

# A Prospective Randomized Controlled Trial to Assess the Effect of Intravenous versus Oral Iron Therapy in the Treatment of Orthopaedic Preoperative Anaemia

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## Abstract

**Background:** Improving preoperative anaemia is associated with a better surgical outcome. There is lack of data regarding treatment of preoperative anaemia with intravenous versus oral iron.

**Objective:** Assessment of efficacy of oral iron sulphate versus a single intravenous iron polymaltose and subsequent effect on perceived quality of life in both treatment groups.

**Patients and methods:** We conducted a prospective randomised controlled trial with iron therapy for the treatment of Iron Deficiency Anaemia (IDA) patients who were undergoing elective joint arthroplasty. At a single institution, we recruited 44 patients who were randomized to a single intravenous iron polymaltose infusion (16/22) versus oral daily iron sulphate (17/22). Median age was 68 years (range, 45-91) with a male to female ratio of 14:19.

**Results:** After iron therapy, the immediate mean preoperative Hb was increased to 128 g/L (SD  $\pm$  11.05) in the IV iron group versus 118 g/L (SD  $\pm$  9.23) in the oral iron group ( $p=0.01$ ) compared to 116 g/L (SD  $\pm$  8.46) in the control group ( $p=0.001$ ). The average length of stay in the hospital for the IV iron group was 6 days (SD  $\pm$  2.51) compared to 8 days (SD  $\pm$  3.62) in the oral iron group and 8 days (SD  $\pm$  4.18) in the control group ( $p=0.04$ ). Average transfused blood units were 1.5 units in the IV iron group versus 2 units in the oral iron group ( $p=0.09$ ) and 2.4 units in the control group ( $p = 0.04$ ). There was a significant improvement of the symptoms of anaemia ( $p=0.03$ ) after treatment in the IV versus oral iron group with further improvement at 3 months follow-up ( $p=0.003$ ).

**Conclusion:** Our data suggest that IV iron therapy is superior to oral iron in improving preoperative Hb and hence overall outcome for patients with preoperative IDA. Further trials that aim to improve and optimize preoperative and postoperative Hb are warranted.

**Keywords:** Preoperative anaemia; Oral iron; Intravenous iron; Orthopaedic surgery; Blood transfusion; Outcome; Quality of life

## Introduction

Both pre and postoperative anaemia are highly prevalent in surgical patients [1,2]. Depending on the type of surgery, underlying disease and the definitions of anaemia, about 11% to 76% of surgical patients may present with pre-operative anaemia [3,4]. Recently, there has been increasing evidence to suggest that pre-operative anaemia can lead to an increased risk of peri-operative adverse outcomes such as increased post operative infections, increase the requirement for blood transfusion, increase of hospital Length of Stay (LoS) and increased overall morbidity and mortality [5-7]. In addition, evidence has shown that pre-operative anaemia increases the chance of receiving unnecessary allogeneic blood transfusion with its consequences when compared to patients with a normal haemoglobin level [5-7]. This is considered as an independent risk factor that increases peri-operative adverse outcomes [5,7]. Many studies demonstrated that there was an increased risk of postoperative mortality and morbidity including pulmonary and infectious complications after receiving intraoperative blood transfusions [8-10]. Thus, there has been an increased emphasis on the correction of preoperative anaemia to improve the patient's outcome and decrease the need for allogeneic blood transfusion.

This trial was designed to compare the efficacy of two interventions designed to treat pre-operative anaemia: standard oral iron (iron

sulphate) and a single intravenous iron therapy (iron polymaltose). Primary endpoint was the immediate pre-operative haemoglobin and secondary endpoints were post-operative complications in terms of blood transfusion requirement, incidence of infection, and length of hospital stay. Furthermore Quality of Life (QoL) measurements were collected, which determined energy level, activity, symptoms of anaemia and the wellbeing of patients via a modified SF36 health questionnaire at initial enrolment, immediate preoperative period (after treatment), 3 and 6 months post-operatively.

## Patients and Methods

### Design overview

A prospective randomised controlled trial was conducted between

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February 2008 and September 2010 at the Launceston General Hospital (LGH), a tertiary referral centre for Northern Tasmania, Australia. An informed consent form was obtained from all patients according to the Code of Ethics. The trial was approved by the Tasmania Human Research Ethics Committee and was registered in the Australian New Zealand Clinical Trials Registry at <http://www.ANZCTR.org.au> under ACTRN12609000596202. The web page of the trial is as following: <http://www.ANZCTR.org.au/ACTRN12609000596202.aspx> and in the World Health Organization (WHO) website: <http://www.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000596202>.

