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Randomised clinical trial: oral vs. intravenous iron after upper gastrointestinal haemorrhage – a placebo-controlled study

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SUMMARY

Background
Nonvariceal acute upper gastrointestinal bleeding (AUGIB) is often accompanied by post-discharge anaemia.

Aim
To investigate whether iron treatment can effectively treat anaemia and to compare a 3-month regimen of oral iron treatment with a single administration of intravenous iron prior to discharge.

Methods
Ninety-seven patients with nonvariceal AUGIB and anaemia were enrolled in a double-blind, placebo-controlled, randomised study. The patients were allocated to one of three groups, receiving a single intravenous administration of 1000 mg of iron; oral iron treatment, 200 mg daily for 3 months; or placebo, respectively. The patients were followed up for 3 months.

Results
From week 4 onwards, patients receiving treatment had significantly higher haemoglobin levels compared with patients who received placebo only. At the end of treatment, the proportion of patients with anaemia was significantly higher in the placebo group ($P < 0.01$) than in the treatment groups. Intravenous iron appeared to be more effective than oral iron in ensuring sufficient iron stores.

Conclusions
Iron treatment is effective and essential for treating anaemia after nonvariceal acute upper gastrointestinal bleeding. The route of iron supplementation is less important in terms of the increase in haemoglobin levels. Iron stores are filled most effectively if intravenous iron supplementation is administered (ClinicalTrials.gov identifier: NCT00978575).

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INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is a common disorder that is associated with a high mortality rate (3–15%).[1–6] The pre-endoscopic management and the endoscopic treatment of AUGIB have been well characterised and standardised.[7–10] Most patients with AUGIB experience significant blood loss prior to endoscopic therapy. AUGIB patients generally require blood transfusions prior to endoscopic interventions; however, guidelines for the monitoring and treatment of anaemia in patients after nonvariceal AUGIB have generally been lacking. A recently published randomised study revealed that a restrictive transfusion strategy was associated with improved outcomes, such as fewer complications and reduced mortality, compared with a more liberal transfusion strategy.[11] These findings indicate that transfusions can be problematic in the treatment of anaemia. The lack of standardisation in the management of post-discharge anaemia is likely due to a limited number of follow-up studies with a focus on the post-discharge phase of patient management. Most follow-up studies of patients admitted with nonvariceal AUGIB have revealed that more than two-thirds of patients diagnosed with anaemia prior to discharge recovered from anaemia after a period of 2–144 months.[12–15] Recently, a retrospective study showed that more than 80% of patients admitted to the hospital with nonvariceal AUGIB were anaemic at the time of discharge from a semi-intensive-care unit. However, only 16% of the anaemic patients received a recommendation to begin oral iron supplementation by their surgeons.[16] Despite the study's limitations in design and available follow-up data, the findings indicate that there has been only a limited focus on post-discharge anaemia. As AUGIB has been estimated to have an annual incidence of approximately 160 admissions per 100 000 inhabitants, post-discharge anaemia globally affects a large number of people.[17] Furthermore, older individuals have been well represented in the group of patients who experience AUGIB, resulting in a higher risk of comorbidities.[18] Anaemia can be sustained for a longer period and can have a greater impact on an individual if a comorbidity is present. The exact impact and risk of being anaemic after AUGIB have not been investigated, but a study calculating the risks of re-bleeding and mortality after AUGIB revealed that patients with haemoglobin (Hb) values <10 g/dL had a twofold greater risk score than patients with Hb values ≥10 g/dL.[19]

Iron supplementation has previously been administered primarily as oral iron. However, oral iron supplementation has been associated with low compliance, most likely due to associated gastrointestinal (GI) side effects.[20–24] A common side effect of iron supplementation is black stool, which AUGIB patients may perceive as re-bleeding.[25]

Furthermore, it has been suggested that oral absorption of iron is reduced when patients are infected with *Helicobacter pylori* or if they are being treated with proton pump inhibitors.[26–28] Intravenous iron supplementation has become an attractive alternative to oral iron supplementation, as a single total dose of 1000 mg can be administered in less than 1 h.[29] A 1000-mg dose of intravenous iron is equivalent to the dose absorbed by taking 200 mg/day of oral ferrous sulphate for 3 months due to the low absorption of oral iron (5–15%).[30, 31]

This randomised, placebo-controlled study was designed to compare the efficacy of iron supplementation (oral vs. intravenous) in anaemic patients discharged after nonvariceal AUGIB.

MATERIALS AND METHODS

Study design

A double-blind, placebo-controlled, randomised trial was conducted between April 2010 and January 2013 at Aarhus University Hospital, Denmark (ClinicalTrials.gov number NCT00978575). The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) Guidelines and was monitored continuously by the GCP unit at Aarhus University, Denmark.

The primary objective of the study was to determine the effects of iron supplementation vs. no treatment in anaemic patients who were discharged after nonvariceal AUGIB. The secondary objective was to compare the effects of a single dose of intravenous iron with those of oral iron supplementation administered over 3 months.

