the host susceptibility for bacterial infections.

No data on critically ill patients are available to support such a hypothesis. The EPIBACDIAL study performed in 988 patients with chronic renal failure requiring hemodialysis did not observe a relationship between iron administration and bacteremia (54.0% in those supplemented with iron vs 52.9% in those without; p=0.88) [29]. The data from the EPIBACDIAL trial were revised by Hoen et al. to evaluate the potential role of IV iron administration on the risk of bacteremia [30]. High-frequency and high-dose IV iron administration were associated with an increased incidence of bacteremia . The incidence also increased if rHuEPO was given (RR 5.5; 95% CI 1.29 to 23.5). These data from chronic renal failure patients could suggest a link between IV iron administration and infection. Therefore, IV iron administration to ICU patients who are already infected could be risky.

In the Corwin et al. study, oral iron supplementation was given with rHuEPO to all patients[13] . If oral iron was not tolerated, patients received IV iron supplementation. Despite the fact that oral iron administration did not appear to produce deleterious effects in the Corwin's study, the safety of iron administration should be further investigated before a widespread utilization of iron replacement in the ICU.

CONCLUSION

So far, six studies have described iron metabolism in critically ill patients. A decrease in the availability of iron along with elevated ferritin levels are generally observed. In these patients, iron metabolism is similar to that found in inflammatory diseases and may contribute to the anemia observed in ICU patients. Iron deficiency is difficult to evaluate in the presence of inflammation. Future studies using a novel approach based on hematologic indices would be useful [31]. Additional studies are necessary to determine the utility of iron supplementation alone in critically ill patients.

At the present time, there is a lack of evidence to support either oral or IV iron administration in critically ill patients. Further studies are needed to determine the safety of iron supplementation in ICU patients, especially the link between iron and clinical infectious risk. A large randomized study comparing IV iron, oral iron and no iron supplement in rHuEPO-treated critically ill patients would be of interest.

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Table 1 :

ARTICLE III (Table 1): Studies describing iron metabolism in ICU patients

Studies	Time of measurements	Iron [μmol/L] mean	Ferritin [μg/L] mean	Transf. Sat. [%] mean	Transferrin [g/L] mean
		Reference Values with Inflammation [8,10]			
		< 9	*30-200*	*10-20*	*< 3*
Surgical ICU patients [18]	Week 1	4.1	652	12.8	1.7
	Week 2	4.1	1234	11.9	1.5
	Week 3	4.6	1536	13.4	1.4
	Week 4	6.9	1367	18.7	1.4
Medical ICU patients ≥ 4 days [3]	Days 1-2	4.8[a]	471[a, b]	16[a]	1.4[a, c]
	Days 6-8	6.0[a]	767[a, b]	15[a]	1.3[a, c]
	Days 13-15	6.5[a]	795[a, b]	22[a]	1.3[a, c]
	Days 20-25	8.1[a]	774[a, b]	24[a]	1.4[a, c]
	Days 31-40	7.8[a]	723[a, b]	20[a]	1.5[a, c]
Medical & surgical ICU patients [19]	Day 2-3	4.9[d]	727[b]	16	NR
General ICU patients [21]					
FID	Day 1	NR	342	NR	NR
No FID	Day 1	NR	292	NR	NR

Multiple mechanical trauma patients [20]	Day 1	9.5	832	NR	1.7[c]
	Day 2	3.9	547	NR	1.7[c]
	Day 4	3.4	466	NR	1.5[c]
	Day 6	4.0	530	NR	1.6[c]
	Day 9	5.0	842	NR	1.6[c]

FID, functional iron deficiency; ICU, intensive care unit; NR, not reported; Transf. Sat, transferrin saturation; [a] median values; [b] Ferritin ng/mL multiplied by 1 to convert to ferritin ug/L; [c] Transferrin mg/dL multiplied by 0.01 to convert to transferrin g/L; [d] Iron ug/dL multiplied by 0.1791 to convert to iron umol/L

ARTICLE III (FIGURE 1) : Decrease in iron recycling in the presence of inflammation