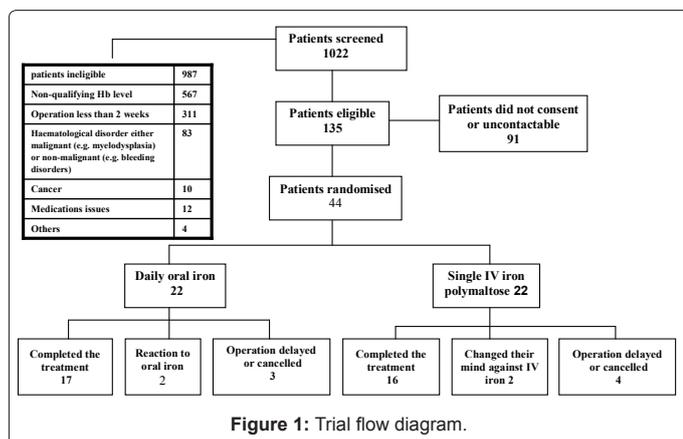
The primary objective of this study was to determine the effectiveness of a single intravenous (IV) iron polymaltose infusion compared to daily oral iron in the treatment of pre-operative anaemia. The primary endpoint was the immediate pre-operative haemoglobin. Secondary objectives were to assess tolerability, safety of iron therapy as well as quality of life of these patients. Furthermore an assessment of post-operative complications such as post operative infection rate, length of hospital stay and number of transfused packed Red Blood Cell (RBCs) units was conducted.

Quality of life and patient's wellbeing were assessed during pre-operative and post-operative periods via a modified version SF36 questionnaire. The modifications incorporated assessment of the physical status, energy levels, symptoms of anaemia and well-being component scale values at each of the time points.

### Participants

We prospectively screened patients who were scheduled to undergo elective joint arthroplasty at the LGH between February 2008 and September 2010 and those with a haemoglobin level of less than 120 g/L for females and <140 g/L for males and above 90 g/L were eligible for the trial. Patients underwent additional investigations with iron, vitamin B12 and folate studies. If patients had any causes of anaemia apart from iron deficiency, they were excluded from the trial (Figure 1). Iron deficiency was defined by ferritin level <30 mcg/L (normal 30-464), while low iron stores were defined by ferritin levels below 100 mcg/L. The causes of iron deficiency were investigated separately. Patients with positive occult blood were transferred for Gastroenterologist (GIT) investigation with appropriate upper and lower GIT endoscopy. Patients with malignancy were excluded from the trial. The study was explained in detail, and a written informed consent was obtained from all subjects.

We recruited 44 patients who presented with low Hb and low iron



stores. The median age was 68 years. The median time between the treatment and surgery was 22 days (range, 14-38).

Exclusion criteria included patients with specific causes for anaemia or haemoglobin below 86 g/L as well as patients with a documented iron overload status. None of the patients recruited in this study had a concomitant diagnosis of cancer. Due to ethical concerns, patients with severe Iron Deficiency Anaemia (IDA) with Hb level <86 g/L were offered IV iron without randomization and were excluded from the trial. A pilot study with the addition of vitamin B12 1000 mcg intramuscular single injection 3-4 weeks prior to surgery was considered within the original trial arms. Patients were randomly assigned to vitamin B12 versus no treatment in each active treatment group. However, due to lack of differences in the both treatments groups, the pilot study was aborted.

### Measurement of Hb and iron studies

The blood samples were taken from the participants in the morning. Only fresh blood samples were analysed at the Australian National Association Testing Authority accredited laboratory at the LGH at the time of presentation to clinics. The blood samples of all participants were processed within 2 hours of collection as per turnaround time for the laboratory. All variables were determined consecutively. The serum iron and transferrin were measured on an Abbott Architect c8000 autoanalyzer (Abbott, NYSE, USA). The serum ferritin was measured on an Ortho Diagnostics ECI Immunoassay analyser (Ortho Clinical Diagnostics, NJ, USA) using Ortho Diagnostics Ferritin reagent (two-step immunometric). The Hb was measured by Australia National Testing Authority accredited LGH standard reference laboratory using a Beckman Coulter LH-500 (Beckman Coulter, CA, USA). Hb and iron studies were performed at baseline, and Hb was measured immediately preoperatively (4 weeks after commencement of treatment) as well as at 48 hours and 6 weeks post operatively.