The included patients were randomised to one of three treatment arms. They were assigned in a block-randomised design with a block size of 9 and randomised in a 1:1:1 ratio to three groups: the oral group, IV group, or placebo group. Randomisation and treatment blinding were performed by the Hospital Pharmacy at Aarhus University Hospital and were monitored by the GCP unit at Aarhus University.

The oral group received 100-mg ferrous sulphate tablets (Recipharm AB, Solna, Sweden) twice per day for 3 months and an intravenous saline infusion at baseline.

The IV group received 1000 mg of intravenous ferric carboxymaltose (FCM) (Vifor Pharma Ltd., Glattbrugg,

Switzerland) in a saline solution at baseline (for patients with a body weight <65 kg, the dose was 750 mg; for patients with a body weight <50 kg, the dose was 500 mg) and two placebo tablets (Recipharm AB) per day for 12 weeks.

The placebo group received an intravenous saline infusion at baseline and two placebo tablets per day for 12 weeks.

The participants were not allowed to take any other iron supplementation during the study period. The intake of multivitamin pills containing a small dose (often <20 mg) of iron was allowed. All of the patients were followed up for 13 weeks after baseline. The end of treatment (EOT) was defined as week 13. Evaluations performed at weeks 1, 4 and 13 were used in the analysis.

Both the participants and the investigators were blinded to the intravenous study drug by the use of dark nontransparent bags and black infusion lines (B. Braun Medical, Melsungen, Germany). Unblinded nurses administered the intravenous study drug. The oral study drugs were blinded, packed and labelled by the Hospital Pharmacy and were administered by the investigators.

If the patients were still anaemic at week 13, they were offered unblinded rescue treatment with intravenous FCM (1000 mg) in a saline solution at baseline (for patients with a body weight <65 kg, the dose was 750 mg; for patients with a body weight <50 kg, the dose was 500 mg). This treatment was administered regardless of treatment allocation because the allocation remained blinded until the end of the trial.

After 42 patients were included and randomised, a protocol amendment was approved and implemented. An unexpectedly large number of patients required rescue treatment (25%), and for ethical reasons, the placebo group was excluded when allocating the remaining patients to the treatment arms. The amendments were approved by all of the relevant authorities, and the study remained blinded until the end of the study period.

Sample size calculations

With three different treatment groups, we calculated a need for 36 patients in each group based on the following assumptions: (i) an increase in Hb of 0.5 g/dL per 100 mg of absorbed iron and a minimum effect size detection of a 1.6 g/dL increase in Hb when comparing the groups; (ii) a standard deviation of 2.4 g/dL; and (iii) an alpha value of 0.05 and a power of 80%.[16, 32] With an estimated drop-out rate of 15%, each group needed to include 42 patients, requiring a total of 126 patients. The estimated numbers of patients in the oral and IV groups remained the same after the placebo group was dropped.

Patients

Ninety-seven patients with nonvariceal AUGIB were included in the trial. The eligible patients were men and women older than 18 years who had been admitted to the hospital with nonvariceal AUGIB. The patients were included approximately 48 h after stabilisation of the bleeding source and endoscopic evaluation. All of the patients were anaemic at inclusion, according to the anaemia definitions of the World Health Organisation (WHO): Hb levels <12 g/dL for women and <13 g/dL for men.[33] Patients were excluded if they had oesophageal variceal bleeding, liver disease (including haemochromatosis), kidney disease, or cancer or were pregnant. Furthermore, the patients had to have been able to follow verbal and written instructions. Known hypersensitivity to any of the treatment drugs excluded patients from participation.

Measurements

Blood samples were collected at baseline and at all of the follow-up visits, and the samples were tested for the following: Hb, ferritin, transferrin, iron, phosphate and C-reactive protein (CRP). Transferrin saturation (TSAT) was used as a measurement of the iron content of circulating transferrin and was recorded as a percentage [quotient of plasma iron concentration (μmol/L)/ 2 × transferrin concentration (μmol/L)]. All of the blood samples were analysed in the Department of Clinical Biochemistry at Aarhus University Hospital.

At baseline, information was collected on the patients' gender, age, diagnoses, comorbidities, bleeding sources, the presence of *H. pylori*, numbers of blood transfusions, endoscopic interventions and concomitant medications. At each follow-up visit, re-bleedings, blood transfusions, re-admissions to the hospital and deaths were registered. The comorbidities were classified, and a total score was calculated using the Charlson Comorbidity Index.[34]

At weeks 4, 8 and 13, the study tablets originally provided to patients were collected and the exact dose taken was calculated.

Efficacy assessments

The efficacy analysis included all of the patients who received intravenous study medication (or placebo) at baseline. The protocol-defined primary end point was

the difference in Hb at the EOT. The secondary end points were the proportion of patients with normal Hb at the EOT; the proportion of patients with Hb increases greater than 2 g/dL; the proportion of patients who reached the mean Hb reference values (13.5 g/dL for women, 15.0 g/dL for men); and the restoration of iron stores. The WHO-specific limits for anaemia were used as cut-off points for anaemia.[33] Both ferritin levels and TSAT were used as measurements of iron stores. A TSAT less than 16% indicated a suboptimal supply of iron for erythropoiesis and was used as the cut-off point for sufficient iron stores.[35] Serum ferritin is a more accurate indicator of iron stores, but ferritin is an acute-phase reactant and can increase if inflammation or an infection is present. Therefore, CRP levels were also measured. Full iron stores were defined as serum ferritin >100 μg/L and CRP less than the upper limit of the normal range (<8 mg/L).

