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Iron metabolism and erythropoiesis after surgery

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Background This was a prospective study comparing the effect of major and minor surgery on haematological variables concerning erythropoiesis, iron metabolism and acute-phase response proteins.

Methods Thirty-one otherwise healthy patients, 15 having major orthopaedic surgery and 16 undergoing minor surgery, were studied. Blood samples were taken before surgery and 1, 4, 10 and 28 days after operation.

Results Haemoglobin concentration was decreased for up to 4 weeks after surgery. Serum erythropoietin concentration and reticulocyte count were raised after major surgery only. Serum iron concentration dropped the day after major (to 23 per cent of its preoperative level) and minor (to 46 per cent of its preoperative level) surgery and remained lower for up to 28 days after major surgery. Serum transferrin concentration and transferrin saturation decreased after both types of surgery while ferritin concentration increased. Serum transferrin receptor concentration increased only 4 weeks after major surgery ($P < 0{\cdot}01$). The interleukin 6 peak (day 1) was greater after major than minor surgery, as was the C-reactive protein peak (day 4).

Conclusion Both major and minor surgery induce a state of hypoferraemia in the presence of adequate iron stores. The degree of this transient form of 'anaemia of chronic disease' is related to the extent of surgery. Iron supplementation in the first weeks after surgery (if iron stores were normal before operation) is ineffective.

Anaemia after surgery could be explained by blood loss during and after operation. However, there is evidence that the characteristics of postoperative anaemia are more similar to those of the anaemia of chronic disease (ACD) rather than iron deficiency[1,2]. ACD is seen in patients with inflammatory disorders and malignancy[3–5]. This type of anaemia is characterized by a decrease in plasma iron and transferrin levels despite adequate iron stores, and a reduction in erythropoiesis[3–5]. The mechanism of postoperative anaemia remains unknown although it could be an acute-phase 'inflammatory' effect of surgery[6–10]. The contribution of tissue damage, anaesthesia and blood loss to the extent of anaemia was studied in patients undergoing major and minor surgery.

Patients and methods

Thirty-one patients were included; 15 had major elective orthopaedic surgery and 16 had a minor surgical procedure (minimal blood loss, short operation). Major surgery included total hip replacement (12 patients), total knee replacement (one) and laminectomy (two). Minor surgery was correction of hallux valgus/exostosis (seven), arthroscopy of the knee (two), shoulder arthroplasty (four), laparoscopic repair of inguinal hernia (two) and laparoscopic cholecystectomy (one). No patient had a history of chronic inflammatory disease and all had normal preoperative levels of haemoglobin, serum ferritin, folic acid and vitamin B_{12}. Participants in an autologous blood transfusion programme were excluded. No patient had evidence of postoperative infection or haemolysis. No oral iron supplements were allowed during the study. This study was approved by the Medical Ethical Committee of Eemland Hospital. Informed consent was given by all patients.

Venous blood was taken at 08.00 hours on the day before the scheduled operation and on days 1, 4, 10 and 28 after operation. Total blood count was measured (E-5000 Hematology Analyser; Sysmex Toa, Kobe, Japan) including reticulocyte count (flow cytometric analysis; Sysmex R-1000)[11]. Serum erythropoietin was measured by an enzyme-linked immunosorbent assay (ELISA) (Boehringer, Mannheim, Germany; normal range 0·4–9·0 units/l). Serum transferrin receptor was determined as described previously (normal range 3·8–7·2 mg/l)[12,13]. Iron metabolism was further analysed by measuring serum iron (Hitachi 717; normal value 10–30 µmol/l), serum transferrin (normal value 2·2–3·6 g/l), transferrin saturation (calculated from serum iron and transferrin concentration; normal value 0·20–0·45) and serum ferritin (normal value 20–200 µg/l). C-reactive protein (CRP) was measured by turbidimetry (Hitachi 717, Boehringer, Mannheim, Germany; normal value 0–10 mg/l). Interleukin (IL) 6 (normal value less than 8 ng/l) and tumour necrosis factor (TNF) α (normal value less than 40 ng/l) were measured in serum using an ELISA[14,15].

Data are given as mean(s.d.). Statistical significance was assessed using Student's *t* test (two-sided). Non-parametric variables were tested with a χ^2 test. Correlations were analysed with the Mann–Whitney *U* test and Spearman rank correlation coefficient. Significance was accorded with a *P* value of less than 0·05.

