Techniques to increase tolerated blood loss

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Introduction

The requirement for blood transfusion during surgery depends on two major variables:

1.) The volume of perioperative blood loss, which is related to the type of surgery, the adequacy of surgical hemostasis and the surgical and anaesthetic techniques used;

2.) The volume of blood loss that the patient can tolerate before transfusion is indicated,

Thus the reduction of the transfusion requirement and of the use of allogeneic transfusion can be obtained by adopting two different strategies:

1.) Reducing of intra and post-operative blood loss; or

2.) Increasing the tolerated blood loss.

Tolerated blood loss can be increased by following guidelines for a correct indication of blood transfusion, lowering intra and post operative transfusion trigger or expanding the circulating RBCs mass of the patients through the preoperative correction of anemia with ematinics, utilizing preoperative blood donation, or stimulating erythropoiesis with rHuEPO treatment.

Indication for blood transfusion in surgery

The objective of blood transfusion in the majority of surgical and traumatic patients is to prevent or correct tissue hypoxia following acute blood loss. For many years has been internationally debated the definition of the values of Hb/Hct to be considered as transfusion trigger. Although there is a general agreement that the decision to transfuse depends not only on the values of Hb or Hct but has to be the conclusion of a thorough clinical evaluation, it is accepted that blood transfusion is rarely necessary when Hb is higher than 9 g/dL, most patients should receive blood transfusion when Hb is lower than 7 g/dL and when Hb is between 9 g/dL and 7 g/dL the decision to transfuse should be based on clinical judgment (1-3).

Recently proposals to lower transfusion trigger have been discussed based on the results of studies performed in critical care patients comparing restrictive versus liberal RBCs transfusion policy, and on the experience acquired in patients refusing blood transfusion. In critically ill patients no difference in mortality at 30 day, organ dysfunction score, length of stay in intensive care unit and total hospital stay between the two groups has been documented (4). Moreover in patients who refuse blood transfusion it has been shown that when Hb is < 5 g/dL in most cases mortality is due to anemia but when Hb is > 5 g/dL there is a lack of substantial rate of mortality due to anemia (5). This might reassure clinicians in their decision to consider lower transfusion triggers. However transfusion at a rigid Hb threshold without consideration of the patient's general clinical condition should become an increasingly infrequent event because there are many conditions limiting the ability to anemia (table 1). Patients at greater risk of undertransfusion are reported in table 2.

Table 1 Conditions limiting the ability to adapt to anemia

Age = impairment of cardiovascular and respiratory adaptation.
Cardiopathy limiting cardiac output adaptation capacity
aortic stenosis;
obstructive cardiopathy, cardiac insufficiency;
fixed-frequency cardiac stimulator, auricular fibrillation;
Coronary insufficiency = patients in whom myocardial ischaemia can be induced by a reduction of circulating Hb.
Chronic hypoxemia = respiratory insufficiency.
History of cerebrovascular accidents.
Assumption of drugs interfering with adaptation mechanisms.

Table 2 Patients at greater risk of undertransfusion

Intensive care patient
High fluctuation of Blood Volume (BV)
Pre-term infants
Variable BV according to clamping time
Elderly "medical" and "post-surgery" patients
Edematous critical care patients
Hypovolemia generally unrecognized

The Policy adopted in our hospital and agreed upon with surgeons and anesthesiologist is reported in table.3.

Tab 3 Transfusion trigger in different operative period

During general anesthesia:	The reduction in metabolic needs reduces the risk of O2 transport insufficiency (Hb = 7 g/dL are well tolerated).
Awakening period:	O2 demand increases (Hb = 8-9 g/dL).
Postoperative period:	Depends on the possible continuation of hemorrage on the energy needs for the reeducation and convalescence (Hb=8-10 g/dL according to cardiovascular considerations).

