INTRAVENOUS IRON FOR IRON DEFICIENCY ANAEMIA

EXECUTIVE SUMMARY
(Adapted from the report by NURKHODRULNADA MUHAMAD LATTEPI)

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Background

Iron deficiency anaemia (IDA) has been recognised as one of the important public health concerns which affects not only growing children, premenopausal, and pregnant women, but also being increasingly considered as a clinical condition that can affect patients presenting to various medical and surgical specialities, especially those with chronic conditions and the elderly. The Global Burden of Disease project estimated around 1.24 billion people (a sixth of worldwide population) are suffering from IDA. In fact, it is one of the five leading causes of years lived with disability in humans and affected women mostly. Aetiologies of IDA may vary widely or tend to coexist in different patient populations, especially those with severe and/or recurring IDA, geographies (developing and developed countries) and specific clinical conditions, which may be categorised into three major groups: 1) imbalance between iron intake and iron needs, 2) blood losses (either occult or overt), and 3) malabsorption. The mainstay treatment of IDA treatment remains to investigate and manage the underlying cause of IDA. Patients age and sex, the underlying condition and cause of IDA, the severity of anaemia or ID and their symptoms, and the time frame available or acceptable for correction are among factors that should be taken into consideration during decision making. Though there is no clear benefit on treating ID without anaemia, patients presenting with IDA should be treated with iron supplementation that can be administered either orally or parenterally. Unless contraindicated, oral iron therapy is the first line of treatment of IDA. Intravenous iron (IVI) can be considered in cases of intolerance or when signs of non-response are noted despite efforts to improve tolerance, adherence, or absorption of oral iron. intravenous iron can be considered with appropriate dosing. Haemoglobin (Hb) and iron indices should be monitored continuously every 1-3 months until normalisation of laboratory values. With regards to IVI use, a recent systematic review discovered that many of the existing national and international clinical guidelines are lacking updated and clarified information on IDA management modalities across different therapeutic areas. In the Ministry of Health healthcare facilities, IVI is mostly prescribed in selected cases, such as in Obstetrics & Gynaecology (O&G) and Chronic Kidney Disease (CKD) patients, and some may even require a prescription from haematologists. It is thought that there is scepticism around the use of IVI for other IDA-related indication due to its limited access in the pragmatic setting. Furthermore, IVI may provide a safer alternative to blood transfusion in treating anaemia. Hence, this technology review was conducted following a request by a transfusion medicine specialist from National Blood Centre, Ministry of Health Malaysia to ascertain the benefit of using intravenous iron for the treatment of patients with IDA, particularly its impact on Hb concentration, blood transfusion requirement and their safety profile.

Objective:

To compare the effectiveness, safety, cost-effectiveness, and organizational issues of IVI preparations that are available in the Malaysian market with oral iron or other alternatives in the treatment of adult patients with iron deficiency anaemia (IDA).

Methods

Electronic databases searched through the Ovid interface: MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to May 19, 2020; EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 14, 2020; EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016; EBM Reviews - Cochrane Central Register of Controlled Trials April 2020; EBM Reviews - Health Technology Assessment 4th Quarter 2016; EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016. Searches were also run on PubMed, the United States Food and Drug Administration (US FDA) and INAHTA databases. No limits were applied. Additional articles were identified from reviewing the references of retrieved articles. The search strategy was updated until 20th May 2020. In addition, Google was used to search for additional web-based materials and information. Detailed search strategy is as in **Appendix 1**.

Results and conclusion:

A total of 3,901 records were screened, and 3,738 studies that did not meet the inclusion criteria were excluded. **One hundred and sixty-three** of potentially relevant abstracts were retrieved in full text and assessed for eligibility. Out of these, **22** studies comprising of six systematic reviews of randomised controlled trials (RCTs), nine RCTs, four prospective cohort studies, and three economic evaluations were finally selected for this review. The studies were conducted mainly in the United Kingdom, the United States of America, India, Spain, Korea, China, Hong Kong, Australia, Singapore, France, Thailand, Turkey, Norway, Romania, Egypt, Greece, Spain, Denmark, and Pakistan. The study populations included were among oncologic, cardiac, obstetric and gynaecologic patients undergoing surgery, traumatic patients with a critical illness as well as non-dialysis chronic kidney disease patients.