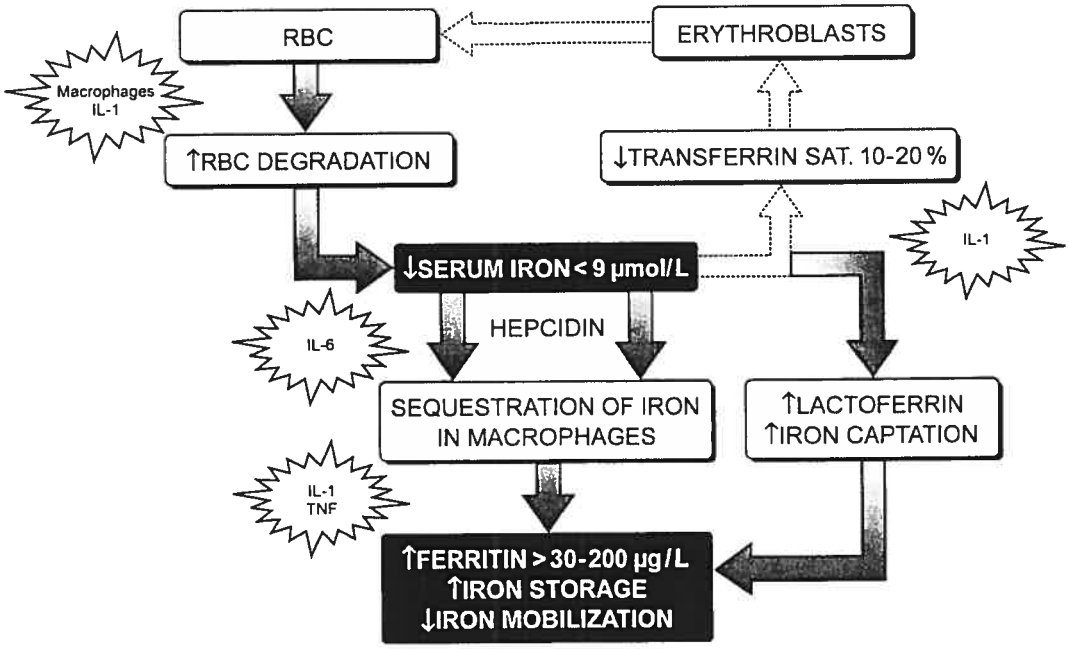

figure 1

Iron metabolism in critically ill patients. Most of the iron available for erythropoiesis comes from the catabolism of senescent red blood cells by the macrophages in the reticuloendothelial system. The synthesis of ferritin is increased by IL-1 and TNF. Hypoferremia rapidly sets in due to an increase in the iron-binding capacity of ferritin to the detriment of transferrin. IL-l also stimulates lactoferrin synthesis. Iron bound to lactoferrin is captured by the macrophages and stored in the form of ferritin. Hepcidin could be a central mediator of iron sequestration in macrophages. **Grey arrows: pathways increased by inflammation; broken lines: pathways decreased by inflammation; IL-1, interleukin-1; IL-6, interleukin-6; RBC, red blood cells; TNF, tumour necrosis factor; TRANSFERRIN SAT, transferrin saturation.**

ARTICLE IV : Epoetin Alfa combined with a restrictive transfusion approach in critically ill patients : is 40 000 units once weekly the optimal dosage ?

INTRODUCTION

Anemia is a frequent complication in intensive care unit (ICU) patients. This multifactorial anemia sets in quickly and increases the use of blood transfusion in critically ill patients. In recent years, clinicians became aware of the importance of limiting blood transfusion. Traditionally, the administration of red blood cell units to critically ill patients has been a common practice in order to maintain hemoglobin concentrations above 100 g/L.[1] The Transfusion Requirement in Critical Care (TRICC) trial demonstrated that this approach does not offer any advantages over a restrictive transfusion approach and, for some patients, may even be harmful.[2] However, blood transfusion is still common in ICUs. Recently, the Anemia and Blood Transfusion in Critical Care (ABC) investigators reported that 37% of ICU patients in western Europe were transfused and that close to 70% of these patients received a transfusion within 48 hours of their admission to the ICU.[3] Also, a prolonged ICU length of stay led to a constant need for transfusion.[3] The CRIT study conducted in the United States showed similar results.[4]

The administration of recombinant human erythropoietin (EPO) is one of the strategies proposed to decrease the need for transfusions in critically ill patients. An important study conducted by Corwin et al. in 2002 showed that administering 40 000 units of EPO once weekly reduced the number of transfused patients by 10% and reduced overall transfusion needs by 19%, compared with placebo.[5] The results of this study are interesting for a blood conservation program but offer no clinical benefits. Moreover, it is not known whether a similar reduction in the need for transfusion could have been achieved simply by using a transfusion threshold of 70 g/L, without having to administer EPO.[6] It has not been demonstrated that EPO provides additional

benefits to a restrictive transfusion approach in terms of either clinical outcome or the conservation of blood supplies. Consequently, in the absence of a restrictive transfusion approach such as the one proposed in the TRICC trial, the administration of EPO in ICU does not appear to be optimal or judicious.[2]

The effect of EPO should be maximized during hospitalization in the ICU, where there is a greater need for transfusion. No pharmacodynamic studies evaluating different EPO regimens are available. Based on the current data in the literature, it is not possible to conclude whether an optimal effect is achieved during the ICU stay with a once-weekly EPO dose of 40 000 units.

Our hypothesis was that a dose of EPO > 40 000 units per week could provide higher reticulocyte count and higher hemoglobin concentrations in ICU patients. We designed a study to determine whether a dose of EPO > 40 000 units per week, combined with a restrictive transfusion strategy, makes it possible to optimize erythropoiesis and hemoglobin concentrations specifically during the ICU stay. Our study also measures variations in hemoglobin concentrations when EPO is administered in the context of a restrictive transfusion approach.

METHODOLOGY

Objectives

The study was a prospective, open-label, multiple center trial. The primary objective was to compare erythropoietic response to different doses of EPO expressed as a mean variation in reticulocytes and hemoglobin during the ICU stay, up to 28 days. When this study was elaborated, EPO use with critically ill patients had not been approved in Canada. Therefore, we also evaluated the adverse events associated with EPO use.

Study Population

This study was conducted in the surgical and medical ICU of three hospitals providing specialized and ultraspecialized care in Quebec between July 2003

and December 2004. The research protocol was approved by the ethics and research committee at each of the hospitals. The criteria for inclusion were: hospitalization in ICU > 72 hours, age > 18 years, APACHE II score > 15, hemoglobin < 110 g/L at time of inclusion and signed informed consent by the patient or a family member. The criteria for exclusion were: known hypersensitivity to epoetin alfa or human albumin, pregnancy or breast feeding, hereditary hemoglobinopathy and coagulation disorders, active bleeding (30% drop in hemoglobin or hematocrit in 24 hours or less), chronic dialyzed illness, poorly controlled epilepsy over the previous 6 months or increased risk of convulsions (head trauma, cerebrovascular accident), cranial trauma, autoimmune hemolysis (Coombs +), recent androgenic therapy and essential thrombocytosis. Were also excluded : patients unable to or not wanting to receive transfusions, patients already on epoietin alfa or darbepoietin alfa, patients with acute ischemic cardiac disease (myocardial infarction or unstable angina) at the time of recruitment, patients who were expected to be discharged within 24 to 48 hours, patients with uncontrolled hypertension (systolic blood pressure >200 or diastolic blood pressure >110) after adequate antihypertensive therapy, acutely burned patients, patients with an admitting diagnosis of acute gastrointestinal bleeding and subjects who had received phase II experimental drug or therapy within 30 days prior to this study. Patients receiving experimental contrast agents were excluded if treated within 3 days prior to study entry.