### Randomization and interventions

Informed consent was obtained from all patients and treatment was randomised in blocks of 4 by the Pharmacy Department, LGH. The oral iron therapy comprised 325 mg of iron sulphate (elemental iron 105 mg) daily while the intravenous iron infusion comprised of a single dose iron polymaltose (Ferrosgic, Sigma Pharmaceuticals, Australia) within a few days after enrolment. In a specially-designed questionnaire addressing dietary iron intake, there were no significant differences between the two groups, in particular there were no strict vegans among the recruited patients. Patients assigned to IV iron polymaltose received a 100 mg test-dose dissolved in 100 ml normal saline infused over 30 minutes after a premedication with 4 mg IV dexamethasone and oral antihistamine. Clinical observation and vital signs were assessed initially and every 15 min from the start of the infusion. If the test-dose was well tolerated, the remainder of the iron polymaltose dose was infused in 500 ml normal saline over 90 minutes [11].

The total dose of IV iron polymaltose was calculated according to the patient's body weight at preadmission visit and entry Hb level according to the product guidelines; iron dose in mg (50 mg per 1 ml) = body weight (maximum 90 kg) in kg × (target Hb (120 g/L) - actual Hb in g/L) × constant factor (0.24) + iron depot (500). IV iron was well tolerated and there were no side effects recorded.

The type of anaesthesia performed in all cases of Total Knee Replacement (TKR) and in 80% of cases of Total Hip Replacement (THR) was epidural anaesthesia. This may have contributed to reduce

blood loss as it has been reported that the neuraxial blocks have less blood loss in orthopaedic surgery [12]. No fibrinolytic agents were used in our cohort of patients as per our standard practice. None of the patients studied was vegetarian. They had been advised to consume food as they normally did prior to the surgery.

### Control group

A dedicated age and sex matched control group with patients who underwent elective joint arthroplasty; TKR (7) and THR (11) and presented with the same trial inclusion criteria was included. These patients were ineligible or declined active participation in the trial, however, they agreed and were consented to allow the researcher to follow up and collect their data without any active intervention. The patients' data served as a control and was compared to the active intervention arms' data. For those, only preoperative preadmission Hb as well as post operative Hb were measured routinely and were available for the study purposes.

### Statistical analysis

A multivariate analysis of the data in correlation with pre- and postoperative Hb, length of hospital stay and outcome was performed using STATA Soft software. Numerical data was summarised with means and Standard Deviations (SD). Data between the three groups was compared using repeated measures mixed methods ANOVA. Assumption of linear regression was checked and if necessary, data was reanalysed using ordinal logistic regression. P value <0.05 was considered as statistically significant. Results associated with laboratory parameters were expressed as odds ratios, with 95% confidence intervals.

### Results

Among 44 recruited patients with preoperative anaemia, there was 33 patients completed the trial. The male to female ratio was 14:19 with a median age of 68 years (range, 45-91). There were 17 out of 22 patients completed the oral iron treatment versus 16 out of 22 patients in the IV iron group. All patients were recruited approximately 3-4 weeks prior to the elective surgery for total knee replacement (16) and total hip replacement (17). Median initial Hb at trial entry for all patients was 110 g/L (range, 90-130) that improved after treatment to 122 g/L (96-149) (p=0.01). In the control group, preoperative Hb was 116 g/L (range, 92-135 g/L). The average length of stay in the hospital for the IV iron group was 6 days (SD ± 2.51) versus 8 days (SD ± 3.62) in the oral iron group (p=0.06) compared to 8 days (SD ± 4.18) in the control group (p=0.04). An average transfused blood unit was 1.5 units (SD ± 0.58) in the IV iron group (median 2) versus 2.2 units (SD ± 0.83) in the oral iron group (median 2) (p=0.09) and 2.4 units (SD ± 0.73) in the control group (median 3) (p=0.04). The trigger for blood transfusion was a Hb level <80 g/L in the immediate post operative period. The percentage of patients receiving blood transfusion in the IV iron group was 25% versus 29% in the oral iron group versus 33% in the control group.