Safety assessments

At each visit, the patients were asked about possible side effects of the treatment. If side effects of oral treatment occurred, the dose could be reduced or terminated. Furthermore, blood parameters were monitored continuously. Special attention was paid to phosphate levels, as a drop in serum phosphate has been suggested to be linked to intravenous iron infusions.[36, 37] A phosphate level less than 1.5 mg/dL and symptoms of increased fatigue required intravenous phosphate infusions. All adverse events (AEs) that occurred during and 3 months after the EOT were recorded, and their relationships with the study drugs were evaluated. All suspected unexpected serious adverse reactions (SUSARs) were reported to the relevant authorities within the specified reporting time frames.

Statistical methods

The statistical analysis was primarily performed according to the intention-to-treat (ITT) principle. Secondary, per-protocol analysis was performed. Summary statistics were used to describe the different groups. Continuous variables are expressed as the means, medians and ranges or confidence intervals (CIs). Outcome measures were analysed using Student's *t*-test, the chi-squared test, ANOVA, or nonparametric tests. The software programs Epidata (Lauritsen JM & Bruus M. EpiData Entry, version 3.02, the EpiData Association, Odense, Denmark, 2008) and Stata 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX, USA) were used for the analyses.

RESULTS

Patient selection

During the study period, 349 patients with AUGIB were screened for study participation. Of these patients, 97 were screening failures, mainly due to cancer or liver or kidney disease, and 155 were not eligible to participate, primarily due to mental dysfunction or logistic (geographical) reasons. A total of 97 patients were enrolled in the study. Of these patients, 41 were randomised to receive oral iron, 42 to intravenous iron and 14 to placebo (Figure 1). The inclusion rate was as planned, accounting for the protocol amendments (the placebo group being dropped from the study).

Baseline characteristics

The treatment groups were well balanced with regard to age, gender, bleeding source and comorbidities (Table 1). The dominant source of bleeding was peptic ulcers, followed by gastritis and nonvariceal oesophageal bleeding (i.e., oesophagitis, Mallory–Weiss tear). The proportions of patients receiving proton pump inhibitors (PPIs) and treatment for *H. pylori* were also well balanced at baseline. The mean CRP levels and the proportion of patients with elevated CRP were higher at baseline in the placebo group compared with the oral and intravenous groups (Table 2).

Patient treatment

The patient flow, treatments and rescue treatments are illustrated in Figure 1.

In the oral group, 41 patients were dosed, 6 patients withdrew their consent (1 after baseline and 5 after week 1) and 35 patients completed the entire study protocol.

A total of three patients received additional blood transfusions, three patients had re-bleeding episodes after inclusion, and one patient had both. At the EOT, two of the patients who completed the study had received blood transfusions or had suffered re-bleeding episodes after inclusion, leaving 33 patients for per-protocol analysis.

No patients were withdrawn due to side effects. Twenty-three patients (56% of the patients allocated to the oral iron group) took more than 80% of the prescribed dose for the entire study period and were classified as treatment-adherent. Due to GI side effects, two patients had dose reductions after 4 and 8 weeks, respectively, and two patients were discontinued from the oral study drug after 8 weeks.

In the IV group, 42 patients were dosed, 3 patients withdrew their consent (2 after week 1 and 1 after week 4) and 39 patients completed the entire study protocol.