Treatment Plan

Patients included in the study received either 40 000 units of EPO (Ortho Biotech, 40 000 units/mL) via subcutaneous injection once a week for a maximum of 4 doses administered on days 1, 8, 15 and 22 during their ICU stay (group A) or 40 000 units of EPO via subcutaneous injection twice a week for a maximum of 4 doses administered on days 1, 4, 8 and 12, during their ICU stay (group B). EPO was discontinued upon discharge from ICU. EPO was discontinued temporarily if hemoglobin > 125 g/L and resumed when

hemoglobin < 125 g/L to complete the missing doses. Patients were recruited successively: the first 30 patients assigned to group A, the next patients to group B. An independent safety committee determined whether the study could be pursued after considering reports of adverse events in patients in group A.

All patients received 300 mg of ferrous sulfate supplement tid either orally or via a nasogastric tube. In the event of gastric intolerance, the oral iron dose could be decreased or discontinued, at the discretion of the physician. Intravenous iron administration was not allowed. Patients receiving total parenteral nutrition could, however, receive an iron supplement by intramuscular injection.

The criteria for red blood cell transfusion were as follows: no transfusions based solely on hemoglobin values. If the patient's clinical condition required it (at the physician's discretion, for example : transient ischemic attack or dyspnea), a transfusion could be administered if hemoglobin < 70 g/L or if hemoglobin < 90 g/L in the presence of acute myocardial infarction or unstable angina.

Baseline Assessment and Follow-up

Demographic and diagnostic data were collected upon admission or at recruitment into the study. The APACHE II score was obtained within 24 to 48 hours of admission to ICU. Reticulocytes, hemoglobin and hematocrit were monitored daily during the patient's stay in ICU. Adverse events attributable to EPO were monitored daily from day 1 to day 28 of the study. Adverse events attributable to EPO were thromboembolic events (stroke, pulmonary embolism, deep vein thrombosis), hypertension, seizures, thrombocytosis and pure red cell aplasia (PRCA) in the case of patients who developed a sudden loss of efficacy or a sudden deterioration of their anemia. If PRCA was suspected and no cause could be identified, antibody titers could be obtained. Baseline screening for PRCA was performed prior to administration of the first dose of EPO and 30 days after the last dose. Blood samples were stored at -20^0C, to be analyzed at

a later time if this implication was suspected during the study. Hemoglobin and hematocrit were measured 14 days and 30 days after the last dose of EPO to monitor patients presenting with an exaggerated response.

Statistical Analysis

This study was a pilot study and was not designed to have high power to detect small differences. For financial and feasibility reasons, the present study has been designed to included 30 patients in each groups. *Baseline characteristics*: Chi Square analysis was used for categorical data; analysis of variance (one-way ANOVA) was used for continuous variables. *Primary end point*: mean changes in reticulocytes and hemoglobin during the ICU stay from baseline up to day 28 were analyzed on group B versus group A with repeated-measure analysis of variance. *Safety*: number of adverse events in group B versus group A, from baseline up to day 28. All adverse events were evaluated in terms of seriousness, causality and relatedness to study drug. Number of adverse events was analyzed with Fisher exact test on group B versus group A. Data are expressed as mean ± SD. A two-sided alpha < 0.05 was considered statistically significant.

RESULTS

A total of 58 patients were included in the study with 30 patients in group A and 28 patients in group B. The baseline characteristics of the patients in both groups were comparable (Table 1). The mean APACHE II score was 21.3 in group A and 21.9 in group B (p=0.68). At the time of inclusion, close to half of the patients were receiving a vasopressor, almost 90% of the patients were receiving an antibiotic, and approximately 73% of the patients in group A were mechanically ventilated versus 96% in group B. The elevated ferritin and decreased transferrin saturation levels observed in both groups were characteristic of an inflammatory state.

Primary Objectives

No statistically significant difference between the groups was observed in terms of daily variation in reticulocytes during their ICU stay (Table 2). An important increase in reticulocytes over baseline was observed in both groups. Reticulocytes increased by a mean baseline value of 51 ± 31 x 10^9/L to a maximum of 191 ± 75 x 10^9/L on day 11 in group A. In group B, reticulocytes increased from 65 ± 50 x 10^9/L to a maximum of 260 ± 70 x 10^9/L on day 21 (Figure 1). Mean hemoglobin during ICU stay was 91 ± 14 g/L in group A compared with 86 ± 12 g/L in group B. No significant difference was observed between the groups in terms of daily variation in hemoglobin concentrations during ICU stay (Table 2 & Figure 2).

Adverse Events and Patient Follow-up

Six patients in group A died during the study compared with 8 deaths observed in group B (p=0.55). Adverse events attributable to EPO are reported in Table 2. Mean follow-up hemoglobin values 14 days after the final dose of EPO were 101 ± 17 g/L for group A compared with 95 ± 13 g/L for group B (p=0.24). Mean hemoglobin values 30 days after the final dose were 105 ± 18 g/L compared with 96 ± 13 g/L (group A vs group B, respectively; p=0.11).

Transfusions during ICU stay

Mean pre-transfusion hemoglobin was 72 ± 9 g/L in group A and 67 ± 6 g/L in group B. Sixty-seven percent (67%) of patients in group A did not receive a transfusion compared with 46% in group B (p = 0.19). In all, 20 units of red blood cells were transfused during ICU stay to all of the patients in group A, corresponding to 0.74 units per patient. Patients in group B received a total of 48 units of red blood cells during their stay in ICU, corresponding to 1.7 units per patient. No patient in group A and 1 patient in group B (2%) were transfused with an hemoglobin > 90 g/L. In group A, pretransfusion hemoglobin

concentrations exceeded 80 g/L in 4 cases (20%) compared with 2 cases (4%) in group B.

Exposure to EPO and Iron

EPO : over half (55%) of the patients in group A received only one dose of EPO; 17% received 2 doses; 10% received 3 doses; and 17% received 4 doses. All patients in group B received at least 2 doses of EPO; 25% received 3 doses and 43% received 4 doses. On average, 80 000 units of EPO per patient were administered in group A compared with 120 000 units per patient in group B. This represents an exposure to EPO 1.5 times higher in group B. *Iron* : eighty-nine percent (89%) of the patients in group A received an oral iron supplement. One patient did not receive an iron supplement and two patients received iron by intramuscular injection. In group B, 96% of patients received oral iron and 1 patient did not receive iron.