Immediate preoperative Hb (after treatment) was increased to 128 g/L (111-149) in the IV iron group compared to 118 g/L (96-137) in the oral iron group. Post operative Hb (48 hours) averaged 92 g/L (SD ± 11.05) in the IV iron group versus 87.75 g/L (SD ± 11.73) in the oral iron group versus 87.91 g/L (SD ± 12.72) in the control group (Table 1). The 48 hours post operative Hb results were not significant among all three groups. At six weeks post operative Hb level showed a maintained

improvement in the IV iron group to 120 g/L (SD ± 13.80) versus 108 g/L (± 11.15) in the oral iron group (p=0.01) (Table 1).

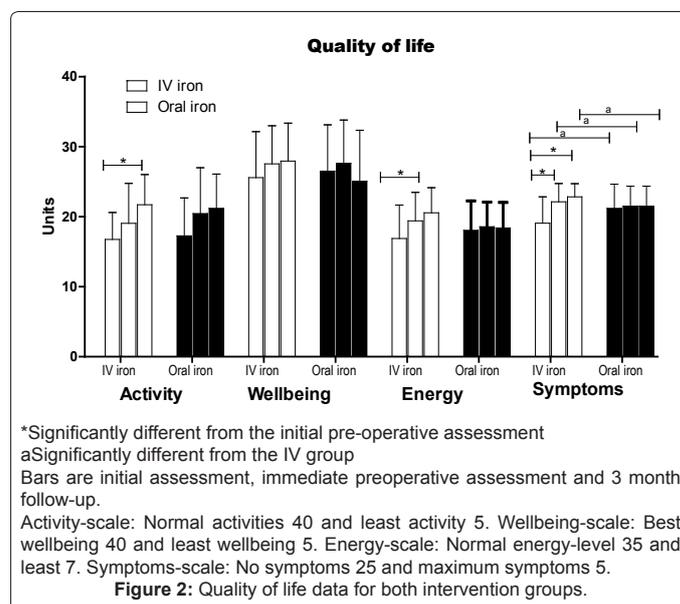
### Quality of life assessment

A truncated modified SF 36 quality of life questionnaire comprising of 24 questions addressing four domains of QoL relevant to the study; anaemia symptoms scale, energy level scale, activities level scale and wellbeing scale was conducted for the patients included in the study. The module was developed according to the guidelines of SF36 [13,14].

The questionnaire was presented to all patients at initial interview, at the time of enrolment and thereafter prior to surgery and conducted 3 and 6 months after surgery via phone interview by a research assistant who underwent special training with the SF36 modified module.

Levels of activity, energy as well as symptoms of anaemia and the participants well being were analysed and scored according to each question in a scale between 5 to 40 in the activity and well being, where a score of 40 indicates maximum activity and well being and a score of 5 was the least. Energy scale was between 5 and 35, where score of 35 reflects maximum energy and score of 5 the least. The symptoms scale was between 5 and 25, where a score of 5 corresponded to maximum presence of symptoms of anaemia while a score of 25 means the least symptoms of anaemia (Figure 2).

There was a significant improvement of symptoms of anaemia in the IV iron group versus oral iron group after commencement of the treatment as measured in the immediate preoperative period (p=0.03) that further improved at 3 months and was maintained at 6 months follow up (p=0.003). There was no significant difference in terms of wellbeing, activity and energy levels at all time points between the two groups, albeit with a tendency for improvement in the IV iron versus oral iron that did not reach a significant statistical difference. Intergroup analysis revealed that there was a significant improvement in the activity and energy levels as compared between the initial assessments and the three months follow-up period in each group separately. These differences were greater in the IV group compared to the oral iron group without reaching a significant difference. However this analysis could be biased as the patients probably were mobilising better after the joint arthroplasty and hence it reflected on their positive assessment



three months after the operation with a corresponding increase of their activities. The patients' wellbeing did not change significantly between the two groups and also in the intergroup analyses at all time points. Assessment of infection complications during and after the operative procedure showed no statistical significance between patients in both treatment groups.

