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Randomized Control Trials

High-dose intravenous versus oral iron in blood donors with iron deficiency: The IronWoMan randomized, controlled clinical trial

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SUMMARY

Introduction: Frequent blood donation often leads to iron deficiency and even anemia but appropriate strategies for detection and prevention are currently not mandatory. At the Medical University of Graz, we conducted a single-center prospective clinical trial to compare oral and IV iron supplementation in iron deficient blood donors including Austrian regular whole blood and platelet apheresis donors. We aimed to determine the difference of transferrin saturation between the treatment groups 8–12 weeks iron administration besides other parameters of iron status and blood count.

Methods: 176 healthy male and female blood donors with iron deficiency (ferritin ≤30 ng/mL) were randomized to either a single dose of IV ferric carboxymaltose (1000 mg, n = 86) or oral iron (II)fumarate (100 tablets of 100 mg [10 per week], n = 90).

Results: Between 2014 and 2016, 172 donors (137 women) completed the study; 4 in the oral group were lost to follow-up. At follow-up, median (IQR) transferrin saturation and ferritin were significantly higher in the intravenous group (27 [23–35]%, vs 21.0 [16–32]%; p < 0.001 and 105 [75–145] ng/mL vs 25 [17–34] ng/mL; p < 0.001, respectively) while median (IQR) hemoglobin levels were comparable (IV, 13.6 [13.0–14.4] g/dL vs oral, 13.6 [13.0–14.2] g/dL). The frequency of adverse effects was comparable (38% in both groups) and no serious adverse events occurred.

Conclusions: A single dose of 1000 mg of intravenous iron is highly effective to counteract iatrogenic iron deficiency in blood donors. Oral iron appears to be an acceptable alternative. The assessment of body iron stores should play a key role in maintaining blood donors' health.

This trial was registered at www.clinicaltrials.gov as NCT01787526 on February 8, 2013 and at www.clinicaltrialsregister.eu (EudraCT identifier: 2013-000327-14) on September 24, 2013.

1. Introduction

Blood donations are an essential element of health care. Each year, blood donors contribute to saving millions of lives in both routine and emergency situations. Blood products like red blood cell units, plasma, platelets and plasma derivatives can improve the life expectancy and quality of life of many patients. Furthermore, several increasingly complex medical and surgical procedures such as allogeneic stem cell transplantation or extracorporeal membrane oxygenation would not be possible without sufficient blood supply. Donating blood is often a voluntary act and usually non-remunerated, and regarding their importance in medical care there is an urgent need to ensure the optimal long term health of blood donors. Regular blood donors are a currently widely neglected population with a high risk for iron deficiency (ID) [1]. With up to 65% of regular blood donors being iron deficient, this

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translates into a considerable number of iatrogenic cases [2–10]. In addition to high donation frequency, low body weight and female gender are important risk factors [2,5,11]. ID occurs when iron loss cannot be compensated by diet [12] and it is associated with adverse effects including restless legs syndrome [13–16], pica [13–15,17], fatigue [18–20], increased risk of adverse pregnancy outcomes [21–23], impaired physical and cognitive performance, headache, hair loss and brittle nails [24–27].

Regular donation and other risk factors predispose to ID through established mechanisms. For example, each whole blood donation (450–500 mL) leads to a loss of 200–250 mg of iron [28–30], and each apheresis donation (as platelets) results in the loss of 20–25 mg iron [31]. Because of a higher possible donation frequency apheresis donations also often cause ID [3] Although the high probability for ID in regular blood donors has been known for decades [32], iron status is not routinely assessed or treated. Donation suitability is usually determined by point-of-care tests (POCT) for hemoglobin (Hb), either by a finger-stick sample using a hemoglobinometer. The lower Hb donation thresholds are 12.5–13.5 g/dL for men and 11.5–12.5 g/dL for women [33]. However, it is well documented that Hb levels are of little value in reflecting body iron [2,34–37] because iron deficiency anemia (IDA) only occurs as a late manifestation of ID. Blood donors might very well be iron deficient even when Hb levels are suitable for donation, thus further deteriorating iron stores.

