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Perioperative plasma erythropoietin levels in hip arthroplasty

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Summary To examine the influence of intra- and postoperative blood loss and operative trauma on erythropoietin (EPO) production we studied patients undergoing endoprothetic surgery of the hip. Immunoreactive plasma EPO was determined in ten patients (seven male, three female, aged 39–68 years), undergoing surgery for hip arthroplasty ($n=8$) or revision hip arthroplasty ($n=2$). EPO levels had already been determined during preoperative autologous deposit, thus allowing direct comparison between EPO response to blood loss alone and the response to blood loss and operative trauma. Perioperative blood loss amounted to 1720 (480–8100) ml (median, range). The hemoglobin concentration decreased from 12.4 (10.6–14.0) g/dl (median, range) before the operation to 10.0 (9.3–12.3) g/dl 2 h after the operation. Thereafter, the hemoglobin concentration increased slowly due to transfusion and erythropoiesis and was not significantly different ($p<0.05$) from the preoperative value on the seventh postoperative day. The EPO concentration was preoperatively 26 (11–28) mU/ml and increased 2 h after the end of the operation, reaching a peak of 64 (45–104) mU/ml at 24 h. This peak was followed by a plateau at lower, but still elevated levels. The EPO concentration remained significantly elevated above the preoperative value on the seventh postoperative day. Plasma EPO concentrations showed an adequate response to postoperative anemia compared with the time course after autologous donation. In the early postoperative phase, they do not seem to be appreciably influenced by the neuroendocrine response to trauma, by mediators of inflammation, or by the postoperative catabolic state. The slightly elevated EPO concentration in the late postoperative phase indicates that factors other than anemia may contribute to EPO production at this time.

Key words Erythropoietin · Erythropoiesis Surgery · Hip arthroplasty · Revision hip arthroplasty · Blood loss · Acute-phase proteins C-reactive protein · Fibrinogen

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Introduction

The glycoprotein hormone erythropoietin (EPO) is the primary humoral regulator of erythropoiesis. Plasma EPO concentrations are generally inversely related to tissue oxygen supply [1]. Thus, plasma EPO levels increase following a reduction of either oxygen saturation or oxygen-carrying capacity of blood. Regarding the latter condition, a significant, albeit temporary increase in plasma EPO levels can be demonstrated after the donation of one unit of blood [2, 3]. Furthermore, in chronic anemias, an inverse exponential relationship exists between plasma EPO concentration and the hemoglobin level [1, 4].

A variety of factors other than blood oxygen content, however, are known to modulate EPO formation [1]. Among these are the acid-base status [5, 6], the nutritional status [7], hypophyseal and adrenocortical hormones [1], prostaglandins [8], and monokines [9, 10]. In the perioperative setting these parameters are modified, and therefore the question arises whether the hormonal and metabolic changes associated with trauma and inflammation, as well as mediators and other circulating agents, may change and, in particular, impair the EPO response to blood loss and anemia intra- and postoperatively. Knowledge about endogenous EPO formation in the perioperative phase gains clinical significance in view of the availability of recombinant human erythropoietin, which may potentially be useful to

support recovery from surgical blood loss and reduce transfusion requirements.

So far, perioperative studies on EPO levels have focused mainly on renal transplantation [11, 12]. In this case, however, EPO levels are influenced by variations in the ability of the grafted kidneys to produce EPO, and these investigations therefore allow few conclusions about the effect of operative trauma itself. The results of the few studies on EPO levels in patients undergoing surgery associated with major blood loss other than renal transplantation are contradictory. Whereas two groups of investigators reported no increases [13, 14], others found that EPO levels increased significantly [15]. Still another study suggested that there is a relative deficiency in EPO production after coronary artery bypass graft, but not after cholecystectomy [16].

In the present paper we report perioperative plasma EPO levels in patients undergoing surgery for hip arthroplasty or revision hip arthoplasty. These patients participated in a preoperative autologous blood donation program. EPO concentrations during preoperative deposit were determined [2], allowing a direct comparison between EPO formation after blood loss with and without operative trauma.

