



Treatment of anaemia after joint replacement

A DOUBLE-BLIND, RANDOMISED, CONTROLLED TRIAL OF FERROUS SULPHATE *VERSUS* PLACEBO

P. M. Sutton, T. Cresswell, J. P. Livesey, K. Speed, T. Bagga

From the Diana, Princess of Wales Hospital, Grimsby, and the Northern General Hospital, Sheffield, England

After total hip and knee replacement arthroplasty, patients may become anaemic and may be prescribed oral iron. There is, however, no published evidence that this is of benefit when used post-operatively. We treated 72 patients who were anaemic after primary total hip and knee arthroplasty by randomly allocating them to receive six weeks of either oral ferrous sulphate (35 patients) or a placebo (37 patients). Both groups of patients were similar in all aspects except for the treatment given. There was no statistically significant difference in the change of haemoglobin levels between the two groups. We therefore believe that the prescription of iron to all anaemic patients post-operatively should be avoided. The level of serum ferritin should be monitored at pre-operative assessment.

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Total hip replacements (THRs) and total knee replacements (TKRs) are common procedures in western societies. In the UK alone an estimated 60 645 THRs are carried out annually.¹ A recent audit of blood loss during hip and knee surgery reported a mean loss of 884 cm³ after THR and 462 cm³ after TKR, which caused anaemia in some patients.²

The severity of post-operative anaemia after these procedures is variable and is influenced by the amount of blood loss, the pre-operative level of haemoglobin, and intra-oper-

ative blood transfusion. Patients also vary in their ability to tolerate anaemia. There is no consensus as to treatment. Patients with marked anaemia may be given blood and others with mild or asymptomatic anaemia may be prescribed iron.

The role of iron supplementation in the treatment of iron deficiency anaemia is undisputed. To our knowledge there is only one published paper that addresses the issue of iron supplements after joint replacement.³ This study reported the results of a randomised trial of ferrous sulphate compared to no treatment for two to three weeks after hip surgery. No difference was found. Patients with low iron stores were excluded and this study, therefore, failed to assess the practice of giving iron supplements to all anaemic patients after joint replacement surgery. Additionally, the patient group was heterogeneous as almost 50% underwent surgery for a fracture of the femoral neck. Another study found some value in treating patients with ferrous sulphate for four weeks prior to joint replacement surgery.⁴

The aim of our study was to determine whether or not the prescription of oral iron to all anaemic patients after primary THR or TKR affects the post-operative haemoglobin level. We also determined the prevalence of iron deficiency in this group of patients.

Patients and Methods

All patients who entered the trial gave informed consent. The Local Research Ethics Committee also gave approval for the trial. During the period of study all 230 patients who underwent an elective primary THR or TKR were considered for entry into the trial. As part of the pre-operative assessment, their serum ferritin was measured as an indirect measure of the stores of body iron.⁵ Their mean serum ferritin was 92.4 ± 91.2 µg/l with 15 patients, having a value below the lower limit of normal (15 µg/l) which suggested a prevalence of iron deficiency of 6.5% in this cohort.

Patients were excluded who had a pre-operative level of haemoglobin <12 g/dl for men and <11 g/dl for women, were not able to give informed consent, were to be followed up elsewhere, had rheumatoid arthritis, as this condition is frequently associated with chronic anaemia, were taking ciprofloxacin, tetracyclines, antacids or bisphosphonates since these are known to interfere with iron metabolism or

P. M. Sutton, FRCS (Trauma & Orth), Consultant Orthopaedic Surgeon
T. Cresswell, FRCS (Ed), Specialist Registrar
Department of Trauma and Orthopaedics, Northern General Hospital,
Herries Road, Sheffield S5 7AU, UK.

J. P. Livesey, FRCS (Trauma & Orth), Consultant Orthopaedic Surgeon
K. Speed, MRC Path, Consultant Haematologist
T. Bagga, FRCS (Orth), Consultant Orthopaedic Surgeon
Diana, Princess of Wales Hospital, Scartho Road, Grimsby, North Lincolnshire DN33 2BA, UK.