Relationship between anemia and transfusion requirement

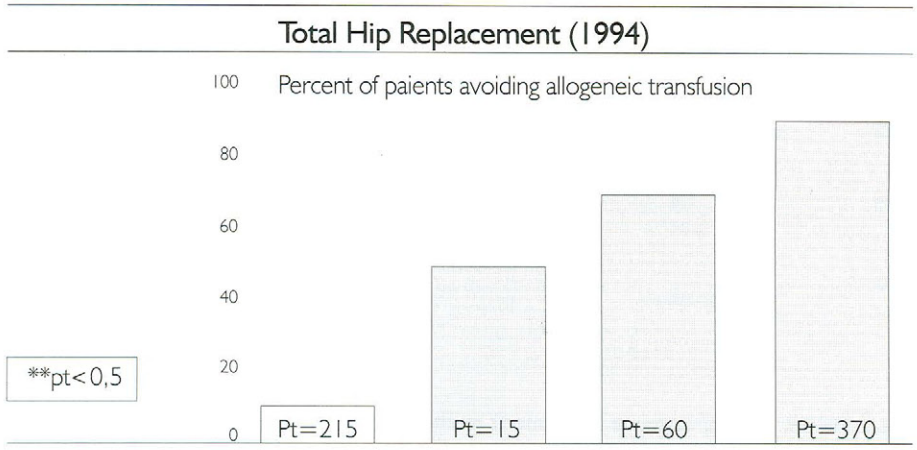
Tolerated blood loss is mainly affected by the clinical conditions of the patient, particularly by the cardiopulmonary condition and the haematological status. Low baseline hematocrit has been shown to be a critical parameter in affecting transfusion requirement. The incidence of preoperative anemia is relevant in many categories of patients but particularly in patients with anemia of chronic diseases [ACD] (1,2). The patients more interested by this type of anemia are those with cancer and rheumatoid arthritis (6,7).

Anemia is common in cancer patients, especially in those with more advanced stages of progressive tumor growth (8) and represents an important component of the morbidity related to the malignancy. Few data are available on the frequency of anemia, however it has been reported that about one half of patients with cancer are anemic, the frequency varying on type of cancer, stage and chemotherapy or radiation therapy used. The pathophysiology of the anemia associated with malignancy is multifactorial and not completely understood. However in the majority of cases the ACD plays a major role. The anemia generally develops slowly and is usually mild to moderate in

severity with hemoglobin values in the 8-10 g/dL range. However, specially in patients receiving chemotherapy values can be < 7 g/dL. It has been reported that the percentage of patients requiring transfusion ranges from 20 to 50% (8). The percentage dramatically increases when patients undergo cancer surgery: in a meta-analysis of 14 studies in colorectal cancer it was calculated that allogeneic blood transfusion was given in 45-84% of subjects (9).

As for cancer patient, anemia is one of the most frequently occurring extra-articular manifestations of rheumatoid arthritis. Although iron, vitamin B12 and folic deficiencies are quite prevalent as indeed is the anemia arising from complications during anti-rheumatic drug therapy, ACD is one of the major underlying causes of low hematocrit values in these patients. The anemia is usually mild and relatively well tolerated (generally no more than 10% of the patients have a severe anemia) (10). However when progression of the disease requires major orthopedic surgery, anemia can preclude the collection from the patient of sufficient blood to cover his or her transfusion needs.

Low baseline hematocrit values, however, have been found detrimental also in surgical patients without underlying diseases candidate to elective orthopedic surgery (11). Indeed it has been demonstrated that in patients enrolled in predonation program the inability to donate the optimal number of autologous units is the major cause of allogeneic transfusion (fig. 1).



	Salvage only	1 AB Pred	2 AB Pred	3 AB Pred
Blood loss (mL rbc)	630	620	643	782
HB units tranf.	2,48	1,23	0,43	0,22 **
Baseline Hct	39,3	40,5	40,1	41,1
Hct 3 days postop	28,2	26	28,3	28,3
Hct 7 days postop	29,9	28,9	27,8	29,2

Fig. 1 Percentage of patients avoiding homologous blood (HB) transfusion, mean perioperative blood loss, mean number of homologous blood units transfused and mean hematocrit values at baseline, 3 days and 7 days after surgery in 660 patients undergoing primary total hip replacement subdivided according the number of autologous blood units predeposited.

