The side-effects of different doses of iron sulfate on women of reproductive age: a randomized double-blind, placebo-controlled study

Efeitos colaterais do sulfato ferroso administrado em diferentes posologias em mulheres em idade reprodutiva: estudo randomizado, duplo cego e controlado por placebo

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Abstract

Objectives:to identify side effects of the use of different doses of iron sulfate (IS).

Methods: an eight-week randomized, double blind, placebo-controlled trial was carried out involving 727 women aged 20-49 years between October 2005 and October 2006. The women were randomly allocated into eight groups with daily or twice-weekly doses administered during or in between meals. The information was obtained by weekly telephone contact. Analysis involved comparison of the proportion of complaints from the different groups.

Results: of 726 women initially selected, 74.2% completed eight weeks of follow up. In the regimens containing IS 95.2% of women reported gastrointestinal complaints. More complaints were reported for daily doses than for ones ($p < 0.001$). Those taken between meals were associated with more nausea than those taken during meals ($p < 0.001$). Of the 95 women who withdrew from the experiment, 88.4% belonged to the IS group and diarrhea was the main complaint (29.8%).

Conclusions: the use of iron sulfate was associated with gastrointestinal side effects, especially when taken daily and diarrhea was the main complaint associated with IS.

Key words *Iron sulfate, Women's health, Anemia, iron-deficiency, Iron*

Resumo

Objetivos: identificar efeitos colaterais com o uso do sulfato ferroso (SF) administrado em diferentes posologias.

Métodos: realizou-se ensaio randomizado, duplo cego, controlado por placebo, com duração de oito semanas, em 727 mulheres de 20-49 anos, entre outubro/2005 e outubro/2006, alocadas aleatoriamente em oito grupos de estudo, segundo o uso do SF ou placebo, frequência de utilização (diária ou duas vezes por semana) e horário de administração - durante (DR) ou no intervalo (IR) das refeições. As informações foram obtidas através de contato telefônico semanal. A análise foi feita por meio da comparação das proporções das queixas relacionadas aos diferentes esquemas posológicos.

Resultados: das 727 mulheres inicialmente selecionadas, 74,2% completaram as oito semanas de seguimento. Os esquemas posológicos contendo SF foram responsáveis por 95,2% das queixas gastrointestinais. Tais queixas estiveram ainda relacionadas aos esquemas posológicos diários quando comparados aos esquemas semanais ($p < 0,001$). As tomadas no IR estiveram mais associadas à náusea do que as tomadas DR ($p < 0,001$). Das 95 mulheres que abandonaram o experimento, 88,4% pertenciam aos grupos do SF e, entre estas, a diarréia foi o principal motivo (29,8%) alegado.

Conclusões: o uso do sulfato ferroso esteve associado a efeitos colaterais gastrointestinais. A diarréia foi a queixa mais associada ao uso do SF e principalmente nos esquemas posológicos de tomada diária.

Palavras-chave *Sulfato ferroso, Saúde da mulher, Anemia ferropriva, Ferro*

Introduction

The improvement of diet, combating intestinal parasites, enriching foodstuffs and taking iron salts in different doses have been some of strategies that have been used since the 1950s to combat iron-deficiency anemia.[1] Although these measures are theoretically well-established, they have not been shown to be effective in solving the problem and it is still highly prevalent, especially in developing countries, such as Brazil, and among children and women of child-bearing age.[2-6] There is, therefore, still no consensus regarding the best strategy to deal with this.[7]

Issues relating to the bioavailability of iron in food, diets rich in substances that hinder its uptake, problems with absorption and low adherence to treatment have been suggested as factors that reduce the efficacy of large-scale anemia prevention and treatment programs.[7-9]

There are many different compounds containing iron, all of which aim to improve the efficacy, tolerance and adherence to use. However, iron sulfate (IS), is still the drug of choice for the treatment of iron-deficiency anemia, since it is effective, low cost, and easily absorbed, compared with other iron salts.[10,11] Its effectiveness in correcting anemia and re-establishing iron deposits is the same as other compounds, but the gastro-intestinal intolerance that it may provoke, has limited this.[12,13] More modern iron compounds, such as iron chelate, despite being more effective and less associated with side-effects,[14] are expensive and cannot therefore be widely used in public health.[1,2]

The side effects of the use of iron salts have led to a tendency to use progressively smaller doses of this mineral, in an effort to reduce the incidence of undesirable gastrointestinal effects, such as a metallic taste in the mouth, nausea, heart-burn, abdominal pain, diarrhea or constipation.[10,13]

Alternatives that minimize the undesirable effects of iron salts include the use of new regimens, such as a reduction in the dosage or in the frequency of doses.[13] These new proposals have improved treatment by reducing the blocking of iron absorption caused by habitual doses considered to be "high" and have, on the other hand, increased adherence by reducing side-effects.[14,15]

The aim of the present study is thus to investigate the side-effects of IS treatment in different doses and the reasons for abandoning treatment of women of reproductive age who use the health services in the Brazilian city of Recife.