Patients and methods

Patients

Ten patients out of a group of 12 who had been studied during preoperative deposit [2] were followed up perioperatively. The general data of these patients are shown in Table 1. Exclusion criteria for the previous study had been: anemia, coronary heart disease, congestive heart failure, uncontrolled hypertension, severe obstructive or restrictive pulmonary disease, infections or malignant disease, cerebral sclerosis, syncopes, and a serum creatinine greater than 1.3 mg/dl.

Operations, anesthesia, monitoring

The patients were undergoing hip arthroplasty or revision hip arthroplasty. General anesthesia was induced with thiopental and maintained with enflurane in nitrous oxide/oxygen, supplemented with small repetitive doses of fentanyl. Intubation and controlled ventilation were facilitated with vecuronium.

Table 1 General data of the patients

Sex m		7
f		3
Age (years)		
	X±SD	56.6±10.0
	range	39–68
Height (cm)		
	X±SD	169.5±12.5
	range	150–190
Weight (kg)		
	X±SD	70.1±16.2
	range	46–110

For spinal anesthesia 3–3.5 ml bupivacaine 0.5% were used; in one revision operation the patient received a combination of spinal anesthesia and epidural anesthesia. The patients received oxygen via facemask.

Blood pressure was monitored by oscillometric measurement, central venous pressure via indwelling catheter. A urine production of at least 1 ml/kg body wt. per hour was required.

Arterial oxygen saturation of hemoglobin was monitored by pulsoxymetry (Pulsoxymeter N-100E, Nelcor) during the operation and on the day of the operation. Intervention levels were 95% intraoperatively, 90% postoperatively.

Blood loss into suction was measured, sponges were weighed, and blood loss into drapes was carefully estimated.

Transfusion

The following amounts of autologous whole blood had been predeposited: 4 units for seven patients, 3 units for two patients, and 2 units for one patient. In the case of patients for whom less than three blood units had been deposited and in the case of patients scheduled for revision hip arthroplasty, intra- and postoperative autotransfusion with a cell separator (Cell Saver III, Haemonetics) was used in addition to preoperative deposit. Autologous blood or homologous packed red cells were transfused if the hemoglobin concentration fell below 9 g/dl.

Laboratory investigations

Blood samples. For blood cell counts and for the determination of hemoglobin, EPO, C-reactive protein (CRP), and fibrinogen, blood samples were obtained prior to anesthesia, immediately prior to the operation, and postoperatively, as well as 2 (only hemoglobin and erythropoietin), 6, 12, 24, and 36 h after the end of the operation and on days 2–5, 7, 10, and 14. Blood samples for analysis amounted to a total of 90 ml during the study.

Determination of erythropoietin. EPO concentration in EDTA plasma was determined by radioimmunoassay as described previously, using a rabbit antiserum derived against rhEPO and iodinated rhEPO as tracer [17]. The geometric mean in healthy adults is 17.9 mU/ml, the 5–95 percentile range 11–31 mU/ml, interassay coefficient of variation 7% ($n=84$).

Blood cell count. Hemoglobin concentration, erythrocyte count, MCV, leukocyte, and platelet counts were determined by automized routine laboratory techniques. Reticulocytes were counted manually.

Determination of C-reactive protein. Serum CRP was determined by fluorescence immunoassay (5–95 percentile range in healthy adults: 0.068–8.2 mg/dl) [18].

Fibrinogen. The fibrinogen concentration was determined by a coagulation method [19].

Statistics

The data were analyzed with SAS. Sample distribution was tested for normality with the Shapiro-Wilk statistic [20]. Samples were compared using analysis of variance for repeated measurements or the Friedman χ^2-test, as appropriate. For the comparison of two samples the Wilcoxon signed rank test was used. The significance level was set at 5%.

Table 2 Anesthesia, operation

Anesthesia	
Regional (*n*)	8
General (*n*)	2
Operation	
Hip arthroplasty (*n*)	8
Revision hip arthroplasty (*n*)	2
Duration of operation (min)	
Median	115
Range	70–280

Results

Three women and seven men participated in the study. The general data are shown in Table 1. Eight patients were operated on for hip arthroplasty, two patients for revision hip arthroplasty. The type of anesthesia, the type of surgery and the duration of the operation are shown in Table 2.

