Double bull's eye for post-operative intravenous iron in patient blood management: better outcome and cost-effective

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The prevalence of pre-operative anaemia in surgical patients varies greatly[1] but in surgical procedures with moderate to high peri-operative blood loss such as elective hip or knee arthroplasty and hip fracture surgery it is quite high, ranging from 24±9% to 44±9%, respectively[2]. In addition, pre-operative anaemia, even if only mild, is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major (non-cardiac) surgery[3]. Therefore, the detection and treatment of anaemia in the framework of a universal patient blood management strategy should become standard care for patients undergoing elective surgical procedures, especially if substantial blood loss is expected. Studies on the epidemiology of anaemia in patients undergoing hip or knee surgery showed that the anaemia is hypochromic and microcytic in 23% to 70% of the subjects[2].

Post-operative anaemia is even more prevalent in patients undergoing the aforementioned elective and non-elective major orthopaedic procedures (51% and 87±10%, respectively)[2]. In fact, it can occur in up to 90% of surgical patients[1] and is mainly due to peri-operative bleeding but may be worsened by blunted erythropoiesis caused by surgery-induced inflammatory responses, especially through decreased iron availability (i.e. hepcidin-dependent down-regulation of intestinal absorption of iron and impaired mobilization of the metal from body stores)[4-7].

It is well known that hepcidin, through modulation of the expression of ferroportin, acts as the main systemic iron-regulatory hormone of iron metabolism and its synthesis is controlled by multiple signalling pathways (e.g. inflammation, hypoxia, erythropoietin)[8]. In general, infections or stimuli causing a systemic inflammatory response can induce hepatic expression of hepcidin, thus reducing serum iron and increasing iron accumulation in reticuloendothelial cells. In patients with increased hepcidin levels oral iron therapy is useless, if not deleterious, because the negative feedback loop on ferroportin inhibits gastrointestinal absorption of oral iron, iron export from stores in hepatocytes or macrophages, and iron transport to the bone marrow thus limiting its availability for erythropoiesis[9-12].

Although the pathophysiology of acute inflammation-related anaemia, such as in trauma or surgery, is somewhat different[4,8,13], the aforementioned principles also apply in the peri-operative period in which the two major mechanisms inducing anaemia are peri-operative or traumatic bleeding as well as blunted erythropoiesis caused by decreased iron availability with concomitant normal or near-normal erythropoietin levels.

Iron-deficiency syndromes include: (i) absolute iron deficiency, the most common nutritional deficiency characterised by absence of stored iron; (ii) functional iron deficiency, defined as "when increased erythron iron requirements exceed the available supply of iron"[14] such as occurs during high stimulation of erythropoiesis; and (iii) iron sequestration, which is mediated by hepcidin that causes the aforementioned unavailability of stored iron[10,15].

Thus, although oral iron supplementation is adequate in most clinical conditions of absolute iron deficiency provided it can be tolerated and the time frame to scheduled surgery is not a limit[16], in the peri-operative period the use of intravenous iron is required as an adequate and quick supply able to bypass hepcidin-mediated inhibition of oral iron absorption or to maintain iron saturation and avoid functional iron deficiency in patients treated with erythropoietin[10,15].

At present, a rapidly increasingly number of studies support the key role of peri-operative intravenous iron, with or without recombinant erythropoietin, in correcting anaemia and reducing the allogeneic transfusion rate in surgical patients and show that its efficacy is associated with a high level of safety[10,13,16-22]. Recently published consensus guidelines include intravenous iron in the pharmacological alternatives to be adopted in the peri-operative period in order to stimulate erythropoiesis and to reduce transfusion rates[23]. In addition, more data on the safety of intravenous iron preparations are available from post-marketing studies carried out in the United States of America (USA) and in Europe[24-26], which show that iron sucrose and sodium ferric gluconate are associated with much lower rates of adverse events per million units sold than iron dextran or ferumoxytol, which are associated with the highest rates of all reported adverse event classifications. In fact, according to the USA Food and Drug Administration database[25], on average, four major or serious adverse events are reported for every 1 million units (1 unit is

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equivalent to 100 mg of iron, otherwise called 100 mg dose equivalent) of iron sucrose sold in this country, 10 per million units for sodium ferric gluconate, 27 per million units for iron dextran, and 184 per million units for ferumoxytol.

