Prophylactic Iron Supplementation After Roux-en-Y Gastric Bypass

A Prospective, Double-blind, Randomized Study

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Objective: To determine whether prophylactic oral iron supplements (320 mg twice daily) would protect women from iron deficiency and anemia after Roux-en-Y gastric bypass.

Design: Prospective, double-blind, randomized study in which 29 patients received oral iron and 27 patients received a placebo beginning 1 month after Roux-en-Y gastric bypass.

Setting: Tertiary care medical center.

Patients and Interventions: Complete blood cell count and serum levels of iron, total iron binding capacity, ferritin, vitamin B₁₂, and folate were determined preoperatively and at 6-month intervals postoperatively in 56 menstruating women who had Roux-en-Y gastric bypass.

Main Outcome Measure: Incidence of iron deficiency and other hematological abnormalities in each treatment group.

Results: Hemoglobin, hematocrit, and vitamin B₁₂ levels were significantly decreased compared with preoperative values in both groups. Conversely, folate levels increased significantly over time in both groups. Oral iron consistently protected development of iron deficiency in the iron group. Ferritin levels did not change significantly in the iron group. However, in placebo-treated patients, ferritin levels 2 years postoperatively were significantly decreased compared with preoperative levels. There was no difference in the incidence of anemia between the 2 groups. However, the incidence of microcytosis was substantially greater ($P = .07$) in placebo-treated than iron-treated patients.

Conclusions: Prophylactic oral iron supplements successfully prevented iron deficiency in menstruating women after Roux-en-Y gastric bypass but did not consistently protect these women from developing anemia. On the basis of these results we now routinely recommend prophylactic iron supplements to menstruating women who have Roux-en-Y gastric bypass.

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Because comparative studies have consistently shown that Roux-en-Y gastric bypass (RYGB) produces better weight loss than several modifications of stapled gastroplasty, RYGB has come to be recognized as the “gold” standard operation for treatment of morbid obesity.¹ ² Exclusion of nearly all of the stomach and the entire duodenum from digestive continuity predisposes patients who have RYGB to develop deficiencies in vitamins and minerals that are metabolized in the upper digestive tract. Although multivitamin supplements are routinely recommended as prophylaxis against the metabolic deficiencies associated with RYGB, our group³ reported that daily multivitamin supplements do not consistently protect patients from developing iron deficiency and anemia after RYGB. Young, menstruating women were particularly prone to this problem. This observation led us to design a prospective randomized study to determine whether prophylactic oral iron supplements could protect menstruating women against iron deficiency and anemia after RYGB.

## Results

Follow-up ranged from 12 to 76 months in the iron group (mean, 39.4 ± 21.3 months) and 3 to 68 months in the placebo group (mean, 28 ± 17 months). Nine of the 56 patients did not complete the minimum 2 years of blood testing, including 3 in the iron group and 6 in the placebo group. Three of these patients were unavailable for follow-up. Six were withdrawn, including 3 who became pregnant, 2 for medical reasons (bleeding mar-
PATIENTS AND METHODS

Fifty-six women agreed to participate in a prospective study in which they were randomly assigned to receive an oral iron supplement, ferrous sulfate (Feosol, SmithKline Laboratories, Philadelphia, Pa) or a similar-appearing placebo after having RYGB. Randomization was carried out before initial distribution by drawing a labeled card from a shuffled stack. The iron and placebo were identically packaged. Labels were removed by the clinical diettian (H.A.K. or L.B.B.) before the vials were distributed to participating patients. The patients and the surgeon (R.E.B.) were blinded to the study medication. The ferrous sulfate was prescribed in 320-mg doses that were taken twice daily beginning 4 weeks postoperatively. Women who were no longer actively menstruating or previously had had a total hysterectomy were excluded from the study. All patients were told to take a multivitamin supplement daily.

A complete blood cell count and serum samples for iron, total iron-binding capacity, ferritin, vitamin B\textsubscript{12}, and folate were obtained preoperatively and at each postoperative visit beginning at 3 months. Blood tests were performed at no cost for a minimum of 5 years postoperatively. We had hoped that all participants would remain in the study for a minimum of 2 years. Table 1 shows the demographic features of the 2 groups of patients before operation. The age of patients in the iron group ranged from 22 to 50 years, as compared with 24 to 49 years in the placebo group. Preoperative weight ranged from 89 to 180 kg in the iron group and 93 to 189 kg in the placebo group. All RYGB procedures were performed by 1 surgeon (R.E.B.) with techniques described in detail elsewhere. The Roux limb in the “standard” RYGB was measured at 50 cm. However, 11 patients who were extremely obese (body mass index, >30 kg/m\textsuperscript{2}) underwent a “long-limb” modification in which the Roux limb measured 130 cm.