Efficacy and Effectiveness

Limited fair to good level of retrievable evidence has shown significant improvement in Hb concentration with preoperative IVI as well as in pregnant and postpartum women when compared to oral iron. This effect, however, was not seen in other populations included in the review, as IVI did not demonstrate any apparent benefit over the control group. In trials that compared IVI to no iron therapy, there was no strong evidence to support that preoperative IVI has led to significant improvement in Hb concentration. Only one study included in this review investigated the postoperative effect of IVI and found that it has shown favourable results on day 14 of operation compared to no iron therapy. In all studies with positive results for perioperative IVI over the control group, IVI was administered at least 14 days prior to surgery, or improvement in Hb level measured 14 days after the first dose of IVI administration. There is also a lack of head-head trial comparing different types of IVI formulations. In one study, both intravenous ferric carboxymaltose (IV FCM) and intravenous iron sucrose (IV IS) markedly improved preoperative haemoglobin concentration, with IV FCM achieving Hb correction about three days earlier than IV IS. However, no significant difference was observed between these two formulations. The impact of IVI on blood transfusion requirement

among surgical patients and other populations cannot be established due to mixed results obtained from the included studies. Almost all studies that reported on serum ferritin level showed that IVI did significantly increase the mean ferritin level compared to the control group with oral iron or no iron therapy. There were mixed results for mean transferrin saturation level as some studies reported significant increased compared to control, while a few reported comparable effects were observed between groups.

Safety

There was a substantial good level of retrievable evidence to suggest that the use of IVI is safe with no significant differences in mortality and severe adverse reactions/events within the follow-up period were observed between IVI and control group. Similarly, infection rates were comparable among groups except for non-dialysis CKD patients treated with IVI documented a higher incidence of hospitalised heart failure and significant lung and skin infection rates. IVI was also associated with decreased risk for gastrointestinal adverse events, particularly with IV IS, intravenous iron dextran (IV ID) and IV FCM, and when compared to oral iron or no iron therapy. On the other hand, the risk for neurologic and muscle and skeletal adverse events increased with IVI, particularly with IV IS and IV FCM, respectively. While there was no significant difference in risk for hypersensitivity reaction between IV FCM and IV IS, the odds of experiencing severe hypersensitivity reaction with intravenous iron derisomaltose (IV IIM) was 59% lower than that of IV FCM, and 49% lower than that of IV IS. The risk for cardiovascular adverse event was reported to comparable between IV FCM and IV IS. However, this risk was noted to be lower with IV FCM, while the use of intravenous ferric gluconate (IV FG) was associated with increased risk. There was also a risk for IVI-related infusion reaction, with increased risk for such reaction was observed for IV IS and IV FCM with more serious infusion reactions were seen with IV FG. Additionally, hypophosphataemia was one the common electrolytes imbalance documented with IVI therapy.

Organisational

There was a limited fair to good level of retrievable evidence to suggest that treatment of IDA with IVI resulted in no significant difference in length of hospitalisation between IVI and control groups, be it in perioperative settings, critical care patients or pregnant women.

Economic Implication

Theoretical simulation comparing preoperative optimisation of Hb with IVI to oral iron in patients with primary knee arthroplasty has shown that IVI resulted in cost savings of €831 and €405 for blood transfusion avoided per patient and each RBC unit spared, respectively. Similarly, preoperative treatment with IVI in patients undergoing abdominal surgery has resulted in cost savings of €786 per case by reducing the blood transfusion rate and costs paid by hospitals for extended hospitalisation when compared with standard medical therapy. From these studies, factors that highly influenced the resulting cost savings were the cost of the outpatient clinic, transfusion rate in all treatment arms, as well as the length of hospitalisation.

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