Results

Demographic and perioperative characteristics are listed in *Table 1*. Blood transfusion was necessary in two patients with excessive blood loss (more than 1200 ml) after total hip replacement.

Mean preoperative values of all haematological variables tested did not differ significantly between the

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Table 1 Demographic and perioperative characteristics of the 31 patients undergoing surgery

	Major surgery	Minor surgery
Sex ratio (F:M)	11:4	6:10
Regional anaesthesia	13	7
General anaesthesia	2	9
Age (years)	65(11)	61(10)
Blood loss during operation (ml)	553(279)	4(13)*
Blood loss after surgery (ml)	530(288)	7(20)*
Duration of operation (min)	127(33)	56(23)*
Intravenous fluids (ml)		
During operation	3400(400)	1300(800)*
After operation	1000(700)	300(800)†

Values are mean(s.d.). *$P < 0.001$, †$P < 0.05$ *versus* major surgery (Student's *t* test)

groups. Changes in haemoglobin and serum erythropoietin concentration are shown in *Fig. 1*. There was a small, non-significant increase in reticulocyte count 1 week after major surgery (preoperative value $68(19) \times 10^9$/l; maximum value $95(23) \times 10^9$/l). The changes in iron metabolism are shown in *Fig. 2*. The decrease in serum iron and transferrin concentration as well as in transferrin saturation the day after surgery was greater after major than minor surgery ($P < 0.01$). The acute-phase reaction after surgery is documented by an increase in serum ferritin and CRP (*Fig. 3*) and IL-6 concentration[6,8,9]. The CRP peak after surgery was significantly higher after major surgery ($P < 0.01$). IL-6 concentration increased the day after surgery from 40(18) to 138(151) pg/ml after major surgery ($P < 0.01$) and from 30(14) to 62(45) pg/ml after minor surgery ($P < 0.01$) with a rapid fall thereafter. No significant increase in TNF-α concentration could be detected after surgery (data not shown). The relation between clinical data, markers of the acute-phase reaction and the haematological variables was tested. The duration of operation correlated significantly with the peak CRP level ($r_S = 0.65$, $P < 0.001$) and the blood loss correlated with the decrease in haemoglobin concentration the day after surgery ($r_S = 0.72$, $P < 0.001$). The lowest haemoglobin value after surgery correlated significantly with the peak serum erythropoietin concentration ($r_S = 0.49$, $P < 0.05$). Peak CRP concentration was proportional to the maximum decrease in serum iron ($r_S = 0.37$, $P = 0.05$) and transferrin ($r_S = 0.54$, $P < 0.01$) concentration as well as with the decrease in haemoglobin concentration on the day after surgery ($r_S = 0.69$, $P < 0.001$) and the peak serum erythropoietin concentration ($r_S = 0.66$, $P < 0.001$). No significant correlation could be found between the peak IL-6 concentration and the other haematological variables. In a subanalysis of the minor surgery group according to the method of anaesthesia (nine general, seven regional) no differences could be found with respect to changes in iron metabolism and erythropoiesis (results not shown).

Discussion

Postoperative anaemia has not been studied extensively because it was thought simply to be due to blood loss at operation. Such anaemia was easily treated with red blood cell transfusion and/or supplementation with iron. The disadvantages of blood transfusion such as transmission of viral infections and impairment of the immune system have drawn attention to alternative options[16]. It has been shown that iron supplementation after hip surgery has no major effect on erythropoiesis[1,2]. Analysis of the mechanism of postoperative anaemia may give more insight into changes in iron metabolism and may have clinical relevance.

In this study, surgery led to distinctive changes in iron metabolism: a decrease in the serum levels of iron and