The *blood loss* during the operation varied within a wide range (390–6500 ml, median 790 ml), as did the substitution with crystalloid and colloid solutions and with autologous and homologous blood (Table 3). The median blood loss on the day of the operation (850 ml) is of similar magnitude as during the operation; the variation, however, is considerably smaller.

The *hemoglobin concentrations* of the patients showed an initial decline due to the expansion of blood volume necessary to maintain a stable cardiocirculatory state after induction of anesthesia, followed by a further decline in the course of the operation (Fig. 1). The lowest hemoglobin concentrations were measured 2 h post-operatively. Thereafter, the hemoglobin concentrations increased gradually due to transfusion and erythropoiesis. The changes were significant ($p < 0.0001$). On day 7 the hemoglobin concentrations were comparable to the preoperative values.

The preoperative values of the *EPO concentrations* (26 mU/ml, median) were significantly different from the value prior to autologous deposit (17 mU/ml; Fig. 2). There was a small decrease immediately postoperatively. Two hours after the end of the operation the EPO concentrations began to rise, reaching a peak at 24 h. Between 24 and 36 h postoperatively the EPO concentrations decreased again. The concentrations remained elevated above the normal range until the fourth postoperative day. The changes are statistically significant ($p < 0.005$). On day 7 the EPO concentrations were still significantly elevated above the preoperative value ($p < 0.05$).

Recticulocyte counts gradually increased from 46000 (0–137000)/μl (median, range) prior to the operation to 73000 (0–207000)/μl on the tenth postoperative day. The changes are not significant.

The serum concentrations of *C-reactive protein* showed an increase beginning 6 h postoperatively, a peak at 36 h after the end of the operation, and a slow decline thereafter (Fig. 3). They remained elevated above baseline values until day 14. The changes are significant ($p < 0.001$).

The *fibrinogen concentrations* demonstrated a slower and less pronounced rise on the second postoperative day and remained elevated during the period of investigation (Fig. 4). The changes are significant ($p < 0.0001$).

Discussion

In a previous investigation during predeposit of autologous blood the hemoglobin concentration of the patients decreased from 14.3 ± 0.1 g/dl (X + SD) prior to donation to a minimum of 11.7 ± 0.7 g/dl [2]. Plasma immunoreactive erythropoietin (EPO) (17.8 ± 5.1 mU/ml prior to donation) demonstrated a moderate, biphasic increase after each donation, with an initial peak 24 h after donation followed by a plateau at lower, but still

Table 3 Blood loss and transfusion

	During operation	Day of operation	After day of operation	Total
Blood loss (ml)				
median	790	850	120	1720
range	390–6500	160–1730	20–780	480–8100
Transfusion (ml)				
Predonated autologous blood				
median	450	700	0	1750
range	0–1800	0–1800	0–1350	850–1850
Autotransfusion				
median	0	0	—	0
range	0–1000	0–475	—	0–1475
Homologous packed red cells				
median	0	0	0	0
range	0–0	0–750	0–750	0–1500

