Oral iron therapy reduced unexplained fatigue in non-anaemic women with serum ferritin concentrations <50 µg/l


Clinical impact ratings GP/FP/Primary care  ****** IM/Ambulatory care  ******

Is iron therapy effective for non-anaemic women with unexplained fatigue?

METHODS

**Design:** randomised, placebo controlled trial.

**Allocation:** concealed *

**Blinding:** blinded (patients, clinicians, data collectors, and outcome assessors)†.

**Follow up period:** 1 month.

**Setting:** an academic primary care centre and 8 private general practices in western Switzerland.

**Patients:** 144 women 18–55 years of age (mean age 35 y, based on n = 136) whose primary reason for consulting was fatigue. Exclusion criteria: anaemia (haemoglobin concentration <117 g/l), other obvious physical or psychiatric causes of fatigue, or chronic fatigue syndrome.

**Interventions:** oral, long acting ferrous sulphate (Tardyferon, Robapharm, Boulogne, France), 80 mg/day, for 4 weeks (n = 75) or matching placebo (n = 69).

**Outcomes:** main outcome was perceived level of fatigue (10 point visual analogue scale [VAS] ranging from 1 = no fatigue at all to 10 = very severe fatigue). Secondary outcomes included adherence to treatment and Patient follow up: 94%.

*See glossary.
†Information provided by author.

MAIN RESULTS

Analysis was by intention to treat. 115 women (85%) had serum ferritin concentrations <50 µg/l, and 69 women (51%) had concentrations <20 µg/l. Mean decrease in the overall intensity of fatigue from baseline to 1 month was greater in the ferrous sulphate group than in the placebo group (table). However, subgroup analysis showed that only women with ferritin concentrations <50 µg/l had decreased fatigue intensity. The groups did not differ for compliance rates (95% v 98%, p = 0.25)

CONCLUSIONS

Oral iron therapy improved perceived level of fatigue more than placebo in non-anaemic women with unexplained fatigue. It was unclear if improvement occurred in women with serum ferritin concentrations >50 µg/l.

Abstract and commentary also appear in ACP Journal Club.

### Oral ferrous sulphate v placebo for women with unexplained fatigue*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ferrous sulphate</th>
<th>Placebo</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in overall fatigue intensity from baseline to 1 month</td>
<td>-1.82</td>
<td>-0.85</td>
<td>0.97 (0.32 to 1.62)</td>
</tr>
</tbody>
</table>

*CI defined in glossary.

Commentary

The small randomised controlled trial by Verdon et al raises several questions.

Firstly, are the results biologically plausible? Iron is an important component in a number of proteins involved in oxidative processes and muscle functioning, and a recent review of animal and human research found some evidence that iron deficiency without anaemia may lead to decreased physical functioning. Maximum oxygen consumption (VO2max) is decreased in non-anaemic women with low iron stores and improves with 6 weeks of iron supplementation.

Are the results clinically meaningful? The authors did not report improvement rates, so numbers needed to treat cannot be calculated. The reported 0.97 point decrease on a 10 point VAS is less than the 1.1 to 1.3 points found to represent the minimal clinically appreciable difference when a VAS was used to measure disability or pain.

How long should the treatment continue? Would more than 1 month of therapy lead to more impressive results?

Is there a target ferritin concentration? The authors’ subgroup analysis is somewhat questionable, since only 21 women in their sample had ferritin concentrations >50 µg/l.

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1 Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S–85S.