Methods

A randomized, double-blind placebo-controlled field trial was conducted with women attending the Centro Integrado de Saúde Amaury de Medeiros (CISAM) which is part of the Universidade de Pernambuco (UPE) between October 2005 and October 2006.

The study covered 727 non-pregnant women aged between 20 and 49 years, resident in the Metropolitan Region of Recife, who had a telephone for subsequent weekly contacts. In order to ensure that the study was double-blind, only the researcher responsible for recruiting the women was aware of the type of treatment given, while the telephone interviewer and the woman herself were not aware of which kind of medication was provided. Women were excluded from the study if they had gastrointestinal disorders, had hemoglobin levels ≥15 g/dL (when allocated to the IS groups) or when they had hemoglobin levels ≤11 g/dL (when allocated to the placebo group).

The sample size of 80 women per group was calculated using the equation based on the difference of proportion.[16] Adherence to the weekly use group was considered to be 90% and 70% for the daily use group and the probability of Type I error was taken to be 0.05 and the probability of Type II error 0.20.

Recruitment for the study was conducted in a random fashion using a systematic technique. The invitation to participate in the experiment was carried out by giving forms numbered one to four in numerical order to women as they arrived at the health service where the study was being carried out.

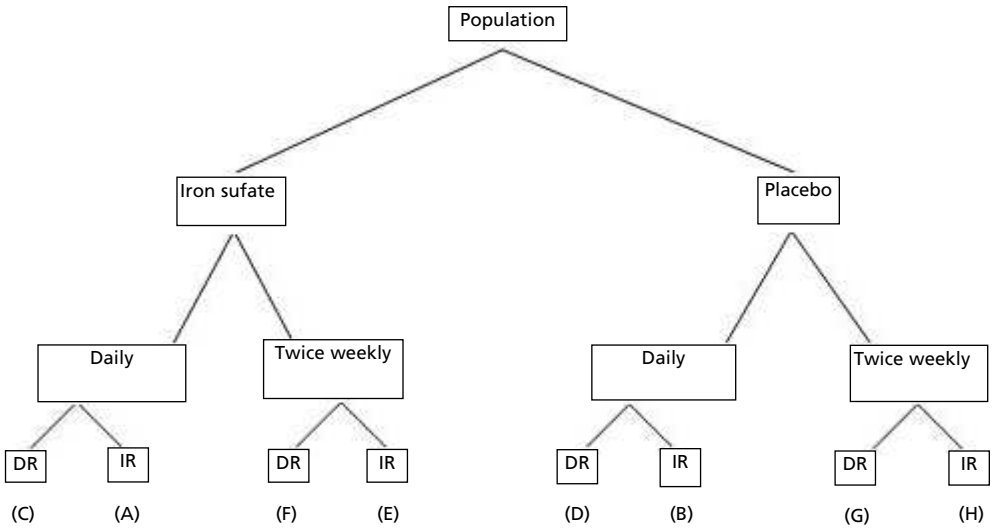
After meeting the inclusion criteria, the women were randomized again and allocated to the eight study groups: daily IS during meal times (group C), daily IS between meals (group A), IS twice weekly during meal times (group F) and IS twice weekly between meals (group E). The other four groups (B, D, G, H) were put on similar regimens, using the placebo instead of the IS (Figure 1).

A questionnaire was applied on recruitment to characterize the population under study, including personal data, telephone numbers, socio-demographic data, the use of medication and pre-existing conditions.

On recruitment, each participant was given a set of instructions, a labeled flask, indicating the dosage, containing enough pills for eight weeks (iron sulfate equivalent to 60 mg of iron or placebo). At this stage a blood sample was obtained to determine the concentration of hemoglobin before the start of the experiment. Neither the women nor the inter-

Figure 1

Strategic plano of study.



Plan for random allocation of women of reproductive age into eight study groups, by use of iron sulfate or placebo, frequency of use (daily or twice weekly) and time of administration (during - DR or in between - IR mealtimes).

viewers were aware which women had been allocated to the placebo and which to the iron sulfate group.