Several trials have evaluated different regimes of iron supplementation in blood donors and demonstrated good treatment efficacy in improving the iron status [8,30,38–46]. Standard oral supplementation with ferrous salts takes many weeks to months and frequent gastrointestinal side effects may lead to poor adherence. An alternative approach feasible in this population would be high-dose IV iron supplementation directly after donation through the same venous access with single doses up to 1000 mg. A recent meta-analysis reporting on the efficacy and safety of IV ferric carboxymaltose in patients with IDA concluded that it was more efficient than oral iron, while having a similar safety profile including a similarly low incidence of serious adverse events Avni et al.[47] showed in a meta-analysis that all IV formulations are equally safe and efficient [48] but a 1000 mg dose of ferric carboxymaltose is unique as total daily dose and compared to others more data for its efficacy and safety are available. In this study, we aimed to compare high dose IV ferric carboxymaltose with a standard oral iron regime with regard to efficacy, safety, adherence and feasibility in iron deficient whole blood and platelet donors. Our hypothesis was that IV iron would be superior to oral iron in improving iron stores. We expected high efficacy accompanied by a low profile of side effects and good product safety, as shown in other populations [47,49].

2. Methods

2.1. Ethical approval

The study was carried out according to GCP guidelines and conforms to the Declaration of Helsinki. It was approved by the Austrian Agency for Health and Food Safety and by the Ethical Committee of the Medical University of Graz. The approval of the institutional ethical committee was given in June 2013 (EK 25–345 ex 12/13) and was renewed yearly.

2.2. Trial design

This clinical study was a single-center prospective, randomized trial and it took place in the apheresis unit of the Department of Blood Group Serology and Transfusion Medicine of the Medical University of Graz, Austria.

The detailed study protocol was published recently [50], screening for ID was performed from remaining blood used for routine infectious disease testing in donors. When ferritin was ≤30 ng/mL in the pre-donation sample by immunoturbidimetry on a cobas 8000 modular analyzer (Roche Diagnostics, Mannheim, Germany), donors were contacted by telephone and invited to participate in the trial. Participant codes were generated by numbers in ascending order and initials by the physicians. During the first visit (visit 0, V0), written informed consent was obtained and inclusion/exclusion criteria were confirmed. Participants were randomized to receive either a single dose of 1000 mg of IV ferric carboxymaltose or 100 mg oral ferrous fumarate. Assuming a 10% resorption rate with oral iron, both groups would be expected to receive 1000 mg [51]. In the oral iron group, 100 tablets containing 100 mg iron (II)fumarate each (Ferretab®, manufacturer Gerot Lannach, Austria) were handed out to the participants together with an exact schedule for tablet intake (ten tablets per week: Monday, Wednesday, Friday: 2 tablets, the other days 1 tablet, intake according to package insert). Participants were advised to return remaining tablets at visit 1 and were then asked how many tables they had taken.

In the IV group, 1000 mg IV iron (ferric carboxymaltose, Ferinject®, Vifor Pharma, Austria) was administered over ≥30 min by a dedicated peripheral line, carried out by the investigators in the presence of a nurse. All participants were monitored for an additional 30 min.

A questionnaire was filled out by each donor (details see supplement).

At visit 1 after 8–12 weeks, a blood sample was drawn and the questionnaire completed. This treatment procedure was chosen because a standard daily dose of 100–200 mg of elemental iron seemed feasible [52–54]. Furthermore, serum ferritin levels are falsely high when analyzed ≤6 weeks after IV iron administration. To assess occult gastrointestinal bleeding, all participants were asked to perform three fecal occult blood tests at home until visit 1. Pregnancy was excluded in premenopausal women by repeated urinary β-human choriongonadotropine testing. Apart from a whole blood count and c-reactive protein, folate and vitamin B12 levels were also assessed. After visit 1, all results were summarized in a written report for each study participant and sent by mail (including recommendations in case of specific findings such as persistent ID or folate/vitamin B12 deficiency).

2.3. Donor characteristics

Participants were regular whole blood or apheresis donors aged ≥18 years and ≤65 years, who had consented to participate in research on the routine donor questionnaire. They needed to fulfill the standard Austrian criteria for blood donation [55], and serum ferritin level had to be ≤30 ng/mL at pre-donation screening. Additional exclusion criteria included known hemochromatosis, acute infection, current iron intake, pregnancy or lactation, a history of anaphylaxis to IV iron or other substances and signs or symptoms suggestive for acute or chronic gastrointestinal or excessive gynecological bleeding.