Patients who developed iron deficiency postoperatively were treated at no cost with oral ferrous sulfate, 320 mg twice daily. Patients who developed vitamin B\textsubscript{12} deficiency were usually treated with oral supplements of 500 µg daily. Because folate deficiency was recognized only in patients who were not regularly taking multivitamin supplements, multivitamins alone were recommended as treatment for it. A positive response to treatment was defined as return of the measurement value of the deficient micronutrient to a level at or above the lower limit of the reference range for our laboratory (Table 2 and Table 3).

Statistical analysis of data was performed with the \chi\textsuperscript{2} test, Fisher exact test, unpaired Student t test, and a 2-way analysis of variance. Patients with preoperative deficiencies were included in the analysis to observe the course of these deficiencies postoperatively. These deficiencies were not treated before operation. Inclusion of the low preoperative laboratory values did not alter the results. Patients in the placebo group who developed iron deficiency were dropped from subsequent analysis if they were compliant in taking prescribed oral iron supplements. Conversely, laboratory results of noncompliant patients in the placebo group were analyzed through the end of the study.

<table>
<thead>
<tr>
<th>Table 1. Clinical Features of Patient Groups*</th>
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<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Iron</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Mean ± SD age, y</td>
</tr>
<tr>
<td>Type of Roux-en-Y gastric bypass, No. of patients</td>
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<tr>
<td></td>
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<tr>
<td>Mean ± SD weight, kg</td>
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* There was no difference in age, preoperative weight, or type of operation between the 2 groups.

Table 2 compares preoperative vs postoperative measurements of the vitamin B\textsubscript{12} and folate levels in both groups of patients. Mean vitamin B\textsubscript{12} levels were significantly decreased compared with preoperative levels at each interval beginning at 12 months postoperatively. Conversely, mean folate levels were significantly increased compared with preoperative levels at 12, 18, and 24 months postoperatively. There was no difference in the incidence of vitamin B\textsubscript{12} or folate deficiency between the 2 groups.

Table 3 compares preoperative and postoperative hematological variables in the 2 groups. Hemoglobin and hematocrit levels were significantly decreased compared with preoperative values in both groups after 12 months postoperatively. Ferritin levels did not change significantly in the iron group. However, in placebo-treated patients, ferritin levels at 2 years or more postoperatively were significantly decreased compared with preoperative levels. Mean iron levels in the placebo group were significantly lower than those in the iron group only at 6 months postoperatively. Moreover, 9 placebo-treated patients (33%) did not develop iron deficiency during the study. There was no correlation between post-
operative weight loss and development of any meto bolic deficiency in this study.

Iron deficiency was recognized preoperatively in 3 patients in each treatment group. One patient in each group had borderline anemia. Folate deficiency was identified preoperatively in 5 patients in the iron group and 3 in the placebo group. Low vitamin B12 levels were noted preoperatively in 1 patient in the iron group and 4 patients in the placebo group. Low preoperative laboratory values did not decline in either group. In fact, preoperative iron levels increased to normal in patients who were given oral iron either at random at the outset of the study or later as treatment for their deficiency. Conversely, hemoglobin levels remained low but stable in the 2 patients with mild preoperative anemia. Deficient preoperative folate and vitamin B12 levels eventually normalized in all but 2 patients who were compliant in taking postoperative multivitamin supplements. Additional vitamin B12 supplements were required in the 2 patients whose deficiency did not respond to multivitamins alone.

Twelve patients were noncompliant in taking multivitamins at 1 or more postoperative intervals, including 5 patients in the iron group and 7 in the placebo group. There was no consistent correlation with compliance in regularly taking multivitamin supplements and development of iron, folate, or vitamin B12 deficiency in this study. Compliance was defined as taking supplements at least 5 times per week.

Six patients in the iron group developed iron deficiency. None of these patients were regularly taking their iron supplement during the interval immediately before recognition of the deficiency. Iron deficiency responded to oral supplements in 5 of these patients but persisted in the remaining patient who did not take the prescribed iron supplements. Of the 8 patients in the placebo group who developed iron deficiency postoperatively, 4 were compliant in taking prescribed oral iron supplements. Iron levels increased to normal levels in all of these patients. Conversely, iron levels remained low in 3 of the 4 patients who did not take prescribed iron supplements. There was a significant correlation between improvement of postoperative iron deficiency and taking prescribed oral iron supplements ($P = .005$ by Fisher exact test).

Eight of the 14 patients with iron deficiency developed a microcytic anemia. Four patients developed severe anemia (in each group), defined as a hemoglobin level of 100 g/L or less. Anemia was not recognized in the 6 remaining patients who developed iron deficiency postoperatively. However, anemia in the absence of iron deficiency was noted in 8 other patients, including 5 in the iron group. The anemia associated with iron deficiency responded to oral supplements in 4 of 7 patients who were compliant in taking prescribed supplements. Conversely, anemia in the absence of iron deficiency persisted in 4 patients throughout the study. Although there was no difference in the incidence of anemia between the 2 groups, the incidence of microcytosis was substantially greater ($P = .07$) in placebo-treated patients. No patient in this study had megaloblastic indies.