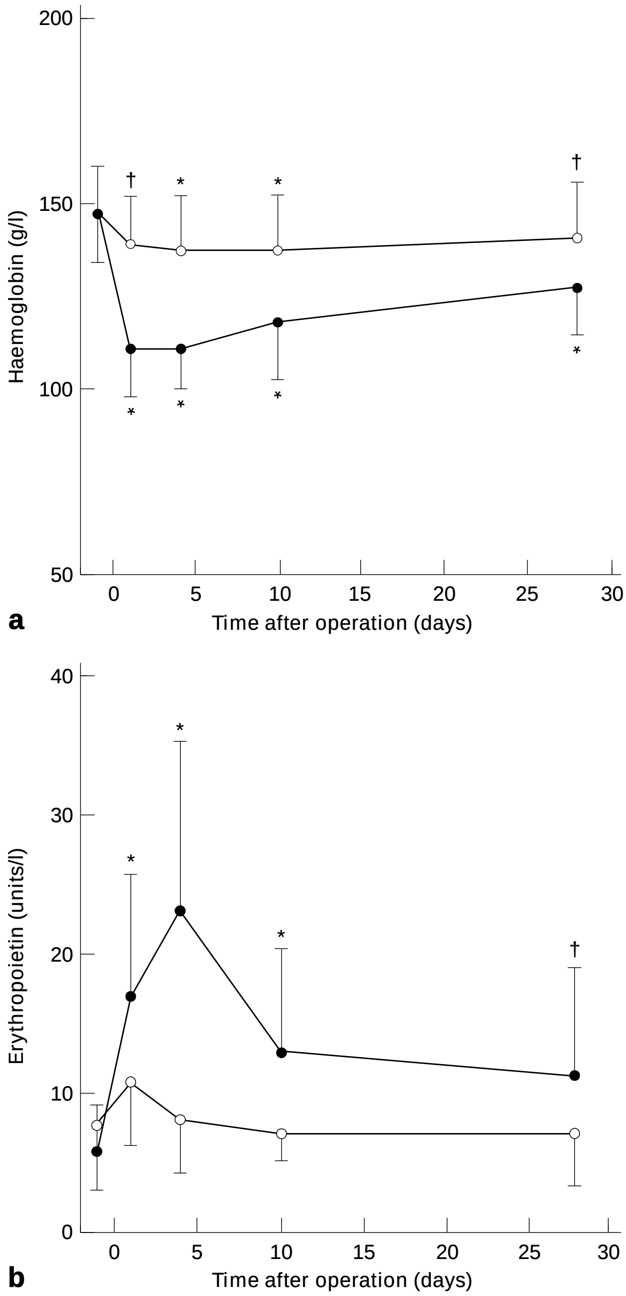

Fig. 1 a Mean(s.d.) haemoglobin concentration and b serum erythropoietin concentration in 31 patients undergoing major (●) or minor (○) surgery. *$P < 0.001$, †$P < 0.01$ *versus* preoperative value (Student's *t* test) transferrin and in transferrin saturation, and an increase in serum ferritin concentration[1,17–19]. These changes mimic those found in ACD and indicate a functional iron deficiency. This is in contrast to uncomplicated iron deficiency where low serum iron levels and transferrin saturation are accompanied by an increase in serum transferrin and a decrease in ferritin concentration. In the present patients serum transferrin receptor concentrations were normal (less than 6·0 mg/l) after surgery. An increase in these receptor values is seen in increased erythropoiesis as well as in iron deficiency (greater than 8·5 mg/l)[12,20]. In ACD, serum transferrin receptor concentrations are believed to be normal[20]. The hypothesis from this study is that after surgery signs of iron deficiency are overruled by those of anaemia of inflammation. In the first weeks after surgery, there is a failure of the bone marrow to increase erythropoiesis in response to the anaemia, as indicated by the minimal change in transferrin receptor levels or reticulocyte count. Only 4 weeks after major surgery was an increase in soluble transferrin receptor concentration observed, indicating increased erythropoiesis, while iron became