DISCUSSION

We assessed whether the administration of EPO at a dose > 40 000 units per week led to increased erythropoiesis stimulation during ICU stay. Our study showed that there is no benefit to using a dose > 40 000 units per week. Prior to our study, there were no data in the literature that would have made it possible to determine the optimal EPO dose for ICU patients. A few studies, using various dosages, have shown that EPO stimulates erythropoiesis in ICU patients.[7-9] Only two studies demonstrated that EPO administration reduced the need for transfusions.[5,10] In a previous study, Corwin et al. used a much higher dose and demonstrated a decrease of close to 50% in the transfusion needs of patients receiving EPO compared with placebo.[10] In this study, the EPO doses corresponded to 300 units/kg once a day for the first five days, then every two days thereafter (approximately 100 000 units of EPO in all during the first five days, then approximately 60 000 units per week for a 70 kg patient).[10] Based on the more modest results of the second study by Corwin et al.[5], it became necessary to determine whether an optimal effect is achieved with an EPO dose

of 40 000 units once a week. A pharmacodynamic study was required before planning a larger trial with clinical outcome such as end-organ morbidity or mortality.

Although there was no statistically significant difference between the two groups in terms of reticulocyte change during ICU stay, it is interesting to note that a trend toward an increase in the reticulocytes of patients in group B occured from study day 14 to study day 21 compared with group A (FIGURE 1 and TABLE 2). However, this observation is difficult to interpret given the small number of patients in each group at the end of the study. The reticulocytes evolution curves were much more similar from study day 1 to study day 14 (FIGURE 1 and TABLE 2). Similar results were observed in a study using EPO 300 units/kg every 2 days for 5 doses (corresponding to 20 000 units of EPO for 5 doses, for a 70 kg patient) with intravenous iron.[9] In this study, reticulocyte counts increased from $56 \pm 33 \times 10^9$/L to a maximum of $189 \pm 97 \times 10^9$/L on day 13.[9] In our study, the comparable reticulocyte variation in both groups shows that an EPO dose > 40 000 units per week does not allow for a faster, higher or more sustained response in ICU patients, with the possible exception of patients with an ICU length of stay > 14 days. This observation is probably secondary to the bone marrow's limited ability to produce adequate erythropoiesis after high doses of EPO have been administered.[11] Consequently, bone marrow stores may be replenished slowly after EPO is discontinued and may contribute to prolonged anemia.[11]

The anemia observed in critically ill patients is multifactorial.[12] Inadequate erythropoiesis secondary to inflammatory states contribute to this anemia.[12] We believe, therefore, that the patients most likely to benefit from EPO are those who are severely ill, with multiple organ failure, and with prolonged ICU length of stay. We tried to target this patient population by including patients with an APACHE II score > 15. Despite a mean APACHE II score around 21 in our study, most patients had an ICU length of stay < 2 weeks, thus leaving little time

to determine whether EPO had had a pronounced effect on hemoglobin concentrations. No differences were observed between the groups in terms of the daily hemoglobin variation during ICU stay. There is no advantage to using a dose of EPO > 40 000 units per week to optimize hemoglobin concentrations. The transfusion thresholds were appropriately implemented in both groups. The mean pretransfusion hemoglobin levels were 72 ± 9 g/L for patients in group A and 67 ± 6 g/L for patients in group B. Despite that, more patients were transfused in group B during the ICU period compared with group A. Patients in group B received also more units of blood during their ICU stay. A complementary analysis was performed to attempt to control for the difference in the transfusion rates and the number of units transfused between the groups (FIGURE 3). Nontransfused patients (FIGURE 3a) and transfused patients (FIGURE 3b) were analysed separately in both groups. When controlling for the transfusion rates, the daily variation in hemoglobin between the two groups during their ICU stay was similar.

In the TRICC trial, Hébert et al. showed that maintaining hemoglobin between 70 and 90 g/L by transfusing when hemoglobin < 70 g/L, was just as effective as a target hemoglobin level of between 100 and 120 g/L with a transfusion given when hemoglobin < 100 g/L.[2] Moreover, with a restrictive transfusion approach, the mortality rate was lower in less critically ill patients and patients < 55 years.[2] There is also no evidence that a liberal transfusion approach can decrease the duration of mechanical ventilation.[13] Only patients with unstable angina or acute myocardial infarction might possibly benefit from a higher transfusion threshold.[14] Tissular oxygen consumption following red blood cell transfusion does not appear to increase as expected.[15,16] Consequently, red blood cell transfusion would not make it possible to achieve clinical benefits that were as significant as anticipated. Moreover, critically ill patients may be more sensitive to transfusion-related complications such as infection[17], pulmonary edema[17], and the formation of microthrombosis.[16] In light of these observations, blood conservation measures must be introduced in ICUs in order to avoid

unnecessary transfusions and conserve blood supplies. Limiting laboratory analyses and decreasing the volume of collection tubes are among the proposed strategies.[3] The introduction of a restrictive transfusion protocol, based on the patient's clinical condition rather than on a single hemoglobin value is an important step to implement a blood conservation strategy in critically ill patients. It has been shown that EPO makes it possible to reduce the need for transfusion in ICU patients, but no clinical benefit has been demonstrated.[5] EPO is an expensive drug. In contrast, a restrictive transfusion approach is inexpensive and improved clinical outcomes.[2] The use of EPO without a restrictive transfusion approach would not be efficient. We believe that, in order to be efficient, EPO use in this context must provide additional clinical benefits.