### PATHOGENESIS OF IRON DEFICIENCY AFTER RYGB

Iron deficiency after gastric bypass results from both malabsorption and maldigestion of dietary iron. The primary site of iron absorption is the duodenum, which is totally excluded from digestive continuity in RYGB. Normally, absorption of iron increases as stores decline. Absorption of iron in the diet is also facilitated by acid secretion in the stomach. In the normal stomach, inorganic iron is solubilized, then ionized to the ferrous form and chelated. The iron chelates are absorbed in the brush border, where they are oxidized to the ferric form and released into the circulation. Studies by Mason and Ito and Behrens et al independently showed markedly reduced acid secretion from the small upper pouch of patients who have had gastric bypass. Decreased acid production in the small gastric pouch probably plays an important role in the pathogenesis of iron deficiency after gastric bypass.

Postoperative changes in eating habits and food preferences may also contribute to development of iron deficiency after RYGB. Red meat is the most important source of iron in the typical American diet. Intolerance for red meat is common after gastric bypass. Avinoah et al reported a significantly higher incidence of iron, vitamin B12, and folate deficiency in patients who had RYGB and ate meat less than once per week vs patients.

### Table 3. Preoperative vs Postoperative Hematological Measures*

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Hemoglobin, g/L</th>
<th>Hematocrit</th>
<th>Iron Saturation</th>
<th>Serum Iron, µmol/L</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Iron</td>
<td>Placebo</td>
<td>Iron</td>
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*Data are expressed as mean ± SD. Reference range for hemoglobin is 125 to 155 g/L; iron, 8.1 to 24.2 µmol/L; iron saturation, 0.20 to 0.55; total iron-binding capacity (TIBC), 44.8 to 71.6 µmol/L, and ferritin, 20 to 120 µg/L.

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who consumed meat more than once weekly. Because a 24-hour recall diet history is routinely performed at each follow-up visit, we performed a post hoc comparison of dietary iron intake and meat-eating habits in 9 patients from each group who were regularly followed up for 36 months or more. There was no difference in either meat intake or estimated iron intake between the 2 groups. Moreover, all 18 patients ate meat occasionally, and 14 (78%) consumed meat at least once a day. This finding suggests that dietary intake of iron postoperatively did not affect the results of this study.

IRON REQUIREMENTS
IN MENSTRUATING WOMEN

The recommended dietary allowance for iron in women of reproductive age is 15 mg, which is the usual amount of iron in multivitamin supplements that contain minerals. Although the multivitamin supplements recommended to our patients contained the recommended dietary allowance for iron, this quantity of iron was not sufficient to protect many of these women from developing iron deficiency. There was no correlation between compliance with taking multivitamin supplements and development of iron deficiency in this study.

Iron stores in menstruating women are estimated at approximately 300 mg, which is about one third of the stores of adult males. Commercially available iron supplements, including the one used in this study, typically contain 50 to 60 mg of elemental iron. The recommended dose of elemental iron required to replete iron stores is in the range of 180 to 220 mg per day. The results of the present study suggest that taking two 320-mg ferrous sulfate capsules daily, containing a total of 100 mg of elemental iron, will prevent development of iron deficiency after RYGB.

Serum ferritin represents an approximation of the body’s iron stores. Low ferritin levels in patients who had RYGB suggest depletion of stored iron as a consequence of either inadequate oral intake or malabsorption. In placebo-treated patients, iron stores gradually became depleted and were significantly decreased compared with those of patients in the iron group at 2 years or more postoperatively. Conversely, ferritin lev-

### PROPHYLAXIS AND TREATMENT
OF POST-RYGB IRON DEFICIENCY

In the present study, nearly all of the patients who developed iron deficiency responded to oral iron supplements. This occurred despite exclusion of the duodenum, which is the primary site of dietary iron absorption. Unfortunately, 6 patients in the iron group did not regularly take their iron supplements. Noncompliance in taking prescribed iron supplements also correlated with persistence of iron deficiency in that iron levels remained low in all but 1 iron-deficient patient who did not take prescribed iron supplements. Conversely, serum iron increased to normal levels within 6 months of commencing therapy in patients with iron deficiency who complied with treatment recommendations.

Although prophylactic oral iron supplements successfully prevented iron deficiency in this study, they did not protect these women from developing anemia. Moreover, 8 subjects in the study (14%) developed anemia in the absence of iron deficiency. Anemia associated with iron deficiency responded to oral iron supplements in only 8 (57%) of the patients with microcytic indices. The development of severe anemia (hemoglobin level ≤ 100 g/L) in 4 patients was invariably related to missing scheduled blood tests and noncompliance with taking prescribed iron supplements. These results suggest that anemia in some women after RYGB may be caused by factors other than iron deficiency.