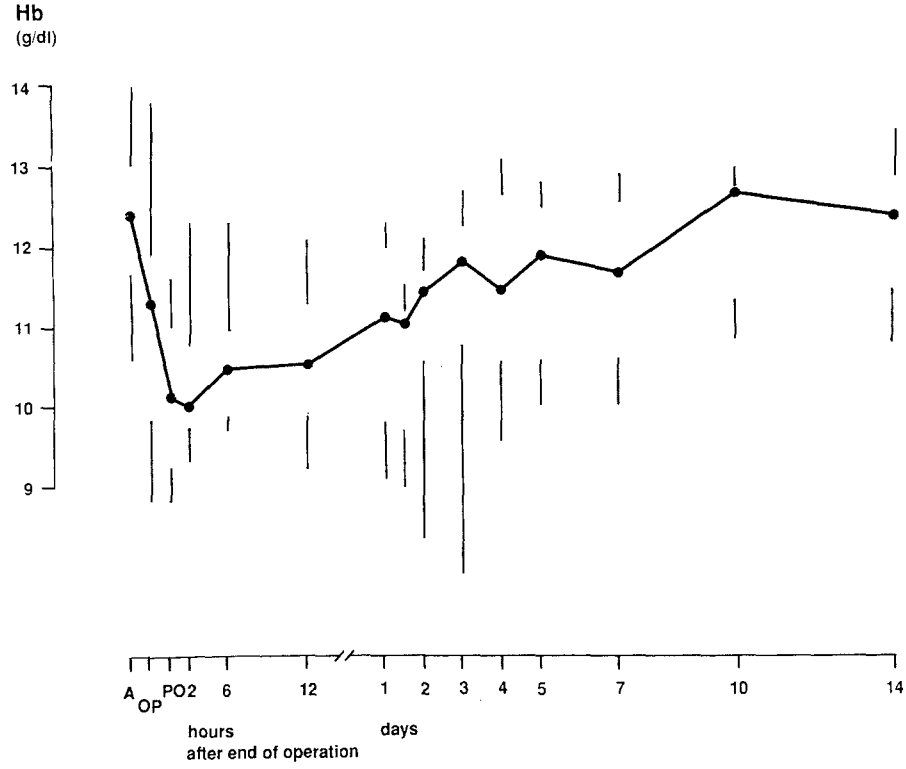

Fig. 1 Hemoglobin concentration (g/dl) minimum – Q_1 – median – Q_3 – maximum. (*A* prior to anesthesia, *OP* begin of operation, *PO* after operation)

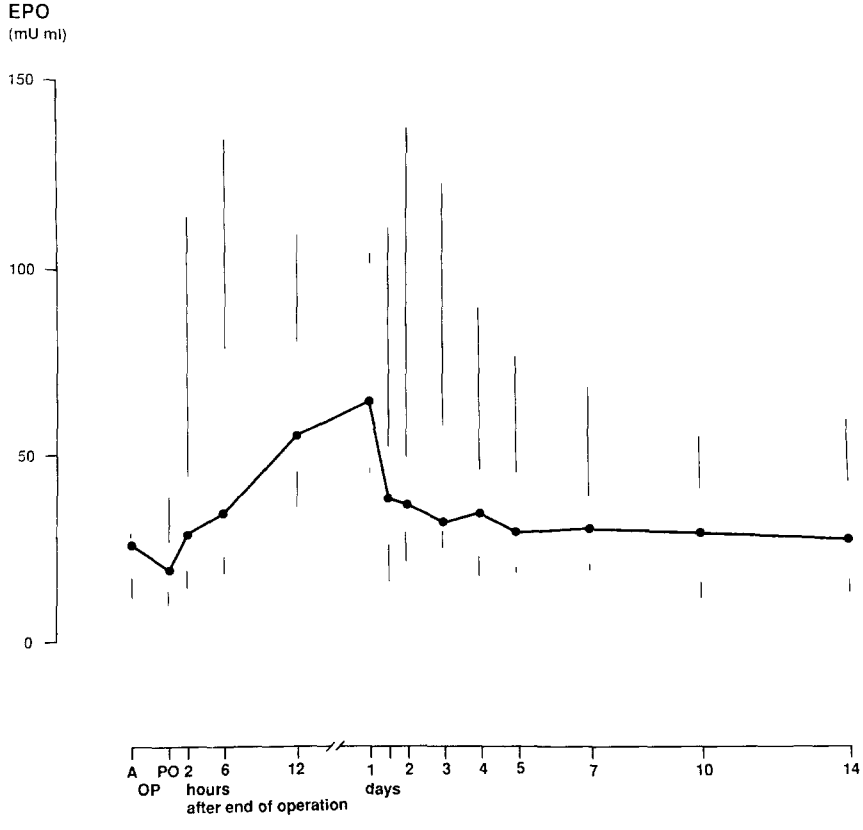

Fig. 2 Plasma erythropoietin concentration (mU/ml) minimum – Q_1 – median – Q_3 maximum. (*A* prior to anesthesia, *OP* begin of operation, *PO* after operation)