### Cost-effectiveness analysis

An approximate figure for the cost of one unit of packed RBC according to unpublished data from the Red Cross, Australia is estimated around \$700 AUD including processing, delivery and administration. However, the predicted cost of transfusing a blood unit in the hospital per-RBC-unit is calculated between \$522 and \$1183 USD (mean, 761 ± 294) in recent studies [15,16]. In addition the cost of nursing staff and materials used to administer this unit is approximately \$300 AUD at our hospital subject to a significant increase depending on occurrence of complications [16]. The cost of one iron sulphate tablet is approximately USD \$0.2-0.3, so the average cost for 4 weeks is calculated to be \$9. The cost of an iron polymaltose ampoule containing 500 mg is \$50, so the average treatment cost for 100 mg is \$100. In Australia the cost of the outpatient hospital visit and nursing time for the IV iron, adds approximately \$100 to the drug cost subject to variations according to different health systems (1 AUD is equivalent to 1 USD at the time of analysis). In our study we saved approximately between 2-5 units of blood weekly, as projected in our cohort of patients by employing IV iron therapy compared to control group. This will result in an approximate yearly cost-saving between USD \$100,000 and \$200,000 to the health system. It is worth noting that the amount of cost-saving per year is proportional to the amount of reduction of transfusion of blood units. Furthermore, the cost of average Length of Hospital Stay (LOS) is approximately \$800 AUD per day which is subject to increases according to different treatments. Thus, if the LOS per patient is shortened by an average 2 days as a result of our study in the IV iron group, it translates to a saving value of \$200,000 for 100 patients per year in addition to a similar amount of saved costs for blood units. Hence, we anticipate a total yearly saving of \$400,000 AUD in a 300-bed hospital, considering the total number of operations per year with an estimated true anaemia rate based on our cohort of patients in addition to the number of blood units that have been required during and after the operation versus the cost per unit and day of hospital stay

compared to the control group. However, we should emphasise that this study is not designed specifically to address the cost issues of LOS or transfused RBCs. Further specific studies to address this important cost issue are warranted.

### Discussion

Reports have demonstrated that about 35% of patients undergoing joint arthroscopy or non cardiac surgery have anaemia while about 76% of patients with Dukes stage D colon cancer have low haemoglobin levels before surgery [17-19]. Furthermore, previously undiagnosed anaemia is common in elective orthopaedic surgical patients and is associated with increased likelihood of blood transfusion and increased perioperative morbidity and mortality [20]. Therefore, a multidisciplinary panel of experts was summoned through the Network for Advancement of Transfusion Alternatives (NATA) with the aim of developing practice guidelines for management of preoperative anaemia in elective orthopaedic surgery [20]. This indicates that there is an increasing interest among health providers for optimizing the management of pre-operative anaemia with the aim of improving outcome and reducing blood transfusion, especially with the current shortage of blood supply. Moreover, many cases of preoperative anaemia are associated with depleted iron stores [19-23].

A recent systematic review showed that the mean prevalence of anaemia in patients undergoing elective knee or hip arthroplasty was 24% compared to 45% in those undergoing surgery because of a hip fracture in elderly populations [1]. It has been observed that the prevalence of anaemia increases among elderly populations, so the proportion of older patients who undergo major orthopaedic surgery is rising progressively, with a high prevalence of anaemia (43%) observed in a retrospective cohort of 57,636 veterans aged 65 years or older who underwent major elective and non-elective orthopaedic surgery [24,25].

As an explanation for the prevalence of IDA among this cohort of patients, elderly patients usually suffer from osteoarthritis and therefore require NSAIDs that may cause occult GIT- blood loss. Also, lack of iron absorption may happen secondary to atrophic gastritis or antacid therapy commonly administered in this cohort of patients. In our study 60% of patients received NSAIDs mainly because of osteoarthritic

Variable	IV	Oral	Control
Length of Stay (days) <sup>1</sup>	6.24 ± 2.51	8.0 ± 3.62 (p value against IV 0.06)	7.72 ± 4.18 (p value against IV 0.04) (p value against oral 0.83)
Immediate pre-operative Hb (post-treatment)	128.47 ± 11.05	118.44 ± 9.23* (p value against IV =0.01)	116 ± 8.46* (p value against IV =0.001 (p value against oral 0.51)
48 Hour Hb	92.65 ± 12.57 <sup>a</sup> P value against pre op <0.001	87.75 ± 11.73 <sup>a</sup> Not different from IV p=0.35 P value against pre op is <0.001	87.91 ± 12.72 <sup>a</sup> Not different from IV p=0.26 Not different from oral p=0.62 P value against pre op =<0.001
6 week postoperative Hb	120.88 ± 13.80 <sup>ab</sup> P value against pre op <0.001 P value against 48 hr Hb <0.001	108.94 ± 11.15 <sup>ab</sup> Not different from IV p=0.7 P value against preop is 0.01 P vale against 48 hr Hb is <0.001	Not available
No. of Packed RBCs units given in the peri-operative period	1.5 ± 0.58	2.22 ± 0.83 P against IV = 0.09	2.44 ± 0.73* P against IV =0.04 P against oral 0.50

Results presented as mean and standard deviation

<sup>1</sup>Data analysed with ordinal logistic regression. \*Significantly different from IV group

<sup>a</sup>Significantly different from Preoperative Hb in the same intervention group; <sup>b</sup>Significantly different from 48 hours Hb in the same intervention.