Another questionnaire was applied by telephone every seven days, in order to confirm that the women had taken the correct dose and to register any complaints or reasons for abandoning the study. The researchers who conducted the telephone interviews did not know which women were taking iron sulfate and which the placebo.

The variables relating to side-effects attributed to the use of the medication were nausea, loss of appetite, colic, itching, vomiting, epigastric pain, diarrhea, headaches, a metallic taste, general malaise, intestinal constipation, loss of appetite and dizziness.

The statistical analysis was carried out using Epi Info 6.04 and STATA. Pearson's chi-squared test was used to compare the proportions from the groups registering complaints: use of iron sulfate versus use of placebo; use of iron sulfate daily versus weekly; use of iron sulfate during meal times versus between meals, and frequency of and reasons for abandoning treatment for the different doses in the iron sulfate and the placebo groups. For all tests the level of significance was set at 5%.

All the participants were informed of the aims of the research and signed Terms of Free Informed Consent before commencing the study. The study was approved by the Universidade de Pernambuco (UPE) Research Ethics Committee.

Results

Of the 727 women who began the experiment, 95 left because of side-effects: constipation, diarrhea and nausea (Table 1), seven for other reasons and 86 during follow up, giving a total of 188 losses (25.8%). Comparison of the age and level of education of the losses with the remaining group (n=539) showed that there were no statistically significant differences (p>0.05 for both variables).

4661 telephone calls were made during the eight weeks of follow-up, of which 2221 (47.7%) were to the IS group and 2440 (52.3%) to the placebo group. It was recorded that 10.8% (504/4661) reported complaints during the telephone conversations, of which 10.2% (n=480) were in the IS group and 0.6% (n=24) in the placebo group (p<0,001), malaise and diarrhea being the most commonly reported side-effects. (p<0.001; Table 2).

Investigation of the 480 complaints in the weekly and daily IS groups found that 78.7% of these occurred among those in the daily group (p<0.001). All complaints were more frequent in the daily IS group and this difference was the greatest in

the case of constipation (Table 3).

No difference was observed in the frequency of complaints when comparing the use of IS during (DR) or between (IR) meals, with the exception of complaints of diarrhea (which were more common with DR) and nausea (which was more common in the IR group). (Table 4).

Of the subgroup of 95 women who abandoned the experiment complaining of side-effects 88.4% belonged to the groups using IS. The groups who used IS daily between and during meals contained the most women who abandoned the experiment compared to the groups taking the placebo according to the same regimen (p<0,001; Table 5).

Table 1

Reasons for abandoning the experiment given by 95 women in the iron sulfate and placebo groups. Recife, 2006.

Reasons	Iron sulfate		Placebo		Total	
	n	%	n	%	n	%
Constipation	20	100.0	-	-	20	21.0
Diarrhea	25	96.2	1	3.8	26	27.4
Nauseas	22	95.6	1	4.3	23	24.2
Headaches	16	69.6	7	30.4	23	24.2
Weight gain	1	33.3	2	66.7	3	3.2
Total	84	88.4	11	11.6	95	100.0

Table 2

Distribution of complaints reported in the groups that used iron sulfate and placebo during the 4656 telephone conversations. Recife, 2005-2006.

Complaints	Iron sulfate		Placebo		Total		*p**
	n	%	n	%	n	%	
Malaise	94	93.1	7	6.9	101	20.0	<0.001
Diarrhea	97	97.0	3	3.0	100	20.0	<0.001
Nausea	78	90.7	8	9.3	86	17.0	<0.001
Constipation	76	97.4	2	2.6	78	15.5	<0.001
Intestinal colic	70	98.6	1	1.4	71	14.0	<0.001
Epigastric pain	33	94.3	2	5.7	35	7.0	<0.001
Metallic taste	32	97.0	1	3.0	33	6.5	<0.001
Total	480	95.2	24	4.8	504	100.0	<0.001

*Pearson's chi-square test.

Table 3

Distribution of complaints in the groups taking iron sulfate, daily and twice weekly during the 2218 telephone conversations. Recife, 2005-2006.

Complaints	Daily		Twice weekly		Total		*p**
	n	%	n	%	n	%	
Malaise	66	68.0	31	32.0	97	20.2	<0.001
Diarrhea	78	83.0	16	17.0	94	19.6	<0.001
Nausea	66	84.6	12	15.4	78	16.2	<0.001
Constipation	71	93.4	5	6.6	76	15.8	<0.001
Intestinal colic	48	68.6	22	31.4	70	14.6	<0.001
Epigastric pain	20	60.6	13	39.4	33	6.9	<0.001
Metallic taste	29	90.6	3	9.4	32	6.7	<0.001
Total	378	78.7	102	21.3	480	100.0	<0.001

*Pearson's chi-square test.