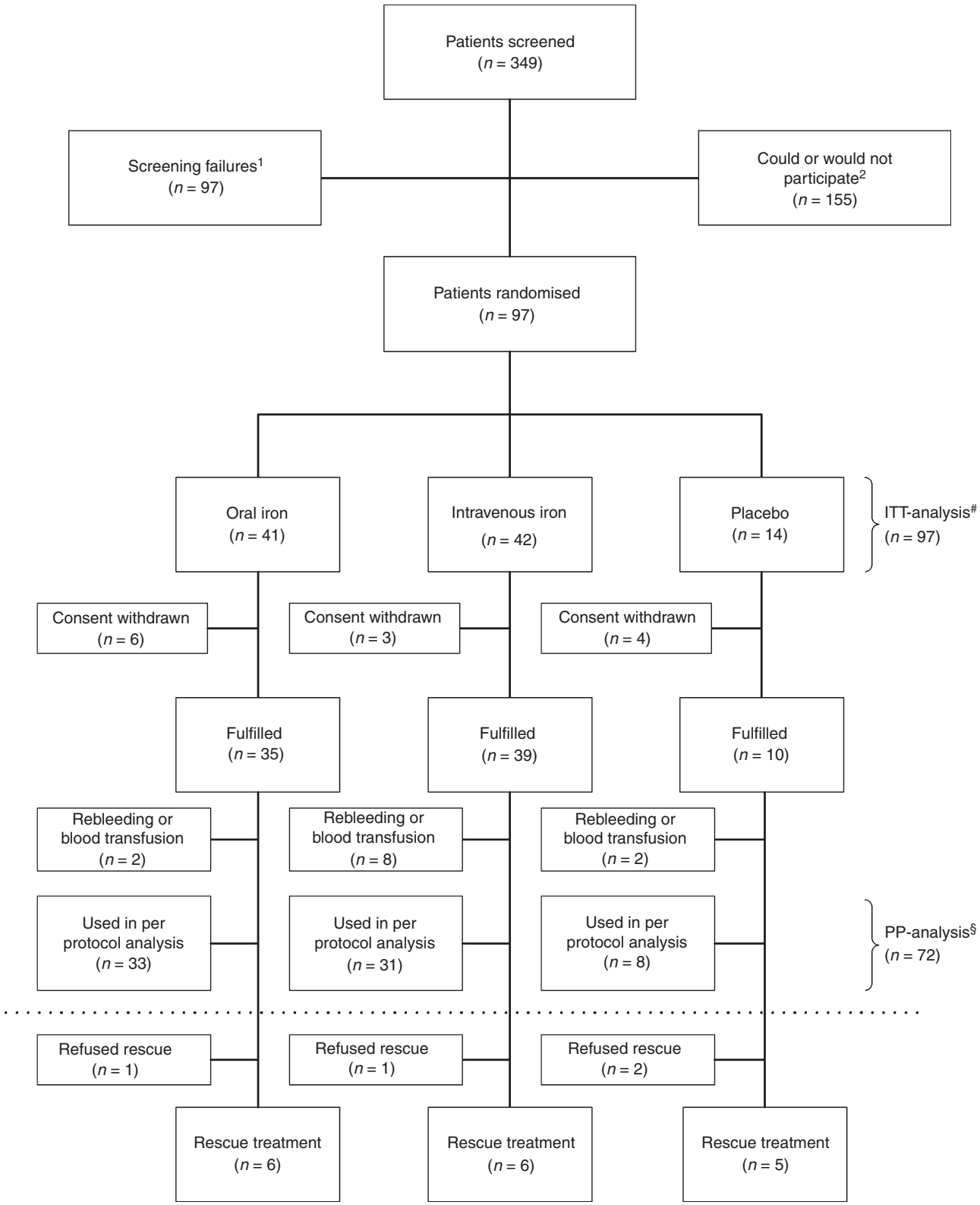

Figure 1 | Patient flow, randomisation, withdrawals and rescue treatment. [1]Mainly due to cancer or liver or kidney diseases; [2]Mainly due to geography or reduced mental function; [#]Intention-to-treat analysis; [§]Per-protocol analysis.

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Table 1 | Patient demographics and disease characteristics at inclusion

	Total (N = 97)	Oral group (n = 41)	IV group (n = 42)	Placebo group (n = 14)	P value*
Demographics					
Age, years, mean (range)	70 (23–95)	71 (23–95)	69 (38–95)	72 (49–92)	0.20†
Gender, male, *n* (%)	51 (52.6)	21 (51.2)	23 (54.8)	7 (50.0)	0.93‡
Source of AUGIB					
Peptic ulcer, *n* (%)	68 (70.1)	26 (63.4)	33 (78.6)	9 (64.3)	0.46‡
Proportion who received PPI treatment, *n* (%)	26 (26.8)	7 (17.1)	15 (35.7)	4 (28.6)	0.15‡
Proportion diagnosed with HP and treated, *n* (%)	70 (72.3)	28 (68.3)	31 (73.8)	11 (78.6)	0.76‡
Blood transfusions prior to inclusion					
Number of transfusions median, (range)	2 (0–9)	2 (0–8)	3 (0–9)	1 (0–8)	0.61†
Proportion who received transfusions, *n* (%)	76 (78.4)	32 (78.0)	33 (78.6)	11 (78.6)	1.00‡
Comorbidity					
No comorbidity, *n* (%)	22 (22.7)	11 (26.8)	11 (26.2)	0 (0.0)	0.07‡
Total Charlson score, median (range)	1.0 (0–4)	1.5 (0–4)	1.0 (0–4)	2.0 (1–4)	0.16†

AUGIB, acute upper gastrointestinal bleeding; PPI, proton pump inhibitor; HP, *Helicobacter pylori*.

* P values for statistical tests over the groups (oral, intravenous, placebo).

† One-way ANOVA test.

‡ Fisher's exact test.

Ten patients received additional blood transfusions, five patients had re-bleeding episodes after inclusion and five patients had both. At the EOT, eight of the patients who completed the study had received blood transfusions or had suffered re-bleeding episodes after inclusion, leaving 31 patients for per-protocol analysis.

No patients were withdrawn due to side effects.