**Table 1:** Comparison between both intervention groups and control group in terms of Hb levels at different trial points entry, length of hospital stay and number of transfused packed RBCs units.

Name of the IV iron preparation	Status of registration	Indications	Test dose	Duration of infusion	Maximum dose in single infusion
Ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Inc., USA)	FDA-approved	Treatment of iron-deficiency anaemia in adult patients with CKD*	None	1 minute	Maximum dose 510 mg
Ferric carboxymaltose (Ferinject®, Vifor Pharma, Glattbrugg, Switzerland)	Approved in Europe, FDA-approval is sought	Treatment of iron-deficiency anaemia	None	15 minutes	Maximum dose 1000 mg. IV rate is 20 mg/kg
Ferrosig® (Sigma Pharmaceuticals, USA)	Approved in Europe, and by FDA	Treatment of iron-deficiency anaemia	Yes	120 minutes	No maximum dose
Iron isomaltoside (MonoFer®, Pharmacosmos A/S, Holbaek, Denmark)	Approved in Europe FDA-approval is sought	Treatment of iron-deficiency anaemia in adult patients with CKD*	None	60 minutes	No maximum dose IV rate is 20 mg/kg body weight

FDA: Food and Drug Administration; CKD: Chronic Kidney Disease

\*Extended approval is sought.

**Table 2:** Current intravenous iron preparations including new agents

pain and 35% were complaining of gastro-oesophageal reflux disease that required ongoing treatment with proton pump inhibitors and/or antacids.

The use of recombinant human erythropoietin or autologous blood transfusion pre-operatively have been suggested as ways to manage pre-operative anaemia [26,27]. A review of the evidence based outcomes of the different supplementations in hip and knee surgery suggested that iron therapy, both oral and intravenous have been shown to reduce the need for allogeneic blood transfusion and significantly reduced the post-operative infection rate [28-31]. In our hand, IV iron was superior to oral iron and both have improved the preoperative Hb, nevertheless, with a greater and significant effect in the IV iron group. This also resulted in a reduction of the number of transfused PRBCs compared to the control (p=0.04). However, there were no significant changes on the infection rate among the three groups.

Furthermore, there was a potential for reduction of length of stay in the IV iron group compared to oral iron and control group (p=0.06 and p=0.04 respectively). A systemic review comparing the evidence of administering erythropoietin with iron supplements to an active control group of either iron supplementation or cell salvage [26,30], showed that the clinical outcomes of post-operative infections, length of stay and 30 day mortality were generally not significant when compared to the active control group in these studies.

Altogether, our study is showing that IV iron polymaltose is well tolerated and has the potential to correct preoperative anaemia in a shorter period of time. This reflected in shortening the period of stay in the hospital with fewer amounts of transfused PRBCs units as well as improvement in symptoms of anaemia. The benefits extended to the post operative follow up period. There was also a considerable amount of cost saving in patients whom received IV iron. Further randomised trials are warranted to address the important issue with preoperative anaemia that significantly affects the already overstretched health budget and compromises the outcome of elective surgery especially in view of short blood supplies. A suggested treatment algorithm or management pathway of preoperative anaemia was discussed in some studies [31,32]. Furthermore, our study has a few shortcomings; first due to the relatively small number of patients studied owing to the technical difficulties to recruit the patients, which is ideally 3-4 weeks prior to surgery, it is hard to draw firm conclusions. However, it is worthwhile to publish these data as a reference due to paucity of clinical trials in this field. Second; the relatively short preoperative duration of treatment with oral iron in some patients, is arguably not sufficient to replenish the iron stores. This perhaps proves the point for effectiveness

of IV iron in replenishing the iron stores in a shorter period of time compared to oral iron as seen in other cohort of patients [25,33]. The IV iron group was also able to maintain the Hb for a longer period of time compared to oral iron. It is worth noting that there is lack of data regarding prospective randomised trials using IV iron in preoperative setting. Therefore it is worthwhile documenