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Preoperative autologous donation of 6 units of blood during rh-EPO treatment

Purpose: To determine if donation of six units of blood in three weeks is possible with self-administered subcutaneous recombinant human erythropoietin (rhEPO) injections and oral iron treatment.

Methods: A prospective trial where a total of 32 otherwise healthy patients were phlebotomised before revision hip arthroplasty during rhEPO and oral iron treatment (ferrofumarate). Adverse events were noted and compliance was controlled. Routine laboratory tests were performed at each visit including reticulocytes and 2,3-DPG. The relative oxygen releasing capacity (RORC) and the oxygen releasing capacity (ORC) were calculated. Blood donation was postponed until the next visit if haemoglobin concentrations was $<115\ g \cdot l^{-1}$ (men) or $<105\ g \cdot l^{-1}$ (women).

Results: All but two patients were able to donate six units of blood with an acceptable haemoglobin concentration on the day of operation. One serious adverse event occurred when the Hb was $119\ g \cdot l^{-1}$, compared with $149\ g \cdot l^{-1}$ before treatment. During the first two weeks before phlebotomy there was no increase in Hb, the mean nadir was reached after six phlebotomies ($31\ g \cdot l^{-1}$ below pre-study level), while at operation it was $19\ g \cdot l^{-1}$ below pre-study level. There was an increase in 2,3-DPG and oxygen releasing capacity after the initiation of rhEPO therapy, before the first phlebotomy.

Conclusion: It is possible to donate six units of blood in a three week period before surgery during self-administered subcutaneous rhEPO treatment and oral iron therapy at a rhEPO dose of $60\ U \cdot kg^{-1}$ BW three times a week. It is suggested that rhEPO *per se* initiates a right-shift of the oxygen dissociation curve via an increased 2,3-DPG level, which could explain that some patients report subjective benefit of rhEPO in spite of no change in Hb concentration.

Objectif : Déterminer s'il est possible de prélever six unités de sang en trois semaines avec l'appoint de l'érythropoïétine recombinante humaine (rhEPO) en injections sous-cutanées auto-administrées et de la sidérothérapie orale.

Méthodes : Cette étude prospective regroupait 32 patients bien portants phébotomisés avant une révision d'arthroplastie de la hanche et l'administration orale de fer (ferrofumarate). Les réactions secondaires ont été notées et la compliance contrôlée. Les épreuves de laboratoire usuelles effectuées à chaque visite incluaient le réticulocytose et les 2,3-DPG. La capacité relative de relargage de l'oxygène (RORC) et la capacité de relargage de l'oxygène (ORC) ont été calculées. On reportait le don sanguin jusqu'à la visite suivante si la concentration d'hémoglobine était $<115\ g \cdot L^{-1}$ (hommes) ou $<105\ g \cdot L^{-1}$ (femmes).

Résultats : Tous les patients à l'exception de deux ont pu donner six unités de sang tout en maintenant une concentration en hémoglobine acceptable le jour de l'intervention. Une complication grave est survenue quand l'Hb était $119\ g \cdot L^{-1}$, comparativement à $149\ g \cdot L^{-1}$ avant traitement. L'hémoglobine n'a pas augmenté pendant les deux premières semaines qui précédaient la phlébotomie et la valeur moyenne la plus basse était atteinte après six phlébotomies ($31\ g \cdot L^{-1}$ sous le niveau antérieur à l'étude), alors qu'au moment de l'intervention l'Hb était $19\ g \cdot L^{-1}$ sous le niveau antérieur à l'étude. Les 2,3-DPG et la capacité de largage de l'oxygène augmentaient après le début du traitement au rhEPO avant la première phlébotomie.

Conclusion : Il est possible de faire un don de six unités de sang en trois semaines avant la chirurgie pendant l'autoadminsitration sous-cutanée du traitement au rhEPO à la dose de $60\ U \cdot kg^{-1}$ trois fois par semaine et la sidérothérapie orale. Il est suggéré que *per se* le rhEPO induit un déplacement vers la droite de la courbe de dissociation de l'hémoglobine par augmentation du niveau des 2,3-DPG, ce qui pourrait expliquer le bienfait subjectif du rhEPO décrit par certains patients malgré l'absence de changements de la concentration de l'hémoglobine.