In the placebo group, 14 patients were included; 4 patients withdrew their consent, one each after week 1, 2, 4 and 8; and 10 patients completed the entire study protocol. Three patients received additional blood transfusions, two patients had re-bleeding episodes after inclusion, and two patients had both. At the EOT, two of the patients who completed the study had received blood transfusions or had suffered re-bleeding episodes after inclusion, leaving eight patients for per-protocol analysis.

Rescue treatment with intravenous iron was offered to a total of 21 patients who remained anaemic at the EOT. Seven patients in each group were anaemic, and a total of four patients refused rescue treatment.

Patients treated with iron supplementation vs. no treatment

An ITT analysis comparing patients in either iron supplementation group with those in the placebo group showed that the treated patients demonstrated statistically significant differences in the median Hb level as early as week 4 (Figure 2).

The proportion of patients who completed the study and had an increase in Hb >2 g/dL at the EOT was significantly greater in the groups treated with iron (Figure 3). A total of 70% of patients completing the trial in the placebo group were anaemic compared to 17% of patients in the iron treatment groups ($P < 0.01$).

The TSAT and ferritin levels were used to monitor the status of the iron stores in the three groups throughout the study (Table 2). At the EOT, the proportion of patients with full iron stores was lowest in the placebo group (10%). The mean TSAT in the placebo group was only slightly greater than the 16% cut-off point, whereas the mean TSAT levels in the oral and IV groups were notably greater than 16%.

Patients treated with oral iron vs. IV iron supplementation

When comparing patients who received oral iron with patients who received intravenous iron in an ITT analysis, no differences between oral iron and IV iron treatment were found in the repeated measure analysis results or in the median levels of Hb at weeks 1, 4 or 13 (Figure 2). No between-group differences were identified in the proportion of patients with Hb increases >2 g/dL

Table 2 | Laboratory data during study period

	Oral group (n = 41)	IV group (n = 42)	Placebo group (n = 14)	P value*
Mean Hb (g/dL), (95% CI)				
Baseline	10.1 (9.8–10.4)	9.7 (9.4–10.0)	10.1 (9.5–10.7)	0.20
Week 1	11.1 (10.8–11.4)	11.0 (10.6–11.4)	10.6 (9.5–11.7)	0.50
Week 4	12.5 (11.9–13.1)	12.9 (12.5–13.2)	11.4 (10.3–12.5)	<0.05
Week 13 (EOT)	13.5 (12.9–14.1)	13.9 (13.4–14.3)	11.5 (10.3–12.9)	<0.01
Mean ferritin (μg/L), (95% CI)				
Baseline	174 (113–235)	161 (64–259)	257 (14–500)	0.54
Week 1	181 (27–335)	874 (767–980)	149 (40–259)	<0.01
Week 4	84 (62–107)	319 (232–407)	300 (0–765)	<0.01
Week 13 (EOT)	88 (66–110)	188 (116–259)	75 (9–141)	<0.05
Proportion with ferritin >100 μg/L and CRP <8 mg/L†, n (%)				
Baseline	10 (24.4)	13 (31.0)	1 (7.1)	0.20
Week 13 (EOT)	8 (23.5)	16 (41.0)	1 (10.0)	0.11
Mean CRP (mg/L) (95% CI)				
Baseline	10.9 (4.7–16.9)	14.6 (8.5–20.6)	44.4 (9.6–79.1)	<0.01
Week 1	13.9 (5.6–22.1)	9.9 (4.8–15.1)	9.4 (1.0–14.8)	0.64
Week 4	7.6 (0.1–15.2)	6.4 (2.4–10.4)	28.1 (0.0–66.2)	<0.05
Week 13 (EOT)	3.7 (2.0–5.4)	4.0 (1.2–6.4)	6.9 (1.2–12.6)	0.44
Proportion with CRP >8 mg/L‡, n (%)				
Baseline	16 (39.0)	20 (47.6)	11 (78.6)	<0.05
Week 13 (EOT)	3 (8.8)	4 (10.6)	3 (30.0)	0.20
Mean TSAT (%) (95% CI)				
Baseline	21 (15–25)	20 (17–25)	27 (15–39)	0.37
Week 1	24 (19–29)	24 (21–28)	13 (10–16)	<0.05
Week 4	25 (19–30)	26 (21–31)	17 (11–23)	0.18
Week 13 (EOT)	26 (21–30)	24 (20–28)	17 (11–22)	0.13

CI, confidence interval; EOT, end of treatment; Hb, haemoglobin; CRP, C-reactive protein; TSAT, transferrin saturation.

* Oneway ANOVA test over the groups or Fisher's exact test.

† An expression of full iron stores.

‡ An expression of inflammation.

or anaemia at the EOT or in the percentage of patients reaching the mean Hb reference value (Figure 3). The ferritin levels in the IV group were higher than those in the other groups from week 1 onwards (Table 2). At the EOT, the proportion of patients with full iron stores was greatest in the IV group (41%). The TSAT levels were the same at the EOT in the oral and IV groups.

Per-protocol analysis

Patients with re-bleeding and/or additional blood transfusions during the study period were omitted from the per-protocol analysis. A total of 25 patients were omitted, namely 8 patients in the oral group, 11 in the IV group and 6 in the placebo group (Figure 1).