Our study is the first to evaluate the effect of EPO in combination with a restrictive transfusion approach as used in the TRICC trial.[2] The mean pre-transfusion hemoglobin value observed in the Corwin et al. study was 86 g/L.[5] Our more restrictive transfusion criteria made it possible to achieve mean hemoglobin pre-transfusion values of 72 g/L for group A and 67 g/L for group B. More than half of the patients in group A and nearly 50% of the patients in group B did not receive any transfusions. Interestingly, despite a mean transfusion threshold of 72 g/L, the overall mean hemoglobin for patients in group A was 91 g/L during their stay in ICU. Generally, a constant decline in hemoglobin of approximately 2 g/L per day is observed in critically ill patients.[18] In our study, we saw a stabilization of hemoglobin concentrations close to 90 g/L for 28 days. The ABC study reported that the hemoglobin concentrations of all ICU patients converged at around 100 to 110 g/L, for a mean transfusion threshold of 84 g/L.[3] Our study shows that 40 000 units per week of EPO maintain hemoglobin levels around 90 g/L when used with more restrictive transfusion thresholds.

The decrease in iron availability seen in inflammatory states may contribute to inadequate response to EPO in ICU patients.[19] Thus, EPO must be used with

iron supplementation to optimize the erythropoietic response. However, the route of choice in that context remains to be determined.[19] Given the hemodynamic adverse effects that are possible with certain formulations of intravenous iron and the risk of infection, the patients in our study received an oral iron supplement. Futures studies comparing intravenous iron supplementation with oral iron in EPO-treated critically ill patients are needed.

Our study was not designed to evaluate the safety of EPO use in critically ill patients. However, given the limited experience with EPO use in ICU, a safety monitoring was required. Two larger trials reported that EPO did not increase adverse events compared to placebo. [5,10] In our study, EPO was temporarily discontinued if hemoglobin concentration increased over 125 g/L in order to reduce the risk of thromboembolic events.

The major limitation to this study is probably our small sample size. This study was designed to explore the erythropoietic response during ICU stay. The number of patients decreased progressively during ICU stay, leaving few patients for the analysis over 14 days. Changes in reticulocyte count in 2 weeks may simply reflect output of shift reticulocytes and not true expansion of erythropoiesis.[20] However, the pharmacodynamic profiles of the 2 groups were similar, reflecting the same trend of response.

CONCLUSION

EPO at a dose greater than 40 000 units per week does not result in faster, higher or more sustained stimulation of reticulocytes or hemoglobin production in ICU patients.

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ARTICLE IV (Table 1) : Baseline characteristics

	Group A (n=30)	Group B (n= 28)	*p* value
Age, mean (SD), years	65.5 (13.1)	63.0 (13.7)	0.48
Sex, No. (%)			
Men	18 (60)	21 (75)	0.27
APACHE II score, mean (SD)	21.3 (4.4)	21.9 (5.7)	0.68
MODS at enrollment, mean (SD)	6.1 (3.6)	6.3 (3.2)	0.82
Primary diagnosis *, No. (%)			
Pneumonia	7 (23)	8 (29)	
Respiratory	4 (13)	5 (18)	
Sepsis	7 (23)	6 (21)	
Post-operative	11 (37)	6 (21)	
Neurologic	1 (3)	0	
Trauma	0	2 (7)	
Cardiovascular	0	1 (4)	
History of coronary disease, No. (%)	5 (17)	4 (14)	1.00
Mechanical ventilation, No. (%)	22 (73)	27 (96)	0.03
Drugs at study day 1, No. (%)			
Any vasopressor†	15 (50)	13 (46)	1.00
Drotrecogin alfa	3 (10)	3 (11)	1.00
Any antibiotic	28 (93)	25 (89)	0.67
Baseline laboratory values, mean (SD)			
Hemoglobin, g/L	89 (11)	82 (13)	0.04
Hematocrit, %	26.7 (4,1)	24.5 (4.0)	0.05
Reticulocytes, x 10^9/L	51 (31)	65 (50)	0.22
Ferritin, ug/L	821 (641)	921 (1066)	0.68
Transferrin saturation, %	19.7 (14.0)	14.7 (9.4)	0.25
Folates, nmol/L	19.4 (13.3)	18.3 (11.3)	0.75
Vitamin B_{12}, pmol/L	713 (491)	588 (520)	0.36

* $p > 0,05$; †dopamine, dobutamine, epinephrine, norepinephrine, vasopressin; APACHE : Acute Physiology And Chronic Health Evaluation; MODS : Multiple Organ Dysfunction Syndrome

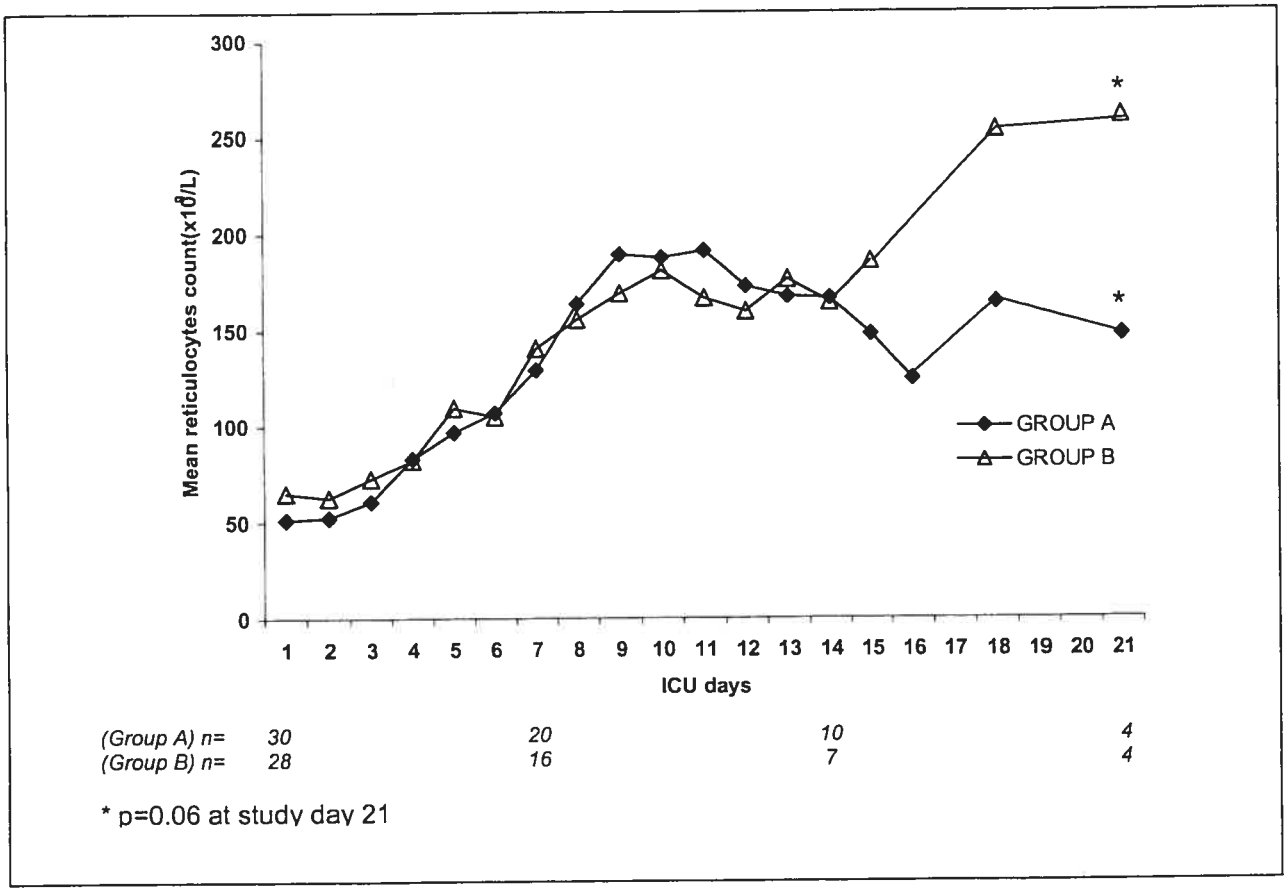
ARTICLE IV (Table 2) : Erythropoiesis parameters during ICU stay