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TRANSFUSION of predonated autologous blood is the safest way to restitute operative blood loss,[1] and for healthy patients, with a haemoglobin (Hb) concentration >120 g·l^{-1} in men and >110 g·l^{-1} in women, four units can be donated within 12 days, two weeks before operation.[2] However, only a limited part of an unselected patient group could donate as many as six units during four weeks.[3]

To increase the efficacy of autologous blood transfusions, administration of recombinant human erythropoietin (rhEPO) is effective in both orthopaedic[4–7] and open heart surgery.[8–10] patients. Since rhEPO is expensive, determination of the optimal dose, and of the interval and route of administration is important.[11]

The aim of our study was to investigate if donation of six units of blood in three weeks was possible with self-administered rhEPO treatment *sc* during iron treatment *po*. We also studied erythrocyte 2,3-diphospho-glycerate (2,3-DPG) and calculated the oxygen releasing capacity.

Methods

After informed consent and approved by the local ethics committee and Medical Products Agency, 36 patients ≤75 yr, scheduled for revision hip arthroplasty were studied. Initially, patients were randomised to receive rhEPO (Recormon®, Boehringer Mannheim), 60 U·kg^{-1} *sc* either three or six times a week during six weeks before operation. After studying 17 patients, and finding no difference between the two doses, the study was limited to determine if, with a low dose regimen, it would be possible to donate six units over six weeks.

Study drug treatment was given for two weeks before the first phlebotomy and continued for six weeks until surgery. Phlebotomy was performed twice weekly for three weeks. Iron supplement, 120 mg·day^{-1} *po* was given for two weeks increasing to 240 mg with blood donation.

If the haemoglobin was <115 g·l^{-1} in men and <105 g·l^{-1} in women, donation was postponed. At each visit, patients were asked about problems with the injections and compliance was controlled. Surgical blood loss was recorded.

Blood samples for 2,3-DPG were drawn, acid-precipitated and the supernatants frozen. All 2,3-DPG analysis was performed at one time (Boehringer Mannheim). The relative oxygen releasing capacity (RORC) was calculated according to Siggaard-Andersen *et al.*[12] assuming PaO_2 of 12 kPa and venous PO_2 of 5 kPa and normal values for pH and PCO_2. The oxygen releasing capacity (ORC) was calculated as RORC × Hb × 0.062. For comparison, ORC was calculated both with an assumed normal value and the measured value of 2,3-DPG.

Results

Two patients were excluded because of poor veins, one because of suspected malignancy, and one because of hepatitis C antibodies. After 17 patients had completed the programme, and since no clinically relevant differences could be detected regarding haemoglobin change, randomisation was abandoned and only the lower dose regimen was continued. Therefore, eight patients received 60 U·kg^{-1} BW rhEPO six times a week and 24 received 60 U·kg^{-1} BW three times a week. The 19 men and 13 women had a mean age of 64 yr (range -45–75).

One patient had a non fatal myocardial infarction after the last phlebotomy, when the haemoglobin was 119 g·L^{-1}, compared with 149 g·L^{-1} before treatment. He was later operated upon after cardiological evaluation.

There was no increase in haemoglobin concentration during the two weeks of rhEPO treatment before phlebotomy. After six phlebotomies a nadir was reached at 112 g·L^{-1}, 31 g·L^{-1} below the pre-study level. At operation, mean Hb was 124 g·L^{-1}, or 19 g·L^{-1} (see Figure 1). The mean reticulocyte count increased to 6% after three phlebotomies and remained at this level until operation.

All but two patients donated six units of blood. They belonged to the lower dose group, due to low haemoglobin concentration. The total mean blood loss was 2.7 liters (range 0.8 – 7.7 l), 4.6 units (range 0–14) were transfused, and 77% of the predonated blood was utilised. Five patients required additional homologous blood transfusions, due to excessive bleeding (>3500 ml).

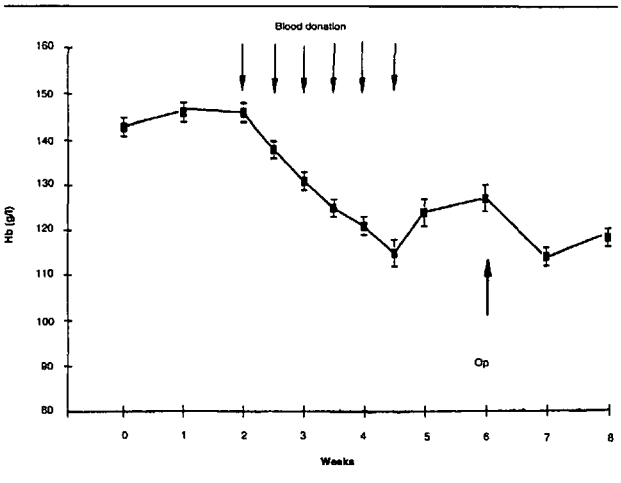

FIGURE 1 Haemoglobin values during the study.