2.4. Outcomes

The primary outcome was the transferrin saturation (TSAT; %) at follow-up. Secondary outcomes included other parameters of iron metabolism and red blood cell count, adverse events and adherence.

2.5. Randomization

Participants were randomized in a 1:1 ratio (stratified by sex) by the physicians to either high dose IV or oral iron using a web-based, GCP compliant randomization tool (http://www.randomizer.at).

2.6. Sample size calculation

A sample size of 172 participants (86 participants in each group) was determined to have 90% power to detect a mean difference of 8% in TSAT estimating a post-treatment TSAT of 28% in the IV iron group and 20% in the oral iron group. This based on results by a similar treatment regimen in otherwise healthy women with postpartum anemia using a two-group t-test with a 0.05 two-sided significance level, assuming a common standard deviation of 16 [49]. Allowing for a drop-out of 14%, a total of 200 participants were planned to be enrolled in the study.

2.7. Statistical analysis

Statistical analyses were performed for the intention-to-treat population and for the per-protocol population. Study participants who had their follow-up and took their study medication at least once were included in the intention-to-treat population; the per-protocol population consisted of all IV and all oral participants who took at least 90 tablets. All primary and secondary outcome measures as well as post-hoc data were analyzed and checked for normal distribution. Normally distributed data were presented as means with standard deviation (SD), while those failing normality testing were presented as medians with interquartile ranges (IQR, 25th and 75th percentiles) and analyzed by non-parametric tests. The Wilcoxon test was used to compare laboratory results between the visits. The Mann-Whitney-U-test served to compare differences between treatment groups. Significance value was set to $p < 0.05$. For significant outcomes, differences in the median between the groups and 95% confidence intervals (CI) were assessed. Statistical analysis was performed using SPSS statistical software (version 24.0; IBM Corp, Armonk, NY, USA). To adjust for different values between groups at visit 0, the differences in the blood parameters between the visits were used in the analysis. To correct for multiple testing, Bonferroni-correction was used. It was planned to analyze a subgroup of ferritin at baseline of $\leq$15 ng/mL.

The body mass index was calculated as the ratio between the weight (kg) and the square of the height (m). Total blood volume was calculated by Pearson's formula. [56].

3. Results

For baseline (visit 0), all available data were analyzed (including dropouts). For follow-up (visit 1), the intention-to-treat was used for all participants who had their follow-up (n = 172). A per-protocol analysis (IV participants and participants with oral iron who took $\geq$90 tablets, n = 168) was performed and showed no differences.

3.1. Screening

Recruitment started in June 2014 and was completed in June 2016. Eight hundred-six donors were screened (Fig. 1). Of those, 339 did not meet all inclusion criteria and 291 declined to participate. Due to an actual substantially lower drop-out rate than anticipated (2% instead of 14%), 176 instead of 200 donors were included in the study (138 women, 78%) to reach a total sample size of 172 participants with a full dataset at visit 0 and 1. One hundred fifty-seven (89%) were whole blood donors and 19 (11%) platelet donors (Table 1). Seventeen postmenopausal women were included in the study. Screening laboratory donor characteristics are summarized in Table 1. Data was analyzed in 2017.