The volume of blood that the patient can predeposit during the period before the operation is a function of the total circulating red blood cells (RBCs) mass and the rate of recovery of Hct after collection. A low baseline hematocrit not only preclude the possibility of predonation when is below 34%, but also significantly affect the quantity of blood that can be donated. For each unit of autologous blood (350-450mL) collected, a mean decrease of 1g/dL of hemoglobin and 3 points of hematocrit is observed. With the collection of 3 units of blood the Hct value is reduced by about 10 points. Consequently in a relevant percentage of patients with baseline Hct below 39-40 % the value drops below 34% (threshold value for donation) after the collection of

the first or second bleeding. It has been estimated that anemia precluded the enrolment into the donation program of 10% of surgical patients and limited the number of units collected in 31% of the patients (11).

To define the critical Hct value below which the patients would be at higher risk of receiving allogeneic blood transfusion we correlated the number of units actually predeposited by the patients and the need to integrate autologous blood with allogeneic blood to the baseline Hct value. We found that when baseline Hct values were lower than 37% the blood that the patients could predeposit (0-1 unit) was generally insufficient to cover their transfusion need; when Hct values were included between 37% and 40% autologous blood donations covered transfusion requirement in approximately 56% of cases, while when Hct values were higher than 40% the patients could predeposit 3 or more units of blood and were exceptionally exposed to the risk of being transfused with donor's blood. (11) (fig3).

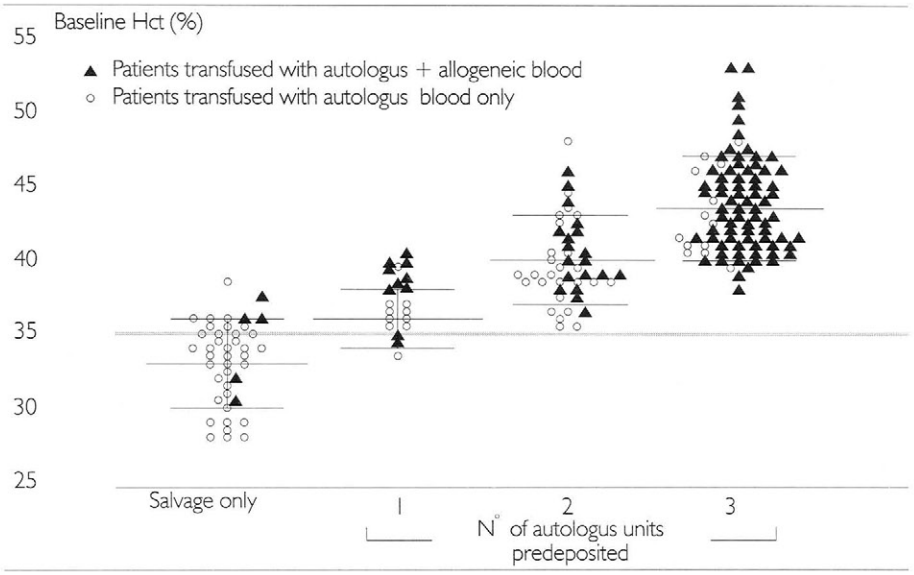


Fig.3 Relationship of baseline hematocrit to the number of autologous units collected and the ability to cover transfusion needs exclusively with the use of autologous blood

To better define the distribution of the baseline Hct values in the orthopedic surgical patients population we analysed the data from 2183 patients candidates to different orthopedic surgical procedures in the Orthopedic Institute of the University of Milan.

Patients have been subdivided into different classes according to the baseline Hct value and the underlying disease conditioning the need for surgical intervention (tab.4). Out of 2183 evaluated patients, a total of 381 patients (18%) had a baseline Hct lower than 34%, value that prevents the use of PABD, method of proven efficacy to reduce the use of allogeneic blood in surgical patients. Moreover a total of 1010 patients (46%) had baseline Hct values between 34% and 40% and are at high risk of allogeneic blood transfusion when undergoing to major orthopedic surgical procedures with expected transfusion need of 2-3 units. Only 792 patients (36%) had optimal baseline values (higher than 40%). As expected the incidence of baseline Hct values lower than 34% was only 7% in patients whose underlying disease was arthrosis but increased to 25%, 30% and 42% in patient with rheumatoid arthritis, cancer or sepsis, respectively. In trauma patients the incidence of such a low value resulted to be 35%.