Correspondence should be sent to Mr P. M. Sutton.

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Table I. Details of the 72 patients who were anaemic after primary joint replacement therapy and who were randomly assigned to receive either ferrous sulphate or placebo

	Placebo group (n = 37)	Treatment group (n = 35)
Primary surgery (number of patients)		
THR	21	16
TKR	16	19
Mean age (years)	70	70
Gender		
F	14	16
M	23	19
Median ferritin (μ g/l)	87	64
Mean haemoglobin (g/dl)		
Pre-operatively	12.9	12.7
Post-operatively	10.5	10.4
At review	12.1	12.4
Median number of days to review (mean)	45 (47)	46 (48)

were already taking iron salts or vitamin supplements which might include iron. There remained 72 patients for inclusion in the trial.

Patients underwent surgery and received post-operative management according to the protocol of each of the consultant surgeons who participated in the trial. This included the transfusion of packed cells when clinically indicated, as in patients with symptoms of anaemia such as dizziness or syncope, or if the haemoglobin level fell below 8 g/dl. All eligible patients had their haemoglobin level measured pre-operatively and between five and seven days after operation. Patients were considered for treatment if the latter measurement was within the range of 8 to 12 g/dl for men and 8 to 11 g/dl for women. These upper limits corresponded to the hospital's lower reference range for a normal haemoglobin level. The haemoglobin level at days five to seven was used as any anaemic patients with symptoms had already been identified and transfused. This prevented the transfusion of patients after entry into the trial. Patients who were transfused before this time were still considered eligible if their haemoglobin fell within the inclusion range.

Those patients who entered into the study were randomly assigned by the hospital pharmacy into two groups using computer generated random numbers (35 patients). One group received ferrous sulphate in 200 mg capsules and the second (37 patients) were given a gelatine placebo. Both groups were prescribed their capsules three times daily for six weeks after discharge from hospital. Both patients and investigators were blind to the treatment allocated until the end of the trial. Details of the patients are given in Table I. After six weeks all participating patients had a proforma completed by the clinic nursing staff. This noted the type of operation, the time from surgery, adverse effects, the pre-operative haemoglobin and ferritin levels and the five- to seven-day haemoglobin level. Measurement of the level of haemoglobin was carried out and patients were asked to return the bottles which contained their capsules, in order to estimate compliance.

Compliance was estimated by dividing the total number of tablets returned by the maximum number of tablets available for return. We assumed that compliance in the patients who did not return their treatment bottles was the same as those who did, and therefore, estimated compliance by using only the data from the patients who returned their treatment bottles.

Statistical analysis. Analysis was on an intention-to-treat basis using a PC statistical package (SPSS Inc, Chicago, Illinois). The study sample size of a minimum of 32 patients in each group was determined by a power calculation designed to detect a difference in the level of haemoglobin between the two groups of 0.75 g/dl with a power of 0.80. The main outcome measures were the differences in the increase in the level of haemoglobin from the post-operative level at five to seven days to the level after treatment in, and between, the two groups. They were normally distributed and for statistical analysis we used an independent samples *t*-test.

The profiles of the two groups were assessed for their similarity and all data were evaluated for normality by using the Shapiro Wilks test. Normality was assumed if $p > 0.05$. In both groups the pre-operative haemoglobin, post-operative haemoglobin and post-treatment haemoglobin were normally distributed and were analysed by using an independent samples *t*-test. The time intervals between surgery and outpatient review and the serum ferritin, and the number of capsules returned, were not normally distributed and were analysed by using the Mann-Whitney test. Categorical variables of gender and operation type were assessed by using the chi-squared test.

Results

As shown in Table I, we reviewed the placebo group at a mean of 47 days (27 to 104, median 45) after operation. Over this period the mean change in haemoglobin level was +1.63 g/dl (-1 to +3.6). The group which received ferrous sulphate was reviewed at a mean of 48 days (36 to 81, median 46). The mean change in haemoglobin level was +1.94 g/dl (-0.3 to +4.2). The treatment group, thus demonstrated a mean increase in haemoglobin of 0.31 g/dl more than the placebo group (95% CI -0.17 to 0.79). This difference was not statistically significant ($p = 0.18$).