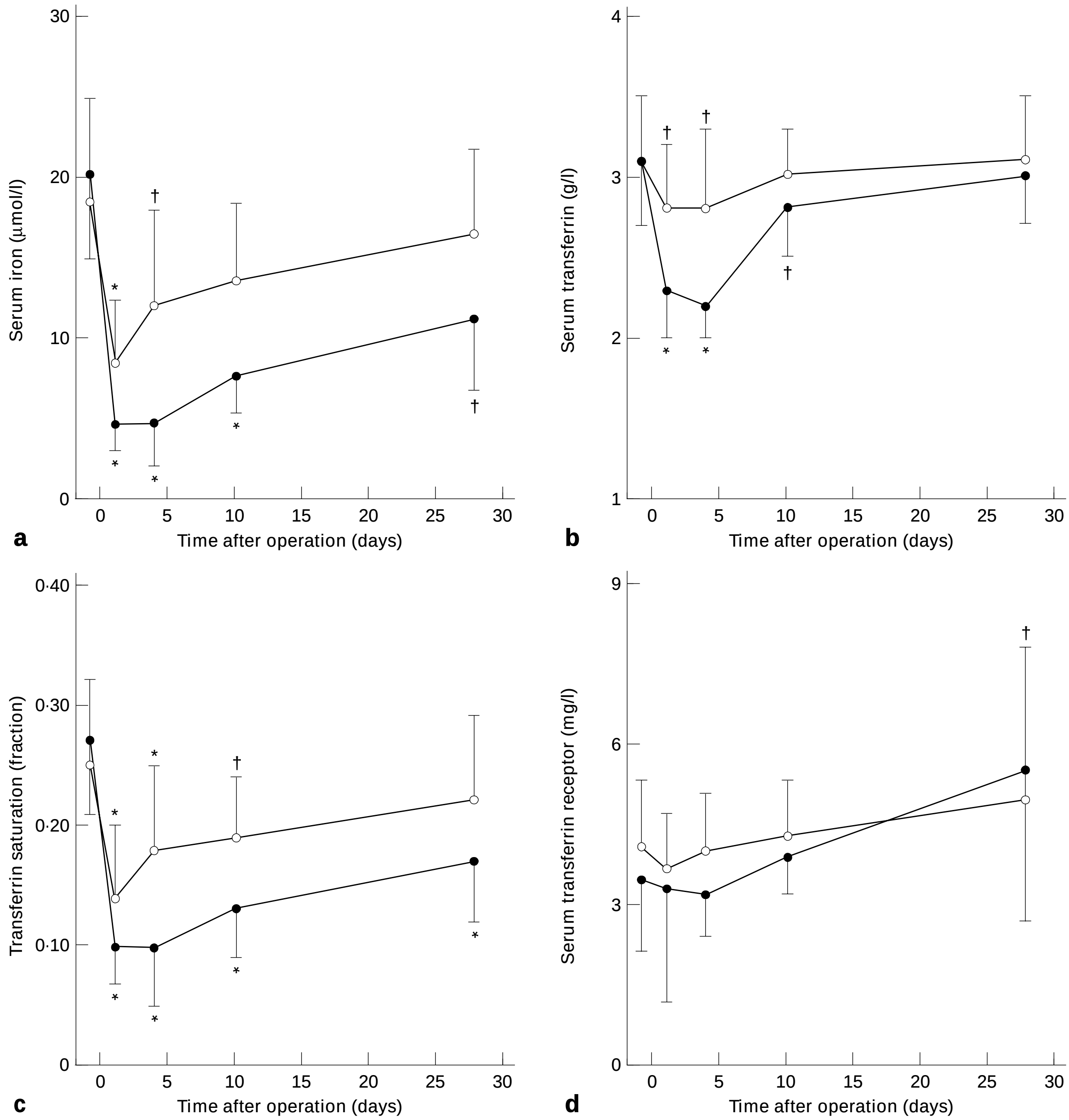

Fig. 2 Changes in iron metabolism in 31 patients undergoing major (●) or minor (○) surgery. Values are mean(s.d.); a serum iron concentration, b serum transferrin concentration, c transferrin saturation and d serum transferrin receptor concentration. *$P<0·001$, †$P<0·01$ *versus* preoperative value (Student's *t* test)

more available, reflected by increased serum iron levels and transferrin saturation. These findings explain the ineffectiveness of iron supplementation during the first weeks after surgery if normal iron stores are present before operation.

This study also shows that even minor surgery has a significant impact on iron metabolism, although changes are milder and recovery is faster than after major surgery. This indicates that blood loss is not essential in inducing changes in iron status. The method of anaesthesia seems to have no influence, in accordance with a study on serum iron after hysterectomy using two different types of anaesthesia[21]. The extent of surgery does influence iron metabolism. A more major operation results in a greater and more prolonged change in iron parameters, suggesting that the changes in iron metabolism are related to tissue damage. A marked acute-phase response was found after both types of surgery, although it was greater after major surgery. The concentration of IL-6, one of the most important acute-phase mediators, was increased the day after surgery. The CRP level was greatest 4 days after operation. The production of CRP by hepatocytes is induced by IL-6[22]. No increase in TNF-α, another mediator of the acute-phase response, was found after surgery in this study. A direct relation between cytokines and altered iron metabolism is described in chronic inflammation[5,23,24]. The release of cytokines leads to iron uptake by activated macrophages[24]. Cytokines (IL-1, IL-6) are directly involved in increased ferritin synthesis, which is under translational control[25,26]. In this study, the rise in CRP and fall in serum iron and transferrin concentration correlated significantly. Minor tissue damage can initiate an acute-phase reaction including the release of cytokines, and is sufficient to produce changes in iron metabolism.