Only a few variations from the ITT analysis were identified in the per-protocol analysis. Statistically significant differences between the groups were noted, as in the ITT analysis.

Ancillary analysis

Of the 21 patients who were still anaemic at the EOT, 4 refused rescue treatment with intravenous iron. Four weeks after rescue treatment, 6 of the 17 treated patients remained anaemic; 5 of these 6 patients had TSAT levels >16%, and 2 had ferritin levels greater than 100 μg/L and CRP levels within the normal range. Thirteen weeks after rescue treatment, 9 of the 17 treated patients remained anaemic; 5 of these 9 patients had TSAT levels >16%, and 3 patients had ferritin levels greater than 100 μg/L and CRP levels within the normal range. This finding indicates that for the majority of the patients who remained anaemic, the iron stores were adequate.

Safety and tolerability

No SUSARs occurred during the study. In all of the groups, some AEs were classified as serious adverse events (SAEs). All of the SAEs resulted in hospital admissions, and it was

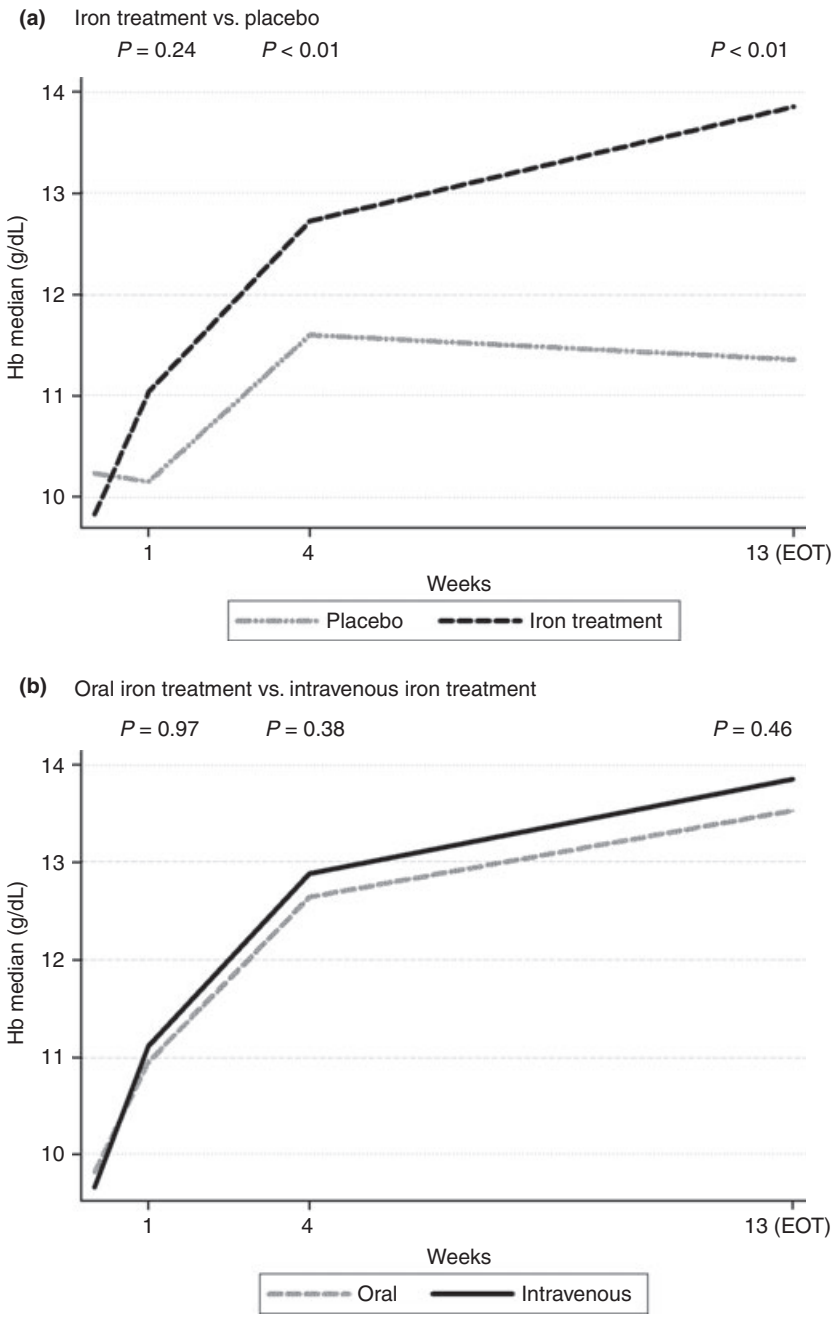

Figure 2 | Median Hb (g/dL) during the study period. Intention-to-treat analysis comparing placebo with iron treatment (a) and oral iron with intravenous iron (b). Student's *t*-test was performed at weeks 1, 4 and 13. Hb, haemoglobin; EOT, end of treatment.

determined that none of the admissions was related to the study medication. Table 3 shows the distribution of SAEs; no differences were noted between the groups.