The last 1034 have been thoroughly examined for iron deficiency. In 73 patients (7%) an iron deficiency has been documented. Sixty of these patients have been treated with intravenous administration of iron sucrose (700-900 mg of elemental iron). In 30 day an increase of Hct from 35.4% + 2.7 to 37.6% + 2.0 was documented with a mean RBCs production of 135 ml.

Tab 4. Distribution of baseline hematocrit in orthopedic surgical patients operated at the Gaetano Pini Orthopedic Institute in 1997

	20.5% - 29.9%	30% - 33.9%	34% - 39.9%	40% - 55.9%	TOTAL
N°of Pts (% of total)	129 (6)	252 (12)	1010 (46)	792 (36)	2183
Female	99 (6.5%)	203 (13.3%)	831 (54.6%)	389 (25.6%)	1522
Male	30 (4.5%)	49 (7.5%)	179 (27%)	403 (61%)	661
Arthrosis	19 (1.5%)	70 (5.5%)	624 (48%)	585 (45%)	1298
Rheumatoid Arthritis	6 (7%)	16 (18%)	42 (52%)	19 (23%)	82
Cancer	14 (14%)	17 (16%)	39 (38%)	33 (32%)	103
Sepsis	8 (14%)	16 (28%)	17 (30%)	16 (28%)	57
Trauma	78 (13%)	126 (22%)	264 (45%)	113 (20%)	581
Other	4 (6%)	8 (13%)	24 (39%)	26 (42%)	62

Accordingly to the analysis a consistent proportion of patients undergoing major surgical procedures can be expected to be unable to face perioperative transfusion need exclusively with the use of autologous blood obtained utilising the currently available autotransfusion techniques (PABD, perioperative blood salvage and ANH). In these patients the administration of recombinant human erythropoietin (rHuEPO) may be a valuable adjunct to increase the efficacy of all the autotransfusion techniques (12,13).

Several studies have evaluated, in different group of patients, the efficacy of rHuEPO in enhancing the collection of autologous blood in patients candidate to elective surgery, in correcting anemia before surgery and in accelerating postoperative erythropoietic response thus reducing the use allogeneic blood (14-20). In all the clinical studies considered, rHuEPO was found to be effective in stimulating erythropoiesis and increasing new RBC production (although this was found to vary considerably 250 to 900 mL) and the number of units predeposited. It was also effective in correcting anemia induced by blood collection.

The increase in the amount of blood deposited correlated fairly well with the dose of rHuEPO administered. The most common treatment protocol used involved IV administration twice weekly for 3 weeks together with oral iron supplements. Total doses of less than 600 IU/Kg were ineffective in promoting sufficient erythropoiesis to significantly increase the volume of predeposited blood. Higher doses yield a dose-dependent production of new RBCs ranging from 250 mL for total doses of 600 IU/Kg to more than 900 mL for doses of 3,600 IU/Kg. It should be noted that, despite oral iron supplementation, the effect of rHuEPO therapy in autologous donors is very often restricted by iron depletion. Intravenous iron administration allows a more adequate iron supply for erythropoiesis, with either an increased Hb response to the same dose of rHuEPO or a reduction in the dose of rHuEPO required. With the use of IV iron sucrose, RBC regeneration and volume of predeposited blood were identical when total rHuEPO doses of 1,800 and 3,600 IU/Kg were compared. The effectiveness of the SC route for rHuEPO has been shown in several studies. In our experience (Fig

4), SC administration for rHuEPO combined with intravenous iron is highly effective in autologous blood donation and, compared with intravenous administration, allows a marked reduction (approximately 55%) in the total rHuEPO dose (26).