Calculated using an assumed normal 2,3-DPG, ORC decreased from the first phlebotomy throughout the study (see Figure 2b). However, the mean 2,3-DPG level increased, from the start of the study, when the rhEPO treatment was initiated (see Figure 2a). The resulting right-shift of the oxygen dissociation curve increased the oxygen releasing capacity. After the start of phlebotomies, ORC decreased along with the Hb concentration, but returned to normal before operation (see Figure 2b). The mean 2,3-DPG level continued to increase after the start of phlebotomies, levelled out before operation and again increased postoperatively (see Figure 2a).

Discussion

The rhEPO treatment was started two weeks before phlebotomy to initiate early increased erythropoietic activity. The increase in reticulocytes indicated that this was successful. There was no rise in Hb concentration during these two weeks. With this rhEPO regimen, we collected six units of blood in 30 patients and five units in two. The total dose, 1080 $U \cdot kg^{-1}$, lower than in most studies is important, because of the high cost of rhEPO which is a deterrent in predonation programs.[13] The difference in Hb level between phlebotomy and surgery of 19 $g \cdot l^{-1}$ was acceptable. The administration of rhEPO is more cost effective by the *sc* than be the *iv* route[14] Our study shows that patients after very limited instruction can learn to handle the subcutaneous injections.

There were no side effects of rhEPO treatment although the myocardial infarction in an otherwise healthy 59-yr-old man may have been caused by the diminished Hb. It may be wise to exclude patients with any cardiovascular disease from such therapy.

The 2,3-DPG curve increased after initiation of rhEPO treatment before phlebotomy and continued to increase during phlebotomy to level out one week later, probably due to the concomitant increase of the Hb. After it increased again, probably due to the blood loss.

During phlebotomy ORC decreased in spite of the increased 2,3-DPG level, but normalised before the operation. If rhEPO treatment initiates a right-shift of the oxygen dissociation curve via increased 2,3-DPG, this may explain why some patients report subjective benefit from rhEPO treatment without any change in Hb.

We conclude that it is possible to donate six units of blood preoperatively during rhEPO and iron therapy: 60 $U \cdot kg^{-1}$ rhEPO *sc* three times per week is sufficient and most patients require little instruction.

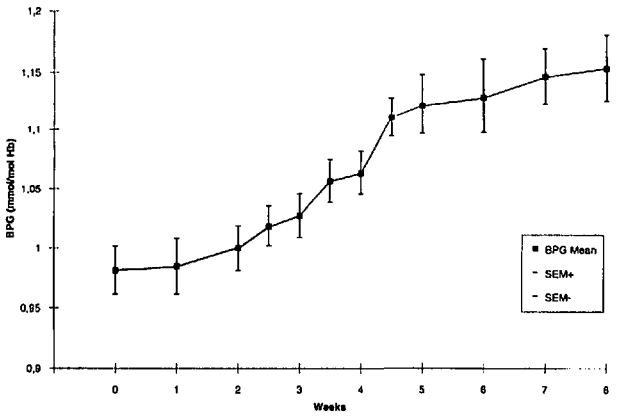

FIGURE 2A 2,3-DPG values during the study. Mean ± SEM.

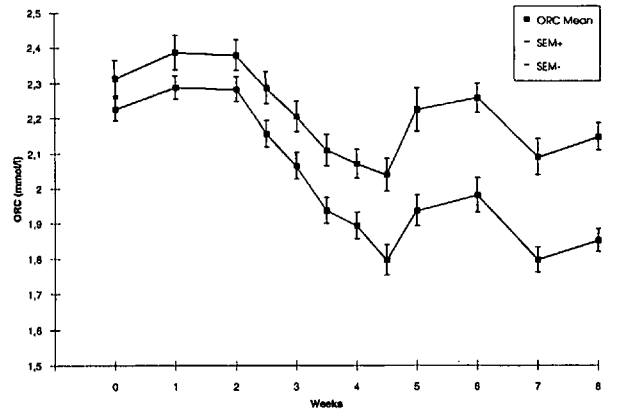

FIGURE 2B Oxygen releasing capacity during the study. Lower curve with an assumed normal 2,3-DPG concentration. Upper curve with the 2,3-DPG increase taken into account.

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