It is possible that individual patients may benefit from iron treatment even if the group as a whole does not. We therefore assessed all patients with an increase in haemoglobin level of >0.75 g/dl. We chose 0.75 g/dl in accordance with our original calculation of sample size. In the treatment group, the haemoglobin increased by more than 0.75 g/dl in 31 patients (89%) compared to 33 patients (89%) in the placebo group.

Treatment bottles were returned by 24 patients (65%) in the placebo group and 23 (66%) in the treatment group. The number of tablets returned ranged between 0 and 126. The patients who received a placebo returned a mean of 29 tablets (median 0) compared with a mean of 30 tablets

(median 11) in those who received ferrous sulphate. This difference is not statistically significant ($p = 0.7$). We, therefore, estimated a compliance of 75% in the placebo group and 77% in the treatment group. At review the patients were questioned about adverse effects which they felt might be attributable to the capsules. There were no major adverse effects in either group, although eight patients in each group reported minor gastrointestinal disturbances.

Discussion

The haemoglobins are a complex group of related molecules which comprise globular proteins and an iron-containing porphyrin derivative known as haeme. It is the haeme portion of haemoglobin which interacts to carry oxygen. Adequate iron stores are essential for normal haeme production and erythropoiesis. In adults, iron losses are usually small and unregulated, although this loss is normally balanced by the amount of iron absorbed in the small intestine. After acute haemorrhage, erythropoiesis is stimulated, and temporarily depletes body iron stores leading to increased iron absorption. In adults, dietary intake exceeds absorption by a mean of between 94% and 97% so that any additional iron requirement is usually met by a normal diet.⁶

The hypothesis of our study was that most patients who undergo hip and knee replacement surgery are not iron deficient, and, therefore, dietary iron supplementation will have no effect. Our results confirm this. The prevalence of iron deficiency in our patients was only 6.5% and there was no statistically significant difference in the effect of either ferrous sulphate or the placebo in increasing the level of haemoglobin.

The lack of any effect by oral iron can be explained on physiological grounds alone, although it is possible that it is partly due to poor patient compliance. Little difference between the two patient groups would be expected if the patients had not taken the iron capsules as instructed. Our assessment of compliance assumed that the patients who did not return their treatment bottles were as compliant as those who did. If the patients who failed to return their treatment bottles had actually taken no capsules, the overall compliance in the treatment group falls to 50%. If true, as this would be an accurate reflection of compliance in clinical practice, it does not alter the fact that the prescription of oral iron is of no benefit. Adverse effects are reported in up to 20% of patients who take iron.⁷ In our study, approximately 22% of patients in each group complained of minor gastrointestinal disturbances including diarrhoea, constipation and nausea. This data is subjective and may be influenced by many factors other than the type of treatment given.

Although we have demonstrated that iron supplementation has no benefit when used to treat all anaemic patients after THR or TKR, it may be of benefit to the small group of patients with iron deficiency many of whom may be identified pre-operatively. All patients who are admitted for THR or TKR should have a full blood count.⁸ We assessed the pre-operative haemoglobin in the 15 patients who were iron-deficient, based on their ferritin levels and found that 11 were anaemic. This left a subgroup of only four patients with iron deficiency and a normal haemoglobin out of the original 230. Patients who are admitted for THR or TKR and found to be anaemic should be investigated and iron deficiency should be detected. Iron supplements will then be of clinical benefit and should be given before operation in order to increase iron stores as this will reduce the fall in the level of haemoglobin after operation.⁴ There is evidence that the inflammatory effect of surgery alters iron metabolism and decreases the efficacy of oral iron given post-operatively.⁹

The practice of routinely prescribing oral iron supplements post-operatively to all anaemic patients after primary hip or knee replacement surgery should be avoided. Iron deficiency should be determined by measuring the ferritin level pre-operatively and oral iron therapy should be reserved for those patients who have a proven iron deficiency and should be given before operation.

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