However, to the authors' knowledge, so far only an economic evaluation of benefits, harms and costs of parenteral versus oral iron administration in anaemic dialysis patients has been carried out[27], while no study has been designed to make a formal cost comparison of the various intravenous iron therapies used in surgical patients in the framework of patient blood management programmes.

In this issue of Blood Transfusion, Manuel Muñoz and colleagues published a retrospective, matched cohort cost-analysis study on post-operative intravenous iron therapy in elective total lower limb arthroplasty[28]. This study was carried out in Spain and the authors retrospectively reviewed data from around 800 patients who underwent total knee or total hip arthroplasty between 2004 and 2011. The objective of the authors was to analyse and compare patient blood management costs in two cohorts of patients who underwent major orthopaedic surgery. The same defined allogeneic blood transfusion protocol was applied for all the patients included. The study cohort (537 subjects) was also treated with post-operative intravenous iron while the control group (257 patients) did not receive intravenous iron therapy. Two intravenous iron preparations were used: iron sucrose (200 mg in 100-200 mL saline over 30-60 minutes for 3 consecutive post-operative days) and ferric carboxymaltose (600 mg in 100-200 mL saline over 15-30 minutes on the first post-operative morning). All the analyses were performed in two matched cohorts of patients (182 in each group). Muñoz and co-workers evaluated in which patients this pharmacological alternative to blood transfusion was most effective with regards to cost-saving and also related this parameter to the iron compound used, to the pre-operative haemoglobin concentration, and the different allogeneic transfusion rates in patients managed with each iron preparation.

Fixed and variable costs related to patient blood management included the costs of allogeneic red blood cell acquisition, the transfusion service, haemoglobin assessment, post-operative intravenous iron administration, and hospitalisation. Similarly to another cost analysis of a different technique of patient blood management carried out by the same author[29], the cost model was developed with the time-driven activity-based costing methodology as this is able to capture a wide spectrum of the indirect costs as well as the unused capacity cost[30].

The results of this economic evaluation showed that iron-treated patients had a significantly lower allogeneic transfusion rate in comparison to control subjects (11.5% versus 26.4%; p=0.001) without any relevant adverse event or increase in post-operative infection rate. Interestingly, the reduction in transfusion rates was more noticeable in anaemic patients and individuals receiving allogeneic transfusion had a longer hospitalisation (+1.9 days; 95% confidence interval: 1.2-2.6). Finally, both iron sucrose and ferric carboxymaltose were cost-neutral in the different cost scenarios evaluated by the authors. Thus, post-operative intravenous iron, in addition to being safe and reducing transfusion rates as well as days of hospitalisation, also proved to be cost-effective.

In conclusion, as correctly pointed out by the authors, their study "was a retrospective, matched cohort study, and as such it does not provide unbiased results"[28]. Therefore, although we believe that subjects included in observational studies more closely resemble those patients we come across in daily clinical practice, utility and cost-benefit of post-operative intravenous iron in elective total lower limb arthroplasty should be confirmed by controlled clinical trials in order to further strengthen the very consistent results from the observational study by Manuel Muñoz and co-workers.

Cost-effectiveness analyses of patient blood management techniques such as the aforementioned[28] are very important and topical as they allow the proper allocation of resources. In fact, many countries of the industrialised world are currently united by the common quest for affordable and sustainable healthcare and the struggle against steadily growing healthcare costs that exceed the constantly pursued increase of the gross domestic product[31]. We, therefore, deem that this study is valuable for all stakeholders actively involved in setting up patient blood management programmes from which patients and health care payer organisations as well as public healthcare providers will undoubtedly benefit.

The Authors declare no conflicts of interest.

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