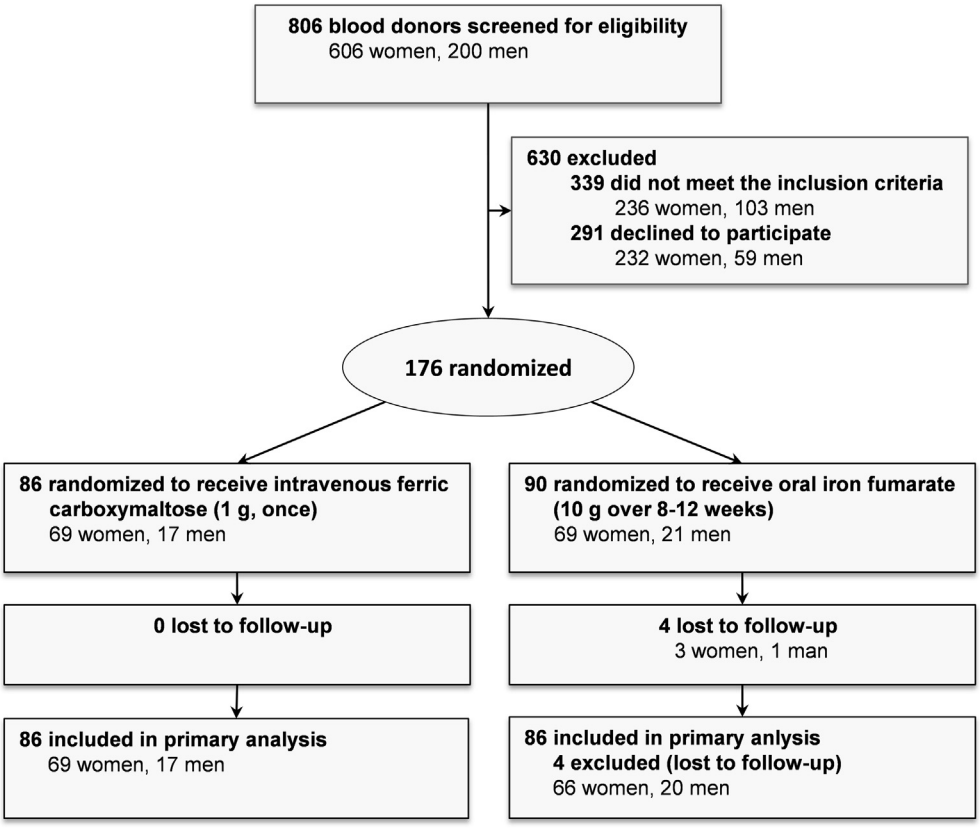

Fig. 1. Flow of participants through the IronWoMan study of IV versus oral iron therapy in blood donors (Consort).

Table 1
Study participants' characteristics and screening results (pre-donation).

Pre-donation information		Oral group	IV group	Total
Type of donor				
Whole blood		78	79	157
Platelet (apheresis)		12	7	19
Sum		90	86	176
Donor characteristics				
Age, mean (SD), years		38 (14)	38 (14)	
Weight, mean (SD), kg		72 (14)	70 (12)	
Body mass index, mean (SD)		25 (4)	24 (4)	
Total blood volume, mean (SD), liters		4.3 (0.7)	4.2 (0.6)	
Vegetarian or vegan, yes/no		3/86	6/80	
Physical activity, yes/no		71/17	70/15	
Premenopausal women, number		60	61	
Screening results	Reference range			
Hb, median (IQR), g/dL (POCT)[a] w/m	>12.5/> 13.5[b]	13.2 (12.9–13.8)	13.0 (12.7–13.6)	
Hb, median (IQR), g/dL (venous)[a]		12.7 (12.3–13.1)	12.7 (12.3–13.0)	
Ferritin, median (IQR), ng/mL	30–150	15 (10–20)	14 (9–21)	
Transferrin, median (IQR), g/L	2.0–3.6	3.5 (3.1–4.0)	3.6 (3.3–4.0)	
Transferrin Saturation, median (IQR), %	16–45	14.0 (9.0–21.0)	12.5 (9.0–17.0)	
Serum iron, median (IQR), µg/dL	50–160	68 (52–97)	63 (48–89)	

Reference ranges were adopted from the laboratory conducting the tests.
Hb indicates hemoglobin; m, men; w, women.
[a] Hb values by POCT were available from whole blood donors.
[b] Hb values refer to eligibility criteria for donation for women and men.

3.2. Baseline (visit 0)

Visit 0 took place for the oral group (mean, [SD]) 30 (17) and the IV group 37 (32) days after donation. At visit 0, practically all iron parameters and red blood cell count had decreased significantly (Supplemental Table 1). One hundred one women (73%) and 31 men (82%) were anemic according to WHO criteria (Hb < 12.0 g/dL for women and <13.0 g/dL for men) [57]. Mean ferritin levels were <10 ng/mL for both, women and men, and mean TSAT well under the lower threshold of 16%. Women had significantly lower Hb, ferritin and erythrocyte count compared to men.

3.3. Outcomes at follow-up (visit 1)

3.3.1. Primary endpoint

Mean (SD) time for follow-up was day 76 (9) for the oral and day 81 (8) for the IV arm. Between the visits, TSAT had increased significantly in both groups ($p < 0.001$, Table 2). The difference in TSAT between the groups was also significant, with substantially higher levels in the IV group compared to the oral iron group, showing a median difference of six percentage points and a significance value of $p < 0.001$ for both, the difference in the values at visit 1 and for the differences in the changes between the visits (Table 2).