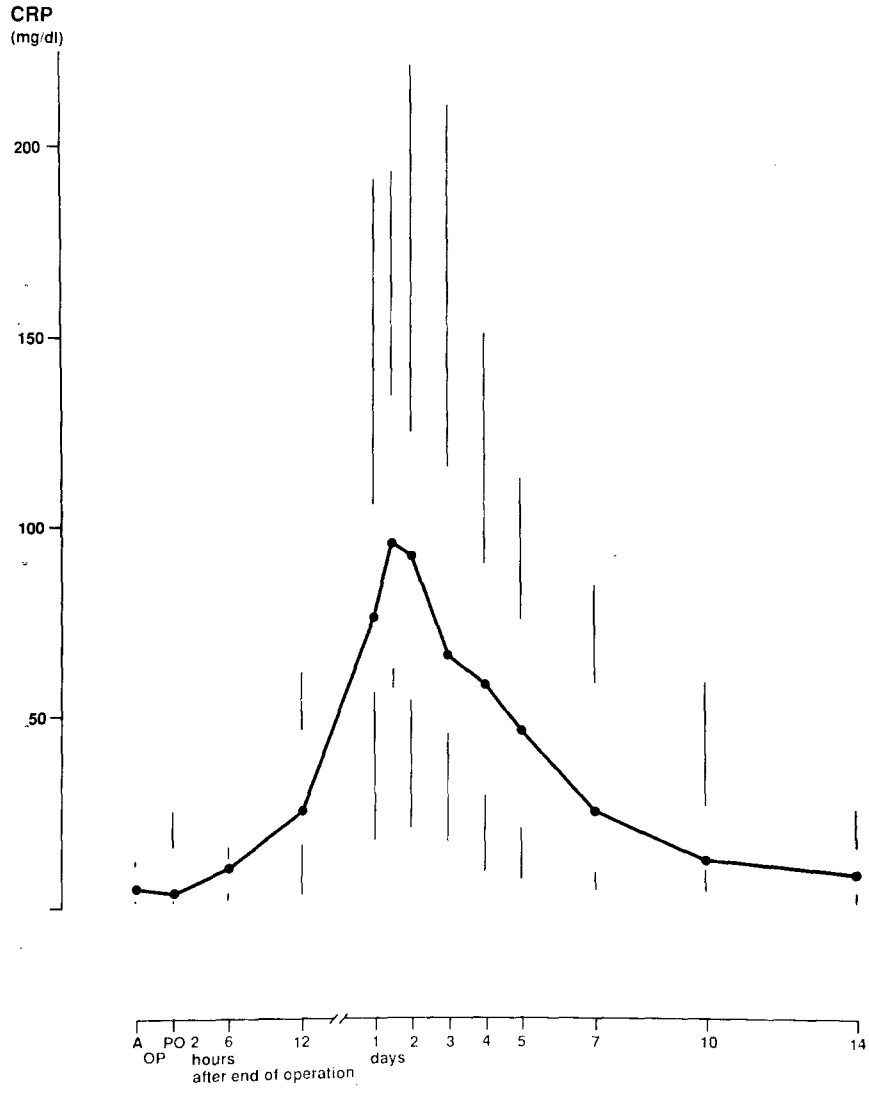

Fig. 3 C-reactive protein (mg/dl) minimum – Q_1 – median – Q_3 – maximum. (*A* prior to anesthesia, *OP* begin of operation, *PO* after operation)

elevated levels. Only the peak concentration after the second (35.5 ± 15.5 mU/ml), third (38.0 ± 14.5 mU/ml), and fourth (36.1 ± 11.0 mU/ml) donation exceeded the 95 percentile of healthy adults.

In the present study the hemoglobin concentrations fell from 12.4 (10.6–14.0) g/dl (median, range) before surgery to 10.0 (9.3–12.3) g/dl 2 h after the operation. The decrease in hemoglobin concentration was followed by a rise in EPO concentration, beginning 2 h postoperatively. A peak concentration of EPO at 64 (45–104) mU/ml (median, range) was measured 24 h after the end of the operation. Between the first and third postoperative day hemoglobin concentrations ranged from 10.4 to 11.1 g/dl, corresponding to an EPO concentration between 38 and 31 mU/ml. In the further postoperative course hemoglobin concentration increased gradually, and it was not significantly different from the preoperative value on the seventh postoperative day. EPO concentration remained significantly elevated above the preoperative value at this time.