	Group A (n=30)	Group B (n=28)	p value
Reticulocytes, mean (SD)			
study day			
1	51 (31)	65 (50)	0.22
7	129 (83)	141 (82)	0.68
14	167 (61)	164 (75)	0.95
21	148 (66)	260 (70)	0.06
Hemoglobin, mean (SD)			
study day			
1	89 (11)	82 (13)	0.04
7	91 (15)	87 (13)	0.34
14	93 (15)	87 (11)	0.34
21	90 (14)	84 (14)	0.52
28	86 (13)	79 (17)	0.67

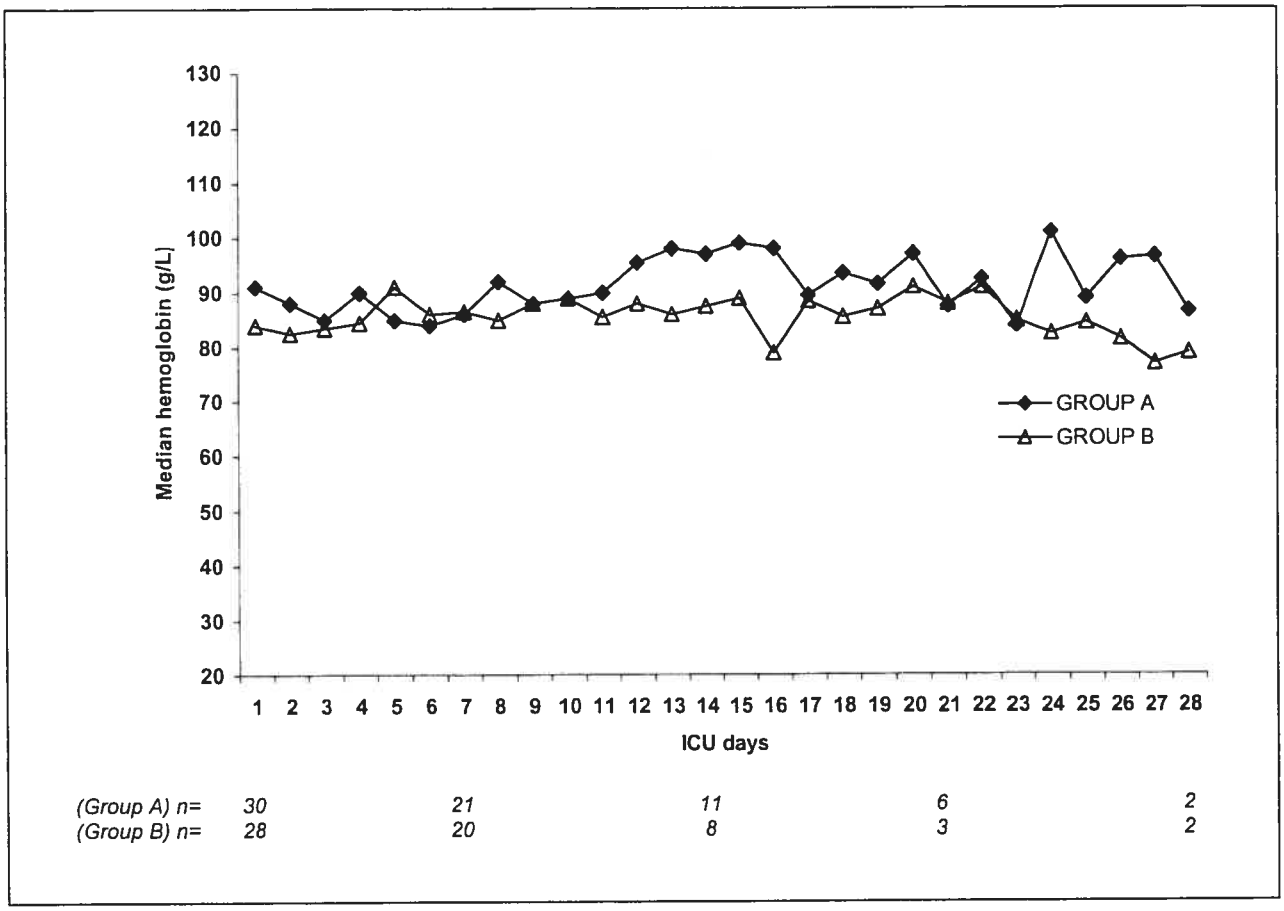
ARTICLE IV (Table 3) : Adverse events possibly attributable to EPO