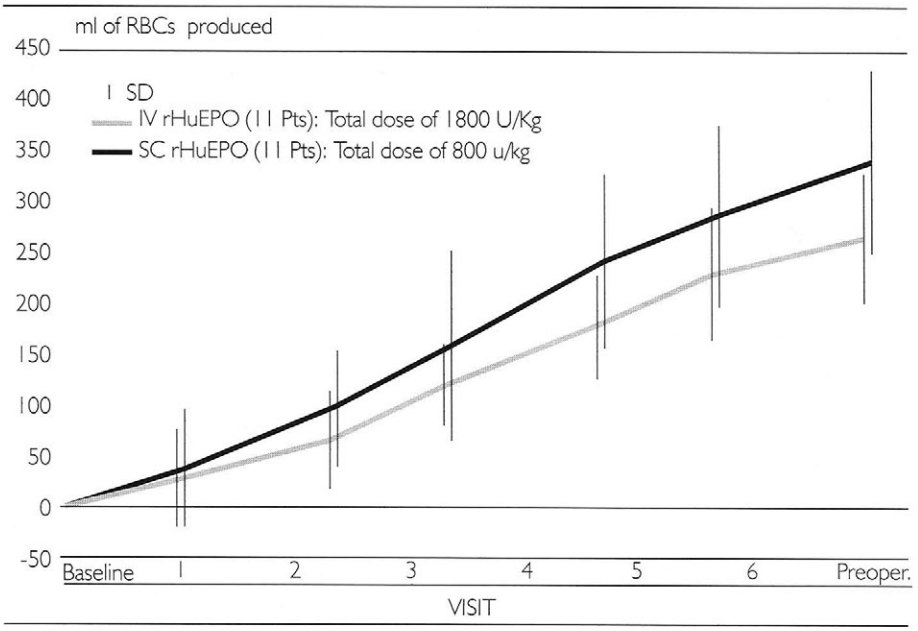


Fig 4 Production of new RBCs in patients treated with IV rHuEPO at a total dose of 1800IU/kg and in patients treated with SC rHuEPO at a total dose of 800IU/kg. Both groups received IV iron supplementation

Recently, some studies have also evaluated the role of rHuEPO in those subgroups of patients for whom preoperative autologous blood donation is not feasible (28). These include patients with anemia or other disorders precluding donation, patients with limited time to surgery, and individuals who are unwilling to participate in an autologous blood donation program because of logistical problems or religious beliefs. For example, postponing the operation in cancer patients or candidates to heart surgery might be more detrimental than receiving allogeneic blood transfusion. In one such study, (29) three different doses of r-HuEPO were used (3000, 6000 and 9000 i.v. 3 times a week for 2 weeks before and after surgery) combined with intravenous iron treatment. In a later perspective placebo controlled double blind study, (30) 2 different doses of r-HuEPO (300 IU/Kg and 150 IU/Kg) were administered subcutaneously for eight consecutive days during the pre-operative period (from day -5 to day +2). A reduced transfusion requirement was evident in both studies.

Perisurgical use of rHuEPO in patients undergoing elective hip replacement reduced from 74% to 33% the portion of patients requiring transfusion when their baseline Hb was less than 13.5 g/dL . (31) Two additional studies have shown significant reduction in transfusion rates with perisurgical use of rHuEPO in subjects undergoing orthopedic surgery with baseline Hb levels between 10 and 13 g/dL. (32,33)

A short-term perisurgical treatment was used in a pilot study at our institute. Sixteen patients for whom predeposit was contra-indicated for various clinical reasons and who were about to undergo major orthopaedic surgery with a predicted transfusion requirement of 2-3 units of blood were enrolled in the study. The protocol involved subcutaneous administration of r-HuEPO at a daily dose of 100 IU/Kg beginning 4 days before surgery (day-4) up to the second day following surgery (day + 2). On the first day of treatment, one 200 IU/Kg bolus was also administered intravenously. Intravenous iron sucrose was administered concomitantly at a total dose of 600 to 1000 mg, according to baseline iron reserve levels. The treatment produced a 2% to 7% in-

crease in Hct, with average increase in circulatory RBC mass of some 100mL (from 0 to 245) before surgery. Twelve of the 16 patients did not require allogeneic transfusion, whereas a total of 6 units of blood was transfused in the remaining 4 patients (34). Although preliminary these findings suggest that rHuEPO administration together with IV iron during a pre-operative period of 4-5 days is able to stimulate erythropoiesis significantly, expand the circulatory red cell mass and reduce the transfusion requirement in patient who, for clinical or logistic reasons (heart surgery and cancer patients) are not able to deposit autologous units prior to elective surgery. Because of the short time period, this protocol could also be offered to a proportion of accident patients about to undergo surgery, when surgery is planned to take place 4-5 days after injury.