The onset of iron deficiency and anemia was rapid in this study in that 7 (12%) of patients developed iron deficiency and 12 (22%) developed anemia within the first 12 months postoperatively. The inherent inability to metabolize and absorb dietary iron is probably responsible for both the rapid development and refractoriness of iron deficiency and anemia in patients who have had RYGB. Because iron deficiency developed after the second postoperative year in several patients, it seems prudent to recommend that menstruating women continue taking prophylactic iron supplements indefinitely after RYGB. Hemoglobin, hematocrit, and iron levels should be checked at least annually until the time of menopause. At present it is not known whether the potential risk of iron deficiency disappears after menstruation ceases.

In summary, these results show that prophylactic oral iron supplements consistently prevent iron deficiency in menstruating women after RYGB. However, compliance in taking both multivitamins and oral iron supplements did not protect many of these women from developing anemia. The high correlation between taking oral iron and absence of iron deficiency in this study supports the use of prophylactic iron supplements in menstruating women after RYGB. These results also suggest that other factors are responsible for anemia in some women after RYGB.
This study was supported by a grant from SmithKline Laboratories, Philadelphia, Pa.

This research protocol (M-077) was approved by the institutional review board at UMDNJ–Robert Wood Johnson Medical School and was reviewed annually according to institutional review board policy.

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REFERENCES

JAMA
Administration of Methylprednisolone for 24 or 48 Hours or Tirilazad Mesylate for 48 Hours in the Treatment of Acute Spinal Cord Injury: Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial

Michael B. Bracken, PhD; Mary Jo Shepard, MPH; Theodore R. Holford, PhD; Linda Leo-Summers, MPH; E. Francois Aldrich, MD; Mahmood Farzad, MD; Michael Felhings, MD, PhD; Daniel L. Herr, MD; Patrick W. Hitchon, MD; Lawrence F. Marshall, MD; Russ P. Nockels, MD; Valentine Pascale, RPh; Phanor L. Perot, Jr, MD, PhD; Joseph Piepmeier, MD; Volker K. H. Sonntag, MD; Franklin Wagner, MD; Jack E. Wilberger, MD; H. Richard Winn, MD; Wise Young, MD, PhD; for the National Acute Spinal Cord Injury Study

Objective.—To compare the efficacy of methylprednisolone administered for 24 hours with methylprednisolone administered for 48 hours or tirilazad mesylate administered for 48 hours in patients with acute spinal cord injury.

Design.—Double-blind, randomized clinical trial.

Setting.—Sixteen acute spinal cord injury centers in North America.

Patients.—A total of 499 patients with acute spinal cord injury diagnosed in National Acute Spinal Cord Injury Study (NASCIS) centers within 8 hours of injury.

Intervention.—All patients received an intravenous bolus of methylprednisolone (30 mg/kg) before randomization. Patients in the 24-hour regimen group (n=166) received a methylprednisolone infusion of 5.4 mg/kg per hour for 24 hours, those in the 48-hour regimen group (n=167) received a methylprednisolone infusion of 5.4 mg/kg per hour for 48 hours, and those in the tirilazad group (n=166) received a 2.5 mg/kg bolus infusion of tirilazad mesylate every 6 hours for 48 hours.

Main Outcome Measures.—Motor function change between initial presentation and at 6 weeks and 6 months after injury, and change in Functional Independence Measure (FIM) assessed at 6 weeks and 6 months.

Results.—Compared with patients treated with methylprednisolone for 48 hours, those treated with methylprednisolone for 48 hours showed improved motor recovery at 6 weeks (P=.09) and 6 months (P=.07) after injury. The effect of the 48-hour methylprednisolone regimen was significant at 6 weeks (P=.04) and 6 months (P=.01) among patients whose therapy was initiated 3 to 8 hours after injury. Patients who received the 48-hour regimen and who started treatment at 3 to 8 hours were more likely to improve 1 full neurologic grade (P=.03) at 6 months, to show more improvement in 6-month FIM (P=.08), and to have more severe sepsis and severe pneumonia than patients in the 24-hour methylprednisolone group and the tirilazad group, but other complications and mortality (P=.97) were similar. Patients treated with tirilazad for 48 hours showed motor recovery rates equivalent to patients who received methylprednisolone for 24 hours.

Conclusions.—Patients with acute spinal cord injury who receive methylprednisolone within 3 hours of injury should be maintained on the treatment regimen for 24 hours. When methylprednisolone is initiated 3 to 8 hours after injury, patients should be maintained on steroid therapy for 48 hours.

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