	Groupe A (n=30)	Groupe B (n= 28)	*p* value
Deep vein thrombosis or pulmonary embolism	0	2	NS
Stroke	1	0	NS
Seizures	0	0	NS
Hypertension	2	0	NS
Thrombocytosis	0	1	NS
Suspected PRCA	0	0	NS

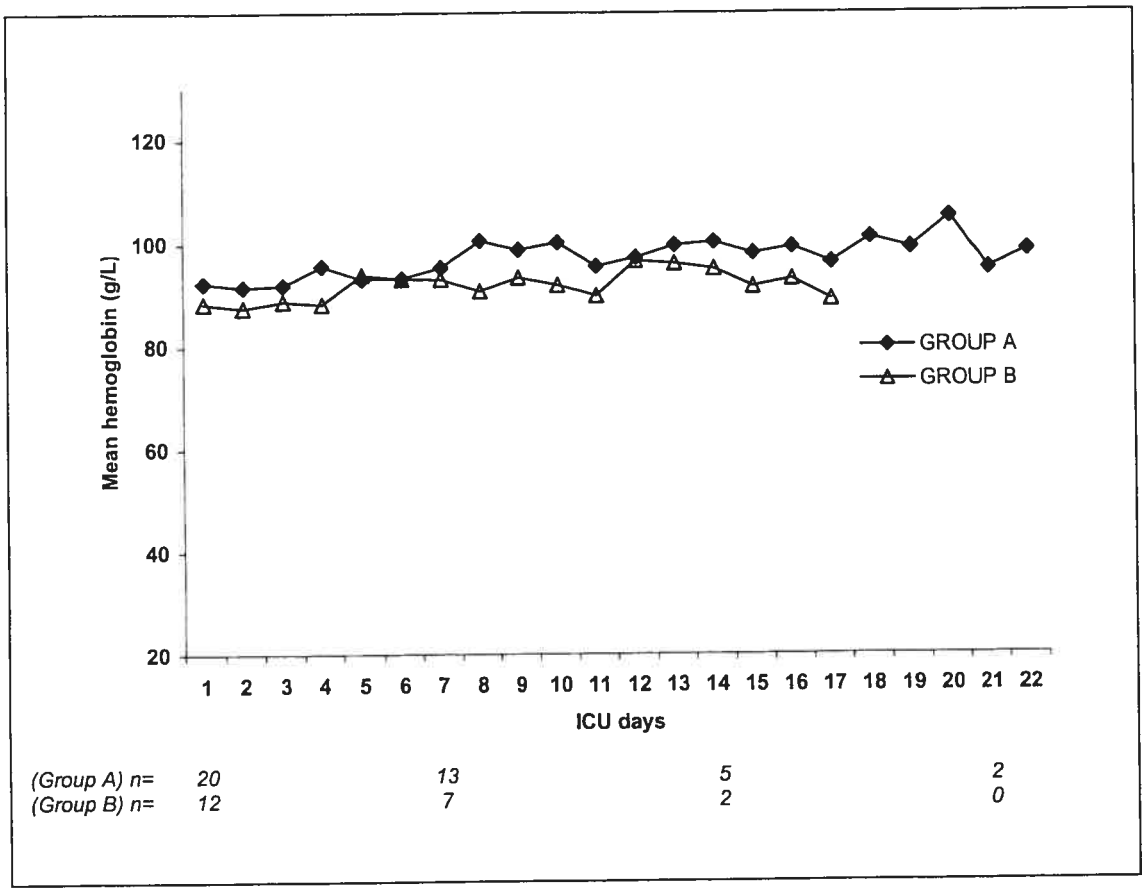
NS : not statistically significant; PRCA : pure red cell aplasia



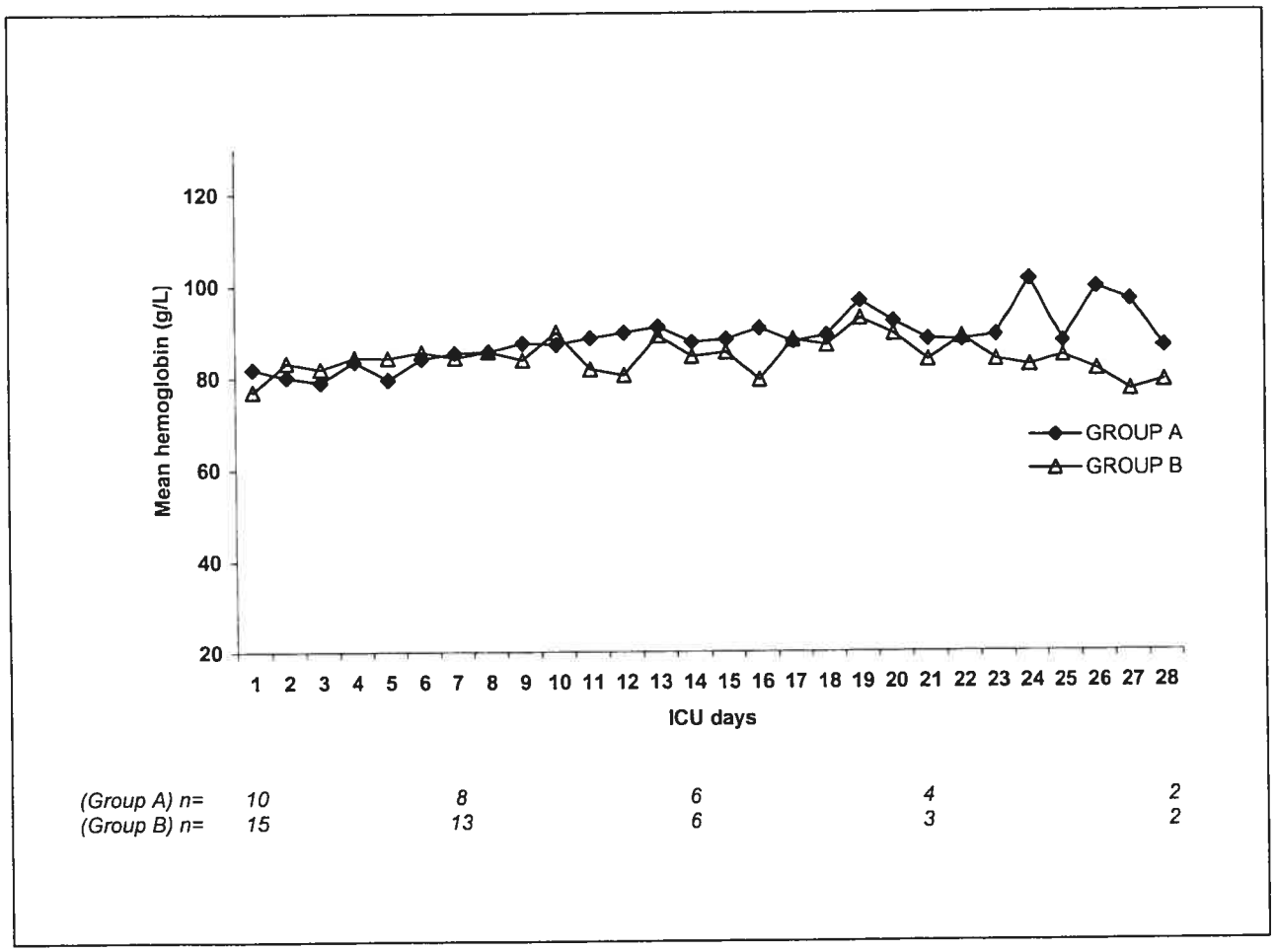
ARTICLE IV (Figure 1) : Reticulocytes count during intensive care