Finally rHuEPO administration ha been investigated also in surgical patients with ACD. In a pilot study carried out in our Centre, 11 rheumatoid arthritis patients candidates to major orthopedic surgery were selected for their inability to donate blood for autologous use because of anemia (Hct <34%) and received rHuEPO 300 IU/Kg in combination with iv iron sucrose (100 mg of elemental iron) twice a week for 3 weeks (35). Transfusion treatment was compared with that of 12 untreated patients with anemia of comparable severity. The study demonstrated the safety and efficacy of rHuEPO in stimulating erythropoiesis, allowing preoperative donation of blood for autologous use and reducing exposure to allogeneic blood in anaemic rheumatoid arthritis patients. Indeed control patients could not preoperatively deposit any blood unit for autologous use, while all but one of the rHuEPO treated patients deposited 2 or more units. The control group received more allogeneic units than control patients (mean 2.6 + 1.6 vs 0.8 + 0.8, $p=0.009$). Moreover 50% of rHuEPO treated patients as compared with 8% of controls completely avoided allogeneic transfusion.

Recombinant EPO has been shown to be effective in combination with ABD in patients undergoing transurethral resection of the prostate for treatment of prostate cancer (36). Of the 266 patients who took part in the study, 134 predeposited blood. The rate of allogeneic blood transfusion was 6.7% in this patient group, compared with 14.7% among patients who did not donate autologous blood preoperatively. Furthermore, in 6 patients who received concomitant rHuEPO therapy during preparative ABD, the reduction in Hb level during the predonation period was significantly less marked than among untreated patients (-0.4 g/dl vs - 1.9 g/dl; $p<0.05$). Another study involved the inclusion of rHuEPO (150 IU/Kg subcutaneously three times weekly) into the intensive neoadjuvant chemotherapy regimen of 15 patients with sarcomas, in order to prevent the development of anaemia and allow preoperative ABD (37). Twelve patients with identical neoadjuvant chemotherapy acted as controls. In total, 14 rHuEPO-treated patients (93%) donated autologous blood; one patient could not donate as a result of severe iron-deficiency anaemia. No patient in this group required blood transfusion during chemotherapy, compared with 8 patients (67%) in the control group. Hence, rHuEPO was found to be effective in reducing the incidence of anaemia and transfusion frequently associated with intensive chemotherapy. In addition, treatment with rHuEPO permitted patients to donate autologous blood preoperatively, thereby reducing the risk of exposure to allogeneic blood.

Owing to the high cost of rHuEPO treatment, its routine use is unlikely to be cost-effective. To better select those patient who are very likely to benefit from this treatment we defined a more personalised approach to calculate the expected transfusion need for each single patient (38).

We retrospectively applied the algorithm to 577 patients each of whom predonated 2 or 3 units of autologous blood prior to total hip replacement surgery and subdivided the patients according to the calculated transfusion requirement (tab.5). It can be observed that in patients with calculated transfusion need higher than 500 mL of RBC (representing less than 5% of total evaluated patients), in spite of the utilisation of all

the currently available autotransfusion techniques only 68% of the patients avoided the use of allogeneic blood while this figure was more than 95% in the group of patients with calculated transfusion need lower than 200 mL of RBC. In this group of patient with low calculated transfusion requirement an overcollection of autologous blood has been documented as demonstrated by the wastage of about 20% of the autologous units collected.

Tab.5 Transfusion results in 577 patients operated for total hip replacement subdivided according to the expected transfusion requirement calculated with the algorithm (38)

Transfusion requirement	*< 0*	*0-100*	*100-200*	*200-300*	*300-400*	*400-500*	*>500*
NO of Pts (% of total)	50 (8,7%)	48 (8,3%)	67 (11,6%)	90 (15,6%)	139 (24,1%)	156 (27%)	27 (4,7)
% male	98	93	77	39	6,5	1,3	0
Units predeposited (unit / Pt)	103 (2,0)	109 (2,2)	155 (2,3)	230 (2,5)	355 (2,5)	372 (2,4)	64 (2,4)
Units not transfused	20 (19,4)	21 (19,2%)	29 (18%)	33 (12%)	28 (8%)	19 (5%)	0 (0%)
Pts transfused only auto	98%	98%	95%	85%	82%	80%	68%
Pts with discarded units	16 (32%)	16 (33%)	22 (32%)	26 (28%)	25 (18%)	17 (11%)	0 (0%)
Pts transf. with all AB units with postop Hct<27 %	7 (14%)	9 (18%)	10 (15%)	22 (24%)	51 (37%)	74 (47%)	18 (66%)

If we had applied the algorithm for the choice of the most appropriate blood conservation strategies we would have been avoided unnecessary collection of AB in patients with low transfusion requirement thus saving resources that could have been utilised for a rHuEPO treatment in patients at higher risk to require allogeneic blood transfusion because of low baseline Hct values..

References

1.) American College of Physicians. Practice strategies for elective red blood cell transfusion. Ann Intern Med 1992; 116: 403-6

2.) Consensus statement on red cell transfusion. Br J Anaesth 1994; 73: 857-59

3.) American Society of Anesthesiologists Task Force on Blood Component Therapy. Practice guidelines for blood component therapy: a report. Anesthesiology 1996; 84: 732-47

4.) Hebert PC, Wells g, Marshall J et al. Transfusion requirement in critical care. A pilot study. JAMA 1995; 273: 1439-44

5.) Cane RD. Hemoglobin: how much is enough? Crit Care Med 1990; 18: 1046-7

6.) Cartwright GE, Lee GR. The anemia of of chronic disorders. British Journal of Haematology 21:147-152, 1971 Lee G.

7.) The anemia of chronic disease. Semin Hematol 20:61-80: 1983.

8.) Van Camp B. Anemia in cancer. Erythropoiesis 2:39-40; 1991

9.) Blumber NL, Heal JM. Transfusion and host defenses against cancer recurrence and infection. Transfusion 29: 236-254. 1989

10.) Vreugdenhil G, Swaak AJG: anemia of rheumatoid arthritis: current concept and recent developments. Erythropoiesis 2:1-15;1991

11.(Mercuriali F, Biffi E, Inghilleri G, et al. Low hematocrit: limiting factor in autologous blood predonation program. In: Castelli D, Genetet B, Habibi B, Nyddeger Y (Eds). Transfusion in europe. Arnette SA Paris ISBT 291-298, 1989

12.) Zanjani ED, Ascensao JL. Erytrhopoietin. Transfusion 1989; 29: 46-57

13.) Cazzola M, Mercuriali F, Bruganra C. Use of recombinat human erythropoietin outside the setting of uremia. Blood 89-(12): 4248-67; 1997

14.) Mercuriali F, Zanella A, Barosi G, et al. Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. Transfusion 33: 55-60, 1993.

15.) Kulier AH, Gombotz H, Fuchs G, et al. Subcutaneous recombinant human erythropoietin and autologous blood donation before coronary artery bypass surgery. Anesthesia and analgesia 76 (1) 102-106, 1993.

16.) Kyo S, Omoto R, Hirashima K, et al. Effect of human recombinant erythropoietin on reduction of homologous blood transfusion in open-heart surgery. A Japanese multicenter study. Circulation 86 (Suppl. II): 413-418, 1992.

17.) Goodnough LT, Rudnick S, Price TH, et al, Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. N Engl J Med 321: 1163-1168, 1989.

18.) Beris P, Mermillod B, Levy G, eet al. Recombinant human erythropoietin as an adjuvant treatment for autologous blood donation. A prospective study. Vox Sang 65;212-8. 1993

19.) Goodnough LT, Price TH, Friedman KD et al. A phase II trial of recombinant human erythropoietin therapy in nonanemic orthopedic patients subjected to aggressive removal of blood for autologous use: Dose, response, toxicity and efficacy. transfusion 34: 66-72, 1994

20.) Watanabe Y, Fuse K, Konishi T, et al. Autologous blood transfusion with recombinant human erythropoietin in heart operations. Ann Thorac Surg 51: 767-772, 1991.

