Striking the balance with intravenous iron: too much or never enough?

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Iron deficiency anaemia (IDA) presents the treating clinician with two issues: first, the need to establish a cause, and second, the need to correct the anaemia to improve symptoms and prevent complications. With a wide spectrum of severity, a host of potential causes ranging from benign to life-threatening, and multiple options for correction, one can expect significant variation in the management of IDA among clinicians.

It is within this context that Brookes *et al* take a macroscopic view of the trends in incidence and management of IDA in England between 2012 and 2018.[1] A number of pertinent observations have been made. Overall, secondary care encounters for IDA increased, presumably due to increased recognition; there was a 68% increase in total hospital encounters for a primary diagnosis of IDA, encompassing a 58% increase in non-elective and 74% increase in day-case hospital encounters. The relative increase in day-case in comparison to non-elective management is important, given the significantly greater costs associated with the latter; while total annual day-case management costs in 2017/2018 (£46 million) were similar to total non-elective costs (£42.4 million), four times as many patients were managed as day-cases (n=103 806) compared with non-electively (n=25 275). However, there was noticeably wide variation among different health networks across England in rates of non-elective management, signifying a need for a unified approach.

Given the large cost discrepancy, an important question to answer is how best to manage patients in order to facilitate day-case management and prevent non-elective admissions. This should begin with ensuring early recognition of IDA. The association between deprivation and non-elective admissions suggests that lower socioeconomic status patients may be more likely to present at a later, more severe stage requiring admission. The reasons for this association deserve to be explored in future studies in order to target specific interventions aimed at ameliorating this disparity.

Regarding IDA management, it was concerning to note that while there was an increase in oral iron prescription, higher rates of oral iron prescription also correlated with non-elective admissions, suggesting that oral iron therapy did not prevent non-elective admissions. Meanwhile, only a very small proportion of patients were managed with intravenous iron prescriptions and this decreased over the study period; in 2017/2018, the rate of prescriptions per 100 000 population of intravenous iron was 2.0 compared with 4.6 in 2012/2013, while oral iron prescriptions per 100 000 population increased from 12 236 in 2012/2013 to 13 549 in 2017/2018. Whether a correlation existed between intravenous iron use and rate of non-elective admissions was not examined due to the small number of infusions seen, however, as the authors suggest, exploring this relationship in future studies would be helpful to see whether more liberal use of intravenous iron may reduce non-elective management. In the meantime, more liberal use seems logical, particularly in certain clinical situations.

There are a number of factors a clinician should consider when deciding on the appropriate route of iron administration in IDA. These include the presence of active inflammation, comorbidities (in particular chronic heart failure, inflammatory bowel disease (IBD) and chronic kidney disease),[2] the degree of iron deficit, the suitable timeframe to achieve iron repletion, the patient's ability to absorb iron, potential compliance issues, tolerability and safety. If given orally, the timing is also important; multiple daily dosing regimens of oral iron directly impairs its own absorption by increasing levels of hepcidin[3] as hepcidin inhibits ferroportin-mediated transport of iron out of enterocytes, limiting the intestinal absorption of oral iron. Single doses of oral iron on alternate days minimise this issue, and hence is preferable.[3]

Intravenous iron, meanwhile, has the ability to deliver a larger supply of iron in a short timeframe, replenishing iron stores more quickly, and bypassing gastrointestinal intolerance and absorption issues. In chronic inflammatory disorders, absorption is particularly relevant as circulating levels of hepcidin are increased by inflammation. In diseases such as IBD and chronic heart failure, intestinal absorptive capacity is further limited by intestinal inflammation, oedema or reduced splanchnic blood flow. Additionally, in IBD, gastrointestinal side effects of oral iron are particularly undesirable, an issue which is not seen with intravenous iron.