ARTICLE IV (Figure 2) : Course of hemoglobin concentration during intensive care



ARTICLE IV (Figure 3a) : Course of hemoglobin during intensive care : ***nontransfused patients***



ARTICLE IV (Figure 3b) : Course of hemoglobin during intensive care : ***transfused patients***

ANNEXE I : Accord des coauteurs

Article I : Darveau M, Notebaert E. Use of Epoetin Alfa in Critically ill Patients (letter). Ann Pharmacother 2004; 38:1325-6.

À titre de coauteur de l'article idendifié ci-dessus, je suis d'accord pour que Martin Darveau inclue cet article dans son mémoire de maîtrise qui a pour titre « Évaluation pharmacodynamique et sécurité d'emploi de l'époiétine alfa chez les patients aux soins intensifs ». Participation de l'étudiant : rédaction complète, corrections, réponse aux modifications de l'éditeur.

Éric Notebaert [redacted] 27/9/4

Coauteur Date

Article II : Darveau M, Notebaert E, Denault AY, Bélisle S. Recombinant Human Erythropoietin Use in Intensive Care. Ann Pharmacother 2002; 36 :1068-74.

À titre de coauteur de l'article idendifié ci-dessus, je suis d'accord pour que Martin Darveau inclue cet article dans son mémoire de maîtrise qui a pour titre « Évaluation pharmacodynamique et sécurité d'emploi de l'époiétine alfa chez les patients aux soins intensifs ». Participation de l'étudiant : rédaction complète, corrections, réponse aux modifications de l'éditeur.

Éric Notebaert [redacted] 7/9/4

Coauteur Date

André Y. Denault 5/10/4

Coauteur Date

Sylvain Bélisle 5/10/4

Coauteur Date

Article III : Darveau M, Denault AY, Blais N, Notebaert É. Iron metabolism in critically ill patients. Crit Care 2004;8(5):356-62.

À titre de coauteur de l'article idendifié ci-dessus, je suis d'accord pour que Martin Darveau inclue cet article dans son mémoire de maîtrise qui a pour titre « Évaluation pharmacodynamique et sécurité d'emploi de l'époiétine alfa chez les patients aux soins intensifs ». Participation de l'étudiant : rédaction complète, corrections, réponse aux modifications de l'éditeur.

[redacted]

André Y. Denault — 5/10/4
Coauteur — Date

Normand Blais — 14/10/04
Coauteur — Date

Éric Notebaert — 27/9/4
Coauteur — Date

ANNEXE II : Permission de l'éditeur pour les articles I & II

From:HARVEY WHITNEY BOOKS COMPANY 15137933600 09/10/2004 15:13 #006 P.002/002

Laval, Canada, september 8, 2004

Harvey Whitney
Editor
The Annals of Pharmacotherapy
P.O. Box 42696
Cincinnati, USA
OH 45242-0696

Subject : Darveau M, Notebaert E, Denault AY, Bélisle S. Recombinant human erythropoietin use in intensive care. Ann Pharmacother 2002;36:1068-74.

Darveau M, Notebaert E. Comment : use of epoetin alfa in critically ill patients. Ann Pharmacother 2004;38:1325-26.

Dear Editor,

I would like to obtain the authorization to include the article "*Recombinant human erythropoietin use in intenstve care*" and the letter "*comment : use of epoetin alfa in critically ill patients*", in my University essay (University of Montreal, Faculty of Pharmacy).

Best regards,

Martin Darveau, *B.Pharm, M.Sc.*

Authorization of the Editor :

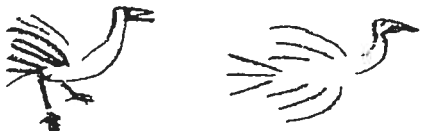
Harvey Whitney [redacted] 9-10-04

Editor Date

Please sign & fax to 450-973-5354

ANNEXE III : Permission de l'éditeur pour l'article III

14/09 2004 14:16 FAX 02076363423 001



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14th September 2004

Dear Mr Darveau,

further to your recent communication regarding the inclusion of your article from Critical Care journal in your university essay, we are writing to confirm that this reproduction is authorised.

Yours sincerely,

[redacted]

Adrienne Hanratty

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