In the oral group, 56% of the patients were classified as adherent to treatment. Whether the inadequate adherence was due to treatment side effects remains unclear, but four patients had dose reductions or discontinuations of oral iron treatment due to GI side effects. In the IV group, no infusion reactions were observed. One patient experienced temporary discoloration of the skin after part of the infusion leaked subcutaneously. Half of the patients in the IV group (n = 21) experienced a decrease in phosphate levels from baseline to week 1, and of these patients, four had phosphate levels of less than 1.5 mg/dL. None of the four patients complained of increased fatigue, and no actions were taken. All of the phosphate levels were greater than 1.5 mg/dL at the EOT. The decrease in phosphate levels between baseline and week 1 was significantly greater in patients in the IV group ($P < 0.01$) compared with patients in the oral group.

DISCUSSION

Iron supplementation for anaemia following AUGIB is essential for normalising Hb and the body's iron stores.

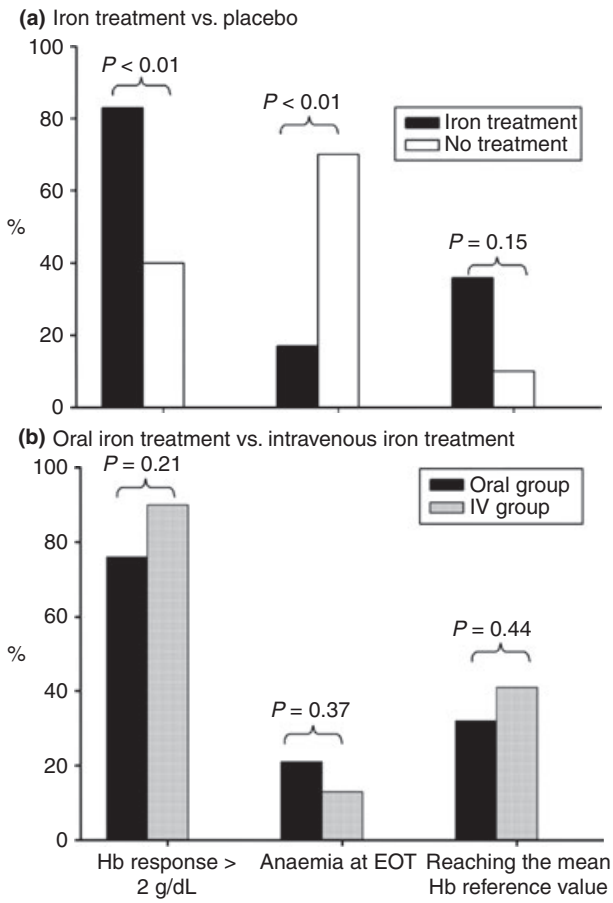

Figure 3 | Proportions of patients with Hb response >2 g/dL, anaemia at the EOT and achievement of the gender-specific mean Hb reference values for a healthy population. Intention-to-treat analysis comparing iron treatment with no treatment (a) and oral iron with intravenous iron (b). Hb, haemoglobin; EOT, end of treatment.

This double-blind, randomised, placebo-controlled study demonstrated a statistically significant difference between iron treatment and no treatment after just 4 weeks.

Oral iron was shown to be as effective as intravenous iron in raising the levels of Hb. This finding occurred despite a treatment adherence rate of only 56%, which was similar to that in other studies.[20–23] In general, participating in a study may even increase adherence to treatment. Because adherence to oral iron treatment has generally seemed to be low, we found that it would be most pragmatic to compare the IV group (with 100% adherence) with the entire oral group, regardless of adherence or dose reduction. A few patients had dose reductions or terminated treatment due to GI side effects. Choosing intravenous iron as the route of iron supplementation would ensure 100% adherence to treatment, particularly if only one dose had to be administered, as in this study. No side effects were detected in the IV group.

As shown in Table 2, the TSAT levels decreased by half if no iron supplementation was administered. The TSAT levels remained low in the placebo group throughout the study.

The proportion of patients with full iron stores, defined as ferritin levels >100 μg/L and CRP levels <8 mg/L, increased most markedly in the IV group. This result illustrates how anaemia due to acute bleeding can be accompanied by iron deficiency if it is not treated.

The findings could explain the large number of patients in the placebo group (7 of 10) who required rescue treatment at the EOT. Furthermore, the data support the investigators' decision to drop the placebo group for ethical reasons during the study period. However, current practice is similar to that used in the placebo group. No guidelines recommend iron treatment after AUGIB, and one study showed that the prescribed rate of oral iron was only 16% for anaemic AUGIB patients.[16]

Phosphate levels were monitored during the study, as a decrease in phosphate levels has been linked to intravenous iron and could be a potential side effect. The

Table 3 | Number of patient having serious adverse events, *n* (%)

	Oral group (*n* = 41)	IV group (*n* = 42)	Placebo group (*n* = 14)	*P* value*
Re-admission due to signs of re-bleeding				
No re-bleeding found	2 (4.9)	2 (4.8)	2 (14.3)	0.40
Bleeding source found	1 (2.4)	1 (2.4)	0	0.84
Admission due to cancer	2 (4.9)	0	1 (7.1)	0.28
Admission due to cardiovascular symptoms	2 (4.9)	2 (4.8)	1 (7.1)	0.94
Elective admissions	0	2 (4.8)	0	0.27

Admission: admission to hospital > 24 h.