Accordingly, multispecialty expert consensus has suggested that in chronic heart failure, active IBD and dialysis-dependent chronic kidney disease, intravenous iron should be considered first line.[2] Likewise, in the elderly, where tolerance of oral iron is often poor, comorbidities may render it less effective and polypharmacy and pill burden are more likely to be an issue, intravenous iron is thought to be favourable from a risk–benefit perspective yet remains underutilised.

Nonetheless, other factors should be included in the decision-making process when considering the use of intravenous and oral iron therapy. First, the cost difference is substantial; a 12-week course of oral iron is approximately £2.30 compared with approximately £1400 for intravenous iron administration over two elective admissions. The costs of selective use of intravenous iron may, however, be offset for example, by preventing poor quality of life associated with ongoing symptoms due to ineffective oral therapy. In addition, intravenous iron may also prevent the need for non-elective admissions or the requirement for blood transfusions, further offsetting costs. Second, the choice of agent needs to be considered. There are currently four intravenous iron preparations available in the UK. The two most commonly used preparations are ferric carboxymaltose and ferric derisomaltose owing to their simple dose calculation and the ability to administer the total iron dose in one to two attendances. Third, and potentially influencing clinicians the most, is the small risk of side effects, particularly hypersensitivity reactions. Although rare, this risk necessitates specific guidance in relation to administration and monitoring, and thus far has limited intravenous iron to predominantly secondary care administration in the UK. However, administration in community general practices, as is carried out elsewhere in the world, could potentially reduce administration costs. Hypophosphataemia is another recognised side effect of

intravenous iron but the overall incidence and clinical significance of this are not yet fully understood. There have been reports of long-standing hypophosphataemia with repeated use, and the incidence is possibly more common with ferric carboxymaltose than ferric derisomaltose.[4] Skin discolouration as a result of extravasation is another well-documented adverse effect of parenteral iron, ranging from self-limiting skin irritation to long-lasting discolouration around the administration site in severe cases. Informing patients of this potential adverse effect is important and those administering intravenous iron should be monitoring patients for signs of extravasation as well as hypersensitivity.

Since the study period included by Brookes and colleagues,[1] a novel oral iron preparation has become available and the impact of this remains to be seen. Ferric maltol is an oral iron that has been shown to be well tolerated and results in haemoglobin normalisation within 12 weeks for a high proportion of quiescent or mildly active patients with IBD intolerant or refractory to other oral iron products.[5] Though not comparable to intravenous iron for use in those with more active inflammation, it offers an alternative oral iron preparation that may prevent the need for intravenous administration. The cost of the preparation (approximately £170 for 12 weeks) means that it is likely to be used only after a failed trial of conventional oral iron, particularly in patients wanting to avoid intravenous replacement.

With many possibilities being available for the management of IDA, it is not surprising that there is significant variability in management across England. However, given the clinical and cost implications, a unified approach is required. The limited use of intravenous iron is striking, and, while the data are not yet iron-clad, more liberal use in the right circumstances may represent a way to manage patients more effectively and prevent costly non-elective admissions.

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REFERENCES

1 Brookes MJ, Farr A, Phillips CJ. Management of iron deficiency anaemia in secondary care across England between 2012 and 2018: a real-world analysis of hospital episode statistics. *Frontline Gastroenterol* 2021;12:363–9.
2 Cappellini MD, Comin-Colet J, de Francisco A, *et al*. Iron deficiency across chronic inflammatory conditions: international expert opinion on definition, diagnosis, and management. *Am J Hematol* 2017;92:1068–78.
3 Stoffel NU, Zeder C, Brittenham GM, *et al*. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. *Haematologica* 2020;105:1232–9.
4 Schaefer B, Tobiasch M, Viveiros A, *et al*. Hypophosphataemia after treatment of iron deficiency with intravenous ferric carboxymaltose or iron isomaltoside—a systematic review and meta-analysis. *Br J Clin Pharmacol* 2020;54.
5 Gasche C, Ahmad T, Tulassay Z, *et al*. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. *Inflamm Bowel Dis* 2015;21:579–88.