3.3.2. Secondary endpoints

3.3.2.1. Iron status. A significant increase in all iron parameters was seen in both groups (Table 2). In the oral group, ferritin levels improved substantially, but 52 donors (60%; 41 women) did not achieve levels above 30 ng/mL. Seventeen participants (12 women) remained below 15 ng/mL. In the oral subgroup with low ferritin levels after therapy, 8 participants had donated either whole blood ($n = 6$) or platelets ($n = 2$). At visit 0, median (IQR) ferritin had been significantly lower in those with persistent ID at visit 1 compared to those with replenished iron stores (7.0 [5.0–9.0] ng/mL vs 8.5 [5.0–13.0] ng/mL; $p = 0.048$ and differences between the medians [95% CI], 2 [0–4] ng/mL).

In the IV group, ferritin levels also increased significantly. Nevertheless, three women and four men failed to reach 30 ng/mL, and one woman and one man still had ferritin levels of <15 ng/mL despite IV iron therapy. In total, two whole blood donations and five apheresis platelet units had been given by four participants with persistent ID at visit 1.

All markers of iron status were significantly better in the IV group (Table 2).

3.3.2.2. Hemoglobin. Hb values were similar at visit 1 between groups (Table 2) and had improved almost by 2 g/dL, although 4 men (2 in the oral group) and 14 women (6 in the oral group) still had values below 13.5 and 12.5 g/dL, the lower thresholds for donating whole blood. [55]. Of those, three men and two women had ferritin levels <30 ng/mL. Anemia was still present in one man and 3 women. None of those had given blood during the interval between the visits.

3.3.3. Drug-related adverse events

No hospitalization was necessary due to adverse effects during the interval between visit 0 and follow-up.

Four participants of the study (all in the oral group) were lost to follow-up but no reasons were given. Seventy-four participants took all tablets as prescribed (85%) and 4 less than 90 tablets (5%).

Thirty-three donors (38%) of the oral group reported side effects of which gastrointestinal reactions were most common (Table 3). Three consulted a physician due to complaints. Eighty participants (93%) stated that they had tolerated the iron tablets well and 68 (79%) would recommend the oral iron therapy while 12 (14%) would not.

In the IV group no infusion related local or anaphylactic reactions were observed. No other immediate adverse effects during the administration of IV iron and the subsequent observation period were seen. At visit 1, 33 donors (38%) described adverse effects (mostly tiredness, headaches or dizziness). Gastrointestinal symptoms occurred too, and some participants complained about flu-like symptoms including fever, chills or pain in the joints and muscles (Table 3). Symptoms lasted in most cases only several hours to 2–3 days after the application of IV iron. In six cases, adverse effects were reported for a duration of up to one week, one participant had symptoms for two weeks (headache, dysgeusia, vomiting, abdominal pain, obstipation, meteorism, general indisposition and tiredness), and one for 6–8 weeks (general indisposition, headache, nausea and vomiting). Nevertheless, five

Table 2
Comparison of visit 0 to visit 1 according to groups.

Parameter	Oral	IV	p between groups
Hb (venous), g/dL			
V0	11.7 (11.3–12.4)	11.6 (11.0–12.1)	.106
V1	13.6 (13.0–14.2)	13.6 (13.0.14.4)	
p in the groups	**<0.001**	**<0.001**	
Transferrin Sat, %			
V0	9.0 (6.0–14.0)	7.5 (6.0–12.0)	**<0.001**
V1	21.0 (16.0–32.0)	27.0 (23.0–35.0)	
p in the groups	**<0.001**	**<0.001**	
Ferritin, ng/mL			
V0	7 (5–10)	5 (4–9)	**<0.001**
V1	25 (17–34)	105 (75–145)	
p in the groups	**<0.001**	**<0.001**	
Transferrin, g/L			
V0	3.5 (3.1–3.9)	3.5 (3.3–4.0)	**<0.001**
V1	3.0 (2.7–3.4)	2.6 (2.3–2.9)	
p in the groups	**<0.001**	**<0.001**	
sTrfR, mg/L			
V0	2.1 (1.8–2.6)	2.0 (1.7–2.5)	0.012
V1	1.3 (1.1–1.5)	1.1 (0.9–1.3)	
p in the groups	**<0.001**	**<0.001**	
MCV, fL			
V0	81.7 (78.7–84.6)	80.1 (77.3–83.5)	**<0.001**
V1	83.8 (81.9–86.6)	83.7 (82.2–87.0)	
p in the groups	**<0.001**	**<0.001**	
MCH, pg			
V0	27.1 (25.7–28.3)	26.9 (25.4–28.1)	**<0.001**
V1	28.7 (27.6–29.6)	28.8 (28.1–29.7)	
p in the groups	**<0.001**	**<0.001**	
Reticulocytes, ‰			
V0	8.9 (7.1–10.9)	8.4 (6.9–10.5)	0.665
V1	7.5 (5.7–10.0)	7.1 (5.9–9.6)	
p in the groups	**<0.001**	0.006	
Erythrocytes, T/l			
V0	4.4 (4.1–4.6)	4.3 (4.1–4.7)	0.715
V1	4.8 (4.5–5.1)	4.7 (4.5–5.0)	
p in the groups	**<0.001**	**<0.001**	
Phosphate, mmol/l			
V0	0.97 (0.87–1.07)	0.99 (0.89–1.08)	0.860
V1	0.96 (0.83–1.10)	0.96 (0.86–1.10)	
p in the groups	0.969	0.729	
CRP, mg/L			
V0	1.2 (0.6–3.4)	1.2 (0.6–3.2)	0.605
V1	1.2 (0.6–3.5)	1.1 (0.6–2.3)	
p in the groups	0.864	0.408	

Comparison of therapeutic success within groups and between groups. P values for the comparison between the groups were calculated from the difference in the change of parameters. Significant p values are indicated in **bold**. Values are given in median (IQR).
Due to multiple analyses the Bonferroni correction was used (alpha = 0.05/11 = 0.004).
Hb indicates hemoglobin; Transferrin Sat, Transferrin saturation; sTfR, soluble transferrin receptor; MCV, mean cellular volume and CRP, c-reactive protein.

participants consulted their family physician. Two of them recommended IV iron application, two did not. Eighty-one participants reported good tolerability of IV iron (94%), and 78 (91%) would recommend this therapy, while four (5%) would not.

3.3.4. Subgroup analysis

3.3.4.1. Baseline ferritin <15 ng/mL (predefined subgroup). At the time of screening, 89 (50.6%) of the donors who entered the study had ferritin levels <15 ng/mL. At baseline, ferritin levels <15 ng/mL were present in 162 participants (92.1%; 127 women). Median (IQR) value was 6.5 (4–10) ng/mL (women, 6.0 [4–9] ng/mL; men, 9 [6–12] ng/mL). Since >90% of the participants were part of the originally proposed subgroup, further analysis was not considered meaningful.

Further subgroup analyses and additional results on baseline values, adherence, blood volume, body mass index, testing for occult gastrointestinal bleeding, donations between visit 0 and 1,

Table 3
Side effects reported by participants by group.

Symptoms	Number of participants	
	IV group	oral group
obstipation	2	15
tiredness	12	0
headache	12	1
dizziness	11	1
meteorism	2	9
diarrhea	3	9
general indisposition	8	4
fever	8	0
abdominal fullness	0	7
sensation of heat	7	0
nausea	6	4
pain in joints and muscles	5	0
chills	5	0
abdominal pain	3	1
gripes/colics	0	3
skin rash/itching	3	0
vomiting	2	1
hematoma at injection site	2	0
longer lasting pain at injection site	1	0
chest pain	1	0
dysgeusia	*1*	*0*
fever blisters	*1*	*0*
subnormal temperature	*1*	*0*
heavy period once	*1*	*0*
heavy feet in the morning	*1*	*0*
minor skin problems	*0*	*1*
tingle in the stomach	*0*	*1*
increased appetite	*0*	*1*

A list of known side effects was offered for selection. Multiple answers were allowed. There was also the possibility to indicate symptoms not included in the list (in italic).

phosphate, c-reactive protein, vitamin B12 and folate levels, dietary habits, and physical activity can be found as Supplementary material.

4. Discussion

In the IronWoMan study, we show that a single IV dose of 1.000 mg ferric carboxymaltose is superior to oral iron supplementation over a 2–3 month period in improving iron stores in iron deficient blood donors while Hb was identical between the groups at follow-up.

In the oral group, the majority - 52 participants (60%) - did not reach a ferritin level of >30 ng/mL, although only a minority had continued blood donations during the study. Other reasons for obvious excessive blood loss had been excluded. Because adherence was very good, it must be assumed that an estimated absorption rate of 10% was too optimistic and that this oral regime is in the majority of iron deficient regular blood donors is unable to restore iron reserves. Recent evidence suggests that iron absorption is reduced in daily regimes because of hepcidin upregulation [58,59].Interestingly, lower doses of iron may be similarly effective for IDA treatment [60].

All drop-outs were in the oral therapy group. The number of participants with adverse effects was comparable in both groups. Participants had been encouraged to report any adverse effect, and in general they were minor and of short duration. As expected, participants in the oral group complained mostly about gastrointestinal symptoms - the most frequent being obstipation. The types of symptoms reported by the participants in the IV arm were very different with a surprisingly high rate of central nervous system-related side effects including tiredness, headache and dizziness, besides fever and joint pain shortly after iron supplementation. Although these symptoms may have been caused by transient hypophosphatemia, a known adverse effect of ferric

carboxymaltose [61,62], we are unable to further explore this hypothesis as phosphate levels were not measured following treatment. Phosphate levels were available at follow up and were similar in both groups; additional investigation did not identify lower phosphate levels in those who had complained about tiredness.

4.1. Comparison with similar studies

Several previous studies have assessed standard oral iron or low-dose IV iron in blood donors. However, we are aware of only two other studies that used the same modern high-dose IV preparation (ferric carboxymaltose). Unfortunately, for both, only abstracts are available to date. Ekermo et al. [63] included 210 donors regardless of their baseline iron stores and used 1000 mg ferric carboxymaltose after the first and 200 mg after each following donation for the IV group, and 20 × 100 mg Fe^{2+} for the oral group after each donation. Women were followed for four and men for five donations. The primary objective was the change in Hb. Generally, there were no differences in Hb and fatigue between the groups, but in the subgroup with ID at baseline, IV iron increased Hb and iron stores more efficiently. Fontana [64] et al. performed a double blind trial including 405 regular blood donors with fatigue and ferritin <50 ng/mL, who received either 800 mg IV ferric carboxymaltose or a placebo. Ferritin levels increased significantly in the IV iron group, but no differences were observed between the groups regarding fatigue.

In summary, our study was targeted at an “at risk population” with actual documented iron deficiency, and compared the current routine therapy for iron deficiency to a novel and more expensive therapeutic approach, while the two other comparable studies either used a nonselective approach or did not treat iron deficiency with the standard therapy.

4.2. Adverse events

More than a third of all participants reported at least one adverse event in each group. Although this seems high, more than 90% in both groups stated to have tolerated the iron medication well. Almost 80% of the oral group and 91% of the IV group would recommend the therapy they received. Interestingly, despite detailed information about possible severe adverse effects donors were considerably more open to the IV therapy than expected. The single dose of IV iron (as opposed to tablet intake over weeks) appeared to be an important reason for the positive perception and therefore adverse effects like fever and flulike symptoms were seen to be acceptable given the risks.

4.3. Strengths and limitations

A strength of our study is that we exclusively included donors with low ferritin prior to blood donation and tested for other contributing factors like vitamin B12 or folate deficiency. One month after blood donation, at study inclusion, 75% of the donors suffered from IDA, and iron stores had also declined further. Several circumstances may contribute to these findings. Donor eligibility for whole blood donations is done by POCT, which is not as accurate as standard venous measurement methods [65,66]. In our study, venous sample Hb testing from the pre-donation samples gave a significantly lower result (mean difference 0.6 g/dL), suggesting that in several cases, donors already anemic at donation were allowed to donate because of falsely high Hb results in POCT. This illustrates that the course of iron parameters is of interest especially in donors with low-normal Hb values. In Austria, as in many other countries, the minimum interval between whole blood donations is eight weeks, corresponding to an annual blood donation volume of three liters for men (six donations). The blood donation volume for pre- and postmenopausal women per year is limited to 2 and 2.5 L (4 and 5 donations), respectively [33,55]. Generally, women are allowed to donate 3–7 times per year and men 4–7 times [33]. Prolongation of this interval, as proposed by the AABB [67] and the European Directorate for the Quality of Medicines & Healthcare [68] is an important measure to reduce iatrogenic depletion of iron stores in regular donors and allow for a longer time window to recover iron stores through nutrition or supplements. However, a recent study convincingly demonstrated that without iron supplementation, 67% of donors do not recover iron stores even within 180 days [43]. This is no surprise as the additional iron needed for the maximum donation frequency is not trivial. For those donating 4–6 whole blood units per year (assuming an iron loss of 200–250 mg per donation), 2.2–4.2 mg of additional iron would need to be consumed per day (as opposed to a normal intake of 1–2 mg) [69]. Therefore, a recommendation to meet usual requirements plus additional losses is no adequate measure, especially in donors with dietary adjustments including vegetarians and vegans.

A limitation of our study is that the observation of participants was terminated after 12 weeks at follow-up, and no details on future development of hemoglobin and iron status are available, which would be especially interesting for donors who keep donating blood with a high frequency.

4.4. Ethical aspects

The ethical dimension of drug administration to healthy individuals such as blood donors is another issue of discussion. In contrast to previous studies in this setting [40,63] aiming to replace donation-induced iron loss, we aimed to treat documented ID. Although a number of symptoms are associated with ID, generally low body iron stores alone are not necessarily regarded as a condition requiring treatment. Some argue that this is a treatment of laboratory values with a potentially unnecessary drug having possible adverse effects. These concerns are relevant and appear to be based on many open questions on the issue of ID and its impact on health. Associated symptoms are often vague and are subjected to individual perception rather than to easily verifiable clinical tests. Furthermore, due to the usually insidious onset of ID the body adapts and unspecific conditions like reduced physical or cognitive performance are often not recognized or attributed to other factors including stressful lifestyle. Therefore, studies on long-term effects of ID assessing objective endpoints need to be done to estimate the value of a timely restitution of body iron stores in blood donors.

4.5. The definition of iron deficiency in this setting

Another point under discussion is the level of ferritin that marks the threshold to ID. There is no general agreement, cut-offs often are arbitrarily chosen, and more so, frequently gender-specific differences are made, assuming that women of childbearing age physiologically have lower normal ferritin levels. Aside from the fact, that this, alongside with cut-off values of other iron store parameters like Hb, has been an issue of discussion in literature [70,71], ferritin thresholds for premenopausal women range from 6 to 20 ng/mL, defining ID, while for men they are set from 15 to 30 ng/mL [3,7,8,44,72]. If gender is not taken into account, cut-off levels between 12 and 30, or even 50 ng/mL are reported [1,5,9–11,17,20,43].

Given the high number of affected individuals and the ethical dimension, there is an urgent need for future studies how to best prevent and treat ID and donation related anemia in blood donors.

Moreover, the awareness of transfusion specialists, general practitioners and internists is often low and needs to be improved [73].

However, apart from high costs, the administration of an IV drug that takes time and could (rarely) provoke allergic reactions is currently not a realistic option in a high-volume blood donation center. Oral iron therapy is also effective, and new preparations like liposomal/sucrosomial iron [74,75] seem to have less adverse effects and better bioavailability.

4.6. Recommendations for clinical routine

Based on the current data showing good efficacy and an acceptable profile of adverse events, it appears reasonable to offer oral iron to all iron deficient blood donors. Intravenous iron should be considered when oral iron is not well tolerated and/or insufficiently effective in restoring donor's iron stores. Unfortunately, the actual implementation of these suggestions will differ largely in different countries/institutions and these challenges will often be accentuated by financial restrictions.

5. Conclusion

A single dose of 1.000 mg of intravenous iron is more effective than a standard oral iron regime to treat iron deficiency in blood donors. The majority of our study participants developed iatrogenic IDA after donation. Because this should not occur, the assessment of ferritin and the preservation of body iron stores by iron supplementation in blood donors are an important strategy. IV iron supplementation is more effective but both, IV and oral iron, are safe and well tolerated.

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Authors

Drexler, Macher and Amrein had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Study supervision: Amrein, Drexler, Macher.

Previous presentation

Preliminary results of the study were presented internationally the 27th Regional Congress of the ISBT in Copenhagen, June 2017.

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Conflict of interest

KA obtained funds by Vifor Pharma, Austria, for financing IV medication. Vifor Pharma had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.03.025.

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