* *P* values for statistical tests over the groups (oral, intravenous, placebo) using Kruskal–Wallis test.

observed decrease in phosphate levels did not have any clinical impact in this study.

The recognised SAEs were all unrelated to treatment and were randomly distributed between the groups. The number of hospital admissions was not surprising, as the mean patient age was 70 years, and 75% of patients were older than 62 years. Additionally, more than 75% of the included patients had one or more comorbidity. The results described above also indicate how patients with nonvariceal AUGIB may be more vulnerable than the remainder of the population and, therefore, more sensitive to both anaemia and iron deficiency. This finding highlights the need for a greater focus on iron supplementation and/or scheduled follow-ups for patients with anaemia after nonvariceal AUGIB. This need is supported by a prospective study on mortality in elderly patients (>60 years old) with peptic ulcers, which revealed a 74% higher mortality rate in the peptic ulcer group compared with matched controls.[38]

Iron supplementation appears to be an effective and obvious alternative to a liberal transfusion strategy, which has been associated with increased mortality.[11] When choosing the iron formulation that is the most suitable, several parameters must be considered. The effects of and adherence to treatment were described in this study; however, different aspects of health economics and patient concerns must also be considered.

As the appearance of black stool has been associated with oral iron, patients who experience black stool after an AUGIB episode may be confused, as it is difficult to separate the potential side effects of oral iron from signs of re-bleeding.[25] If intravenous iron is chosen for supplementation, an unnecessarily anxious call to health service providers can be avoided. We did not register the frequency of black stool in this study.

This double-blind, randomised, controlled study could have been limited by the risk of unblinding the study drug if black stool was observed by the patient during the study and no re-bleeding was present. Although the collected blood samples were not influenced by unblinding, this protocol may have impacted patient adherence to treatment. Another possible limitation could have been the dropping of the placebo group during the study; as a result, the group was one-third the size of the other groups. Despite this limitation, a clear difference was observed between the patients who were and were not treated with iron. Subsequently, when the study was unblinded and the patients in the placebo group were identified, the decision to drop the group was clearly correct from an ethical point of view.

Ferritin levels were used as one marker of iron stores. Because ferritin is an acute-phase reactant, the levels can be elevated by inflammation or infection. Therefore, CRP levels were measured to evaluate this correlation. The ferritin levels in the IV group were markedly increased at weeks 1 and 4, which was expected in the IV iron group. The primary observation period in this study was 13 weeks. At the EOT, the placebo group had lower iron stores than the other groups. The majority of patients in the placebo group also had anaemia at the EOT. For ethical reasons, we chose to offer rescue treatment to all of the anaemic patients at the EOT. We do not know what would have happened to these patients if the anaemia remained untreated, although the situation may be close to current practice.

Treatment with PPIs or the presence of *H. pylori* in the stomach has been suggested to inhibit oral iron absorption.[26–28] The distribution of these parameters was equal between the treatment groups at baseline. In addition, treatment with PPIs was least common in the oral group. It is unlikely that these parameters had any significant impact on our results.

The number of screened patients was more than three times the number of included patients, which may have resulted in selection bias. However, two-thirds of the patients not included were considered screening failures due to geography or reduced mental function.

Clinically, our findings clearly indicate that iron supplementation is essential in anaemic nonvariceal AUGIB patients. Patients who were excluded from this study due to geographical reasons or reduced mental function could easily benefit from iron treatment. Furthermore, for patients with reduced mental function, IV iron could be considered to ensure adherence.

Finally, the direct cost of anaemia for selected groups of patients has been estimated at 18.000–78.000 US dollars per patient annually, although patients with AUGIB were not among the patients investigated.[39] Poor adherence to oral iron treatment is well known and was in accordance with our findings. Despite low absorption of oral iron and poor adherence, the cost of the quantity of intravenous iron actually delivered for use in erythropoiesis is many times greater than that of oral iron.

In conclusion, our study suggests that any patient who is anaemic after nonvariceal AUGIB will clearly benefit from iron supplementation. Oral iron and IV iron appeared to have equal effects in raising the level of Hb. Iron stores are replenished most effectively if IV iron supplementation is administered. Furthermore, if treatment adherence must be guaranteed, a single infusion of

IV iron administered before hospital discharge should be chosen for anaemic nonvariceal AUGIB patients.

AUTHORSHIP

Guarantor of article: Palle Bager.

Author contributions: Palle Bager: designed the research study, performed the research, collected the data, analysed the data and wrote the manuscript. Jens F. Dahlerup: designed the research study, contributed to perform the research, to analyse the data and to write the manuscript. Both authors have approved the final version of the manuscript.

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