Table 4

Distribution of complaints in the groups taking iron sulfate, during and between mealtimes in the 2218 telephone conversations. Recife, 2005-2006.

Complaints	During mealtimes		Between meals		Total		*p**
	n	%	n	%	n	%	
Malaise	59	60.8	38	39.2	97	20.2	0.040
Diarrhea	41	43.6	53	56.4	94	19.6	0.164
Nausea	20	25.6	58	74.4	78	16.2	<0.001
Constipation	39	51.3	37	48.7	76	15.8	0.903
Intestinal colic	36	51.4	34	48.6	70	14.6	0.892
Epigastric pain	17	51.5	16	48.5	33	6.9	0.918
Metallic taste	20	62.5	12	37.5	32	6.7	0.176
Total	232	48.4	248	51.6	480	100.0	

*Pearson's chi-square test.

Table 5

Distribution of the 95 women who abandoned treatment complaining of side-effects by iron-sulfate or placebo group. Recife, 2005-2006.

Groups	Iron sulfate		Placebo		*p**
	n	%	n	%	
Daily and between meals	34	94.4	3	5.6	<0.001
Daily and during meal times	28	100.0	-	-	-
Twice weekly and between meals	9	64.3	5	35.7	0.266
Twice weekly and during meal times	13	81.2	3	18.8	0.009
Total	84	88.4	11	11.6	

*Pearson's chi-square test.

Discussion

Studies of adherence and the side-effects of iron salts are very diverse, differing in terms of population and duration, dosage, concepts and the way adherence, abandonment of treatment and reported complaints are measured. This is one of the main difficulties for interpretation and analysis of the results reported here.[9-11] On the other hand, the studies are unanimous in choosing IS as the most efficient treatment for anemia.[1,12-15]

A peculiarity of this study that should be taken into consideration was that fact that the follow-up was carried out by way of telephone interviews, which are rarely used for studies of adherence,[17] although there are some reports that this technique can provide results similar to those of face-to-face interviews in terms of reliability.[18,19] It was striking that even though this study was conducted with a sample of low-income individuals using public health services, all the women had a telephone number at which they could be contacted. The loss of follow-up for reason of not being able to contact the women was roughly 12%, suggesting that this loss did not bias the results of the experiment.[20] It is important to note that the level of education of those women lost to the study did not differ from that of those who remained in it, as it has been reported that low levels of schooling may be a restriction on efforts to combat anemia.[21,22]

The duration of the study of eight weeks is similar to that of most studies involving daily and weekly IS regimens, which vary from eight to 16 weeks.[12,15]

The present study found that the use of IS was responsible for the gastro-intestinal complaints reported by the women, corroborating previous findings.[1,9,10,23] Reported complaints were more frequent among those taking IS daily than among those taking it twice a week. This is in accordance with various other studies that suggest that two intermittent doses, when treating anemia, may be more

effective in improving adherence, owing to the lower incidence of side-effects.[7,12,13,15,23]

The side-effects, taken in isolation show that the most frequently reported complaints were malaise, diarrhea and constipation, especially in the groups that took IS on a daily basis. Other studies have found variations in the frequency for various different complaints relating to the gastrointestinal tract that this is probably due to the fact that studies examined such effects in different sectors of the population,[21-23] although most complaints still refer predominantly to the gastrointestinal tract. The findings of this study are in accordance with the literature, where it has been noted that the presence of such gastrointestinal effects interfere with adherence to treatment for anemia.[6,10-12]

A study conducted among pregnant women in the same locality observed that abandonment of treatment for reason of diarrhea or epigastric pain was found only in the group that used IS on a daily basis and not in those groups that took the medication twice weekly. The study further found that side effects, especially epigastric pain and diarrhea, were directly proportional to the frequency of use of iron supplements.[12]

In the present study, the administration of IS led to the development of diarrhea as a side-effect, regardless of the regimen, although this was more common when the drug was taken on a daily basis. It can thus be suggested that the twice-weekly regimen, rather than the daily one, leads to greater adherence and thus lower levels of abandonment for reason of side effects, especially gastrointestinal ones, since it would appear to have been shown that iron salts administered in lower doses on a weekly basis may reduce side-effects.

Nevertheless, more in-depth studies are still needed to investigate any possible difference in side-effects between groups who take the drug between and during mealtimes.

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