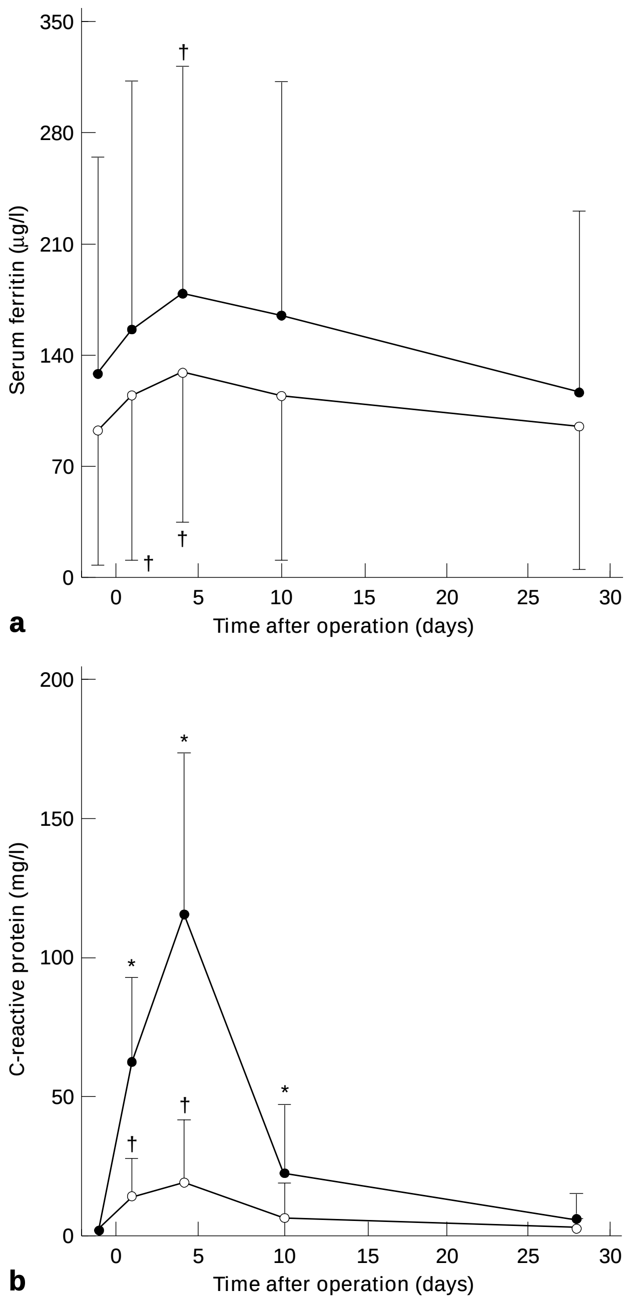

Fig. 3 a Mean(s.d.) serum ferritin and b C-reactive protein concentration in 31 patients undergoing major (●) or minor (○) surgery. *$P<0{\cdot}001$, †$P<0{\cdot}01$ *versus* preoperative value (Student's *t* test)

Even 1 month after both types of surgery, the haemoglobin concentration had not returned to the preoperative level. This cannot be ascribed to perioperative blood loss, dilution or blood sampling for this study. The changes in iron metabolism and the relative unavailability of iron for erythropoiesis after surgery may contribute to this prolonged postoperative anaemia. The inflammatory cytokines may also have a direct influence on postoperative erythropoiesis[5]. IL-6 may, unlike IL-1, stimulate rather than depress erythropoiesis[27], but IL-6 also induces anaemia by increasing plasma volume[28,29]. Further studies are necessary to gain more insight into a possible stress factor. An effect of cortisol has been suggested but is unlikely since cortisol concentration can be decreased after surgery too, similar to serum iron[21].

In conclusion, both major and minor surgery induce a state of hypoferraemia in the presence of adequate iron stores, and a marked acute-phase response. The degree of this transient anaemia is related to the extent of the surgical insult. Iron supplementation in the presence of normal iron stores is ineffective at this time.

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