21.) Biesma DH, Kraijenhagen RJ, Marx JJ, et al. The efficacy of subcutaneous recombinat human erythropoietin in the correction of the phlebotomy-induced anemia in autologous donors. Transfusion 33: 825-31, 1993

22.) Mercuriali F, Inghilleri G, Biffi E, et al. Epoetin alfa in low hmatocrit patients to faciliate autologous blood donation in total hip replacement: a randomized, double-blind. placebo-controlled, dose ranging study. Acta Haematol (in press)

23.) Biesma DH, Kraaijenhagen RJ, Poortman J, e al. The effect of oral iron supplementation on erythropoiesis in autologous blood donors. Transfusion 32: 162-165, 1992

24.) Van Wyck DB. Iron management during recombinant human erythropoietin therapy. Am J Kidney Dis 14 Suppl. 1: 9-13, 1989

25.) Brugnara C, Chambers L.A., Malynn E., Golberg M.A. and Kruskall M.S. Red blood cell regeneration induced by subcutaneous recombinant erythropoietin: Iron-deficient erythropoiesis in iron-replete subjects. Blood 81: 956-964, 1993.

26.) Mercuriali F, Inghilleri G, Biffi E, et al. Comparison between intravenous and subcutaneous recombinant human erythropoietin (Epoetin alfa) administration in presurgical autologous blood

donation in anemic rheumatoid arthritis patients undergoing major orthopedic surgery.. Vox Sang 1997; 72:93-100

27.) Hayashi J, Kumon K, Takanashi S et al. Subcutaneous administration of recombinant human erythropoietin before cardiac surgery: a double-blind, multicenter trial in japan. Transfusion 34: 142-7. 1994

28.) Adamson J. Perisurgical use of epoetin alfa in orthopedic surgery patients. Semin Hematol 33: 55-60. 1996 (suppl 2)

29.) Kyo S, Omoto R, Hirashima K, et al. Effect of human recombinant erythropoietin on reduction of homologous blood transfusion in open-heart surgery. A Japanese multicenter study. Circulation 86 (Suppl. II): 413-418, 1992.

30.) D'Ambra MN, Lynch KE, Boccagno J Vlahakes GJ. The effect of perioperative administration of recombinant human erythropoietin (rHuEPO in CABG patients: a double blind, placebo controlled trial Anesthesiology 77:A159, 1992

31.) Canadian Orthopedic Perioperative Erythropoietin Study Group. Effectiveness of perioperative recombinant human erythrpoietin in elective hip replacement. Lancet 341: 1227-1232, 1993

32.) Stowell C. Epoetin alfa reduces perioperative transfusion requirements in patients undergoing major orthopedic surgery. Transfusion 1995; 35:27s (abstract).

33.) deAndrade JR, Frei D, Young DC. Recombinant human erythropoietin (Epoetin alfa) reduces allogeneic transfusions in subjects undergoing orthopedic surgery. Abstract presented at AAOS, February 1996.

34.) Mercuriali F, Inghilleri G, Biffi E, Colotti MT. Short-term, low dose recombinant human erythropoietin administration in surgery. British Journal of Anesthesia 1997; 78 (suppl 1): 64.

35.) Mercuriali F, Gualtieri G, Sinigaglia L et al. Use of human erythropoietin to assist autologous blood donation by anemic rheumatoid arthritis patients undergoing major orthopedic surgery. Transfusion 1994;34:501-6

36.) Ihara H, Yabumoto H Shima H et al. Predeposit autologous blood transfusion in elderly patioents udergoing transurethral resection of the prostate. Int Urol Nephrol 25: 571-6, 1993.

37.) Oblon D, Johnson T, Scarborough M. Recombinant human erythropoietin (rHuEPO) reduces the transfusion requirements due to intensive neo-adjuvant chemotherapy and allows presurgical autologous blood donation (abstract n° A282). Exp Hematol 21: 1087, 1993

38.) Mercuriali F. Inghilleri G. Proposal of an algorithm to help the choice of the best transfusion strategy. Current medical Research and Opinion 1996, 13 (8): 465-478