

Editorial

The pale evidence for treatment of iron deficiency anaemia in older people

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The management of iron deficiency anaemia (IDA) in older individuals might appear relatively simple and uncontroversial. However, a combination of diagnostic challenges and increasing evidence for common treatments being poorly effective, arguably render this a false assumption. The long-established practice of prescribing oral ferrous supplements is increasingly challenged by the wider availability and promotion of modern intravenous iron supplementation. It has brought into focus the need for evidence of efficacy and cost-effectiveness, particularly in terms of the balance of affordable person-centred benefits versus harm ('realistic medicine').

Why iron deficiency matters

Anaemia is a particularly common finding in older people. It is associated with fatigue, impaired functional capacity, increased hospitalization and mortality [1]. The World Health Organisation defines anaemia as a haemoglobin level <130g/L in men and <120g/L in women [2]. Its prevalence among community-dwelling adults aged 65 years and older in the USA is 11.0% and 10.2% in men and women, respectively, [3] rising to more than 20% in those >85 years and over 50% of those in nursing homes [4].

IDA is relatively common, typically accounting for approximately 30% of cases of anaemia in older individuals in most Western countries [5,6]. It is diagnosed by the presence of low ferritin levels or low serum iron and transferrin saturation levels [7]. However, ferritin levels are higher in older people and increase in disease, making diagnosis less certain. In older people, chronic kidney disease, gastrointestinal problems and poor diet more commonly underpin anaemia [6]. Up to half of all elderly anaemic patients have multifactorial anaemia, characterised by a combination of underlying problems such as iron deficiency, chronic inflammation, renal insufficiency, folate deficiency and/or vitamin B12 deficiency. Thus, oral

iron supplementation might only have a modest impact on haemoglobin level [8]. In a Scottish study, 5% of the population aged 65 or over received at least one prescription for oral iron in the year 2015-2016 [9]. Large numbers of people are therefore treated for iron deficiency, many for a long time, making the question of how to treat this condition most effectively an important one for patients, clinicians and healthcare funders.

Do oral iron supplements really work?

Despite the widespread use of oral iron to treat even mild IDA in older people, evidence is lacking on the best way to treat this condition, or indeed whether treatment is required at all in mild cases. A recent systematic review found only three RCTs in older people testing the efficacy of oral iron compared to placebo or no iron, all in the setting of orthopaedic surgery. The treatment effect was trivial; haemoglobin levels increased by a mean of only 3.5g/L (95%CI:1.2-5.9g/L) [10]. Routinely collected data from older people in Scotland support these findings with a mean improvement in Hb after treatment of only 5g/L in those with iron deficiency relative to those without treatment [9]. In an observational study involving 50,319 adult chronic kidney disease patients, oral iron therapy was less effective than no iron replacement [11]. In another study, Rimon et al showed low dose oral iron treatment was as effective as higher dose in increasing haemoglobin in elderly people [12]. However, there was no placebo control group, so the absence of a dose-response association potentially suggests that oral iron is ineffective. The current practice of daily dosing and/or splitting doses **might** adversely affect iron absorption by increasing hepcidin levels [13], **showing the need to re-evaluate our current knowledge on how best to administer oral iron.**

Hepcidin regulates entry of iron into the circulation but high hepcidin levels are also seen in chronic inflammation and chronic kidney disease resulting in reduced iron absorption from gut mucosa [14]. Also, iron supplements may not be well absorbed in those with atrophic

gastritis (most of those aged 80 or over) or proton pump inhibitors due to achlorhydia [10]. Another important reason why oral iron may be ineffective is that adherence is poor due to side effects in up to 40% of people - particularly gastrointestinal symptoms with subsequent impact on diet, nutrition and health related quality of life [12, 15]. For a review of iron absorption and metabolism, see Anderson et al. [16].

Is intravenous iron better?

Intravenous iron can overcome many of the above problems with oral supplementation, but it is more expensive and carries a small, but non-trivial risk of anaphylactoid reactions. A meta-analysis assessing safety and efficacy of intravenous iron in various clinical groups showed intravenous iron increased haemoglobin concentration (standardised mean difference 6.5 g/L, 95% confidence interval 5.1 g/L to 7.9 g/L) and reduced risk of requirement for blood transfusion (risk ratio 0.74, 95% confidence interval 0.62 to 0.88). Side effects of IV iron were rare, occurring in 0.5 to 1% of the patients, including self-limiting fever, arthralgia and myalgia, usually within 24 hours of infusion. Anaphylactic reactions with IV high molecular weight iron dextran prohibited widespread use, but were extremely rare with other preparations of IV iron (<1:200,000) [17]. The efficacy and safety of IV iron in IDA in different settings suggest that IV iron supplementation could be considered for more elderly anaemic patients. However, whether the result of this meta-analysis applies to the elderly population is questionable. A further problem with the existing evidence for iron supplementation through any route is that the available trials did not aim to measure outcomes relevant to older patients – such as improvement in symptoms, physical performance, activities of daily living or quality of life [5, 9]. Moreover, a review of the evidence for intravenous iron found no precise comparison of the clinical benefit of different iron preparations [18]. There is better evidence of benefit in some specific patient groups,

particularly those with heart failure and iron deficiency. However, even in this setting only one trial has demonstrated clear and consistent improvement in quality of life [19]. Patients in this trial had a mean age of only 67 years, so it is uncertain if this result can be generalised to other, older patient groups.

The evidence gap

A satisfactory response ($>20\text{g/L}$) to oral iron is usually expected within 6-8 weeks of commencing treatment but our research group's data show many patients continue oral iron even if a suboptimal or no response is seen. The optimal dosing regimen and balance of benefit versus harm for oral iron in older people is unclear. The best strategy for those not responding to oral iron is also uncertain. It is also unclear whether further oral or IV iron therapy improves physical function and quality of life compared to no therapy in older patients with IDA.

A recent survey of geriatricians and general practitioners carried out through the British Geriatrics Society confirmed uncertainties and inconsistent approaches to IDA in clinical practice across the UK (unpublished data). Improved medical education on the nuances of iron deficiency is needed. The treatment strategies for older people with IDA that do not respond to initial treatment should be explored. Evidence of clinical effectiveness using outcomes most relevant to older people, such as quality of life and functional ability, rather than haemoglobin levels, is urgently needed.

Conflict of Interest Statement

The authors have received funding to carry out a pilot randomised controlled trial on management of iron deficiency anaemia in older people from the Chief Scientist Office, Scotland.

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