The time lag between the decrease of the hemoglobin concentrations and the increase of EPO is similar to the time lag after exposure to normo- or hypobaric hypoxia [21]. It is probably due to the same factor – the time required for transcription and translation of the EPO gene [22].

The initial time course of the EPO concentrations after the operation – showing a peak followed by a plateau – mimics the time course after blood donation [2, 3]. In contrast to the situation during and after blood donation, intra- and postoperative blood loss was substituted by crystalloid and colloid fluids to maintain isovolemia. Thus, although short periods of limited hypvolemia cannot be excluded, it does not seem likely that postoperative correction of hypovolemia plays an important role in this biphasic pattern of EPO concentrations. Since oxygen saturation of hemoglobin was measured continuously for 24 h perioperatively, transient hypoxemia can be excluded as a cause of increased EPO concentrations during this time.

Interestingly, a similar time course with an early decline of EPO levels has also been observed in human beings and rodents [23, 24] exposed to continuous hypo- or normobaric hypoxia. The precise mechanisms

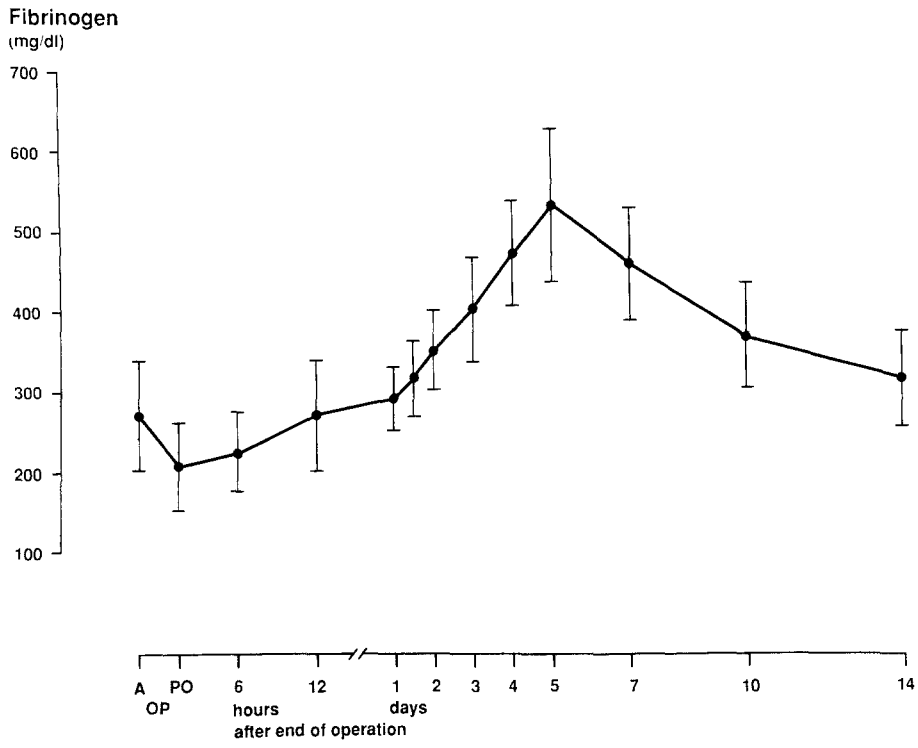

Fig. 4 Fibrinogen (mg/dl; X ± SD). (*A* prior to anesthesia, *OP* begin of operation, *PO* after operation)

leading to this phenomenon have not been defined [2]; it may be due to adaptation to hypoxia of the cellular sensor that controls EPO production, or to compensatory mechanisms increasing oxygen availability. It does not seem to result from short-loop feedback inhibition [25].

The higher concentrations attained during the peak as well as during the plateau phase after operative blood loss compared with the values attained after autologous donation [2] may be explained by the more pronounced degree of anemia. Plateau phase values are similar to the EPO concentration found in patients with anemia not due to renal disease or with aplastic anemia with comparable hemoglobin concentrations [4, 26]. Thus, EPO plasma levels in the early postoperative phase show an adequate response to anemia and do not seem to be appreciably influenced by the neuroendocrine response to trauma, by mediators of inflammation, or by the postoperative catabolic state. C-reactive protein and fibrinogen – as early and late acute-phase proteins, respectively [27, 28] – show the postoperative time course previously described for major operative trauma not complicated by infection [27, 29] and indicate that reparative processes persist during the whole period of investigation. There is no close relation, or inverse relation, between EPO levels and the levels of these acute-phase proteins; i.e., EPO production does not seem to be distinctly modified in the manner of or by acute-phase or anti-acute-phase proteins.

Efficient stimulation of EPO secretion by intra- and postoperative anemia of the degree attained in this study is of short duration only. It is feasible that postoperative anemia may be alleviated more quickly by treatment with rhEPO, if this seems desirable. Such treatment is effective in anemia due to end-stage renal disease [30] and in autologous deposit [31]. On the other hand, there may be other factors limiting erythropoiesis during the immediate postoperative period, i.e., the availability of iron [32] and the postoperative catabolism.

In the late postoperative phase the EPO concentrations remain significantly elevated, although the hemoglobin concentrations return to values comparable to those measured preoperatively. This is in accordance with the results of another investigation [15] and indicates that factors other than anemia may contribute to the increased EPO concentration during this phase. At this time the early, neuroendocrine response to trauma ("ebb phase") has been superseded by the "flow phase" with an increase in metabolic rate, body temperature, oxygen consumption, and cardiac output due to the new, metabolically active granulation tissue [33]. Although limited in the case of hip arthroplasty [34], these changes may influence renal EPO production by changing the global or local renal oxygen balance.

There may also be an increase in extrarenal production of EPO. The liver is normally responsible for approximately 10% of the EPO synthesis. As a response to trauma and inflammation the production of acute-phase proteins in the liver is increased manifold. It can be speculated that, in the context of these metabolic changes, hepatic EPO production may also be increased to some extent. Since EPO synthesis has been demonstrated in free macrophages [35–37], these cells involved in multiple ways in the inflammatory and reparative process may also contribute.

The time course and level of plasma EPO concentrations described here are similar to those found in another investigation in hip arthroplasty determining EPO at longer intervals [15]. A study investigating two groups of patients undergoing surgery for either cholecystectomy or coronary artery bypass graft found moderately increased EPO levels in the cholecystectomy group (postoperative mean hematocrit 34–36) and similar EPO levels in the CABG group (postoperative hematocrit 30–35) [16]. Although the hematocrit was significantly different in the two groups, EPO levels were not. The investigators suggested that the lower levels in the CABG group constitute a relative EPO deficiency. Interpretation of these data seems difficult, however, since the two groups were not comparable with respect to sex, age, and kidney function. The highest postoperative mean values of EPO (cholecystectomy group, first postoperative day; CABG group, second postoperative day) are similar to the highest values found in the present study. Preoperative EPO levels, however, were higher.

Two other investigations did not find a relevant increase in EPO concentration postoperatively [13, 14]. One of these studied patients after major surgery during postoperative ventilator therapy. Measurements were taken on the third day after the operation only. A mean hemoglobin concentration of 10 g/dl corresponded to EPO levels within the normal range. Reticulocyte counts, however, were elevated. The study may have missed an initial peak concentration of EPO. Since baseline values were not established, EPO levels on the third postoperative day – although not above normal – may still have been increased. A study of 50 patients undergoing surgery for hip arthroplasty did not show increases in postoperative EPO levels [14]. In this investigation an enzymatic immunoassay was used, resulting in considerably higher baseline values than those found in our study. It must be taken into consideration that the preoperative values in our study were already significantly elevated due to autologous blood donation [2]. No published data seem to be available on the validity of the immunoassay used in the range of low and moderately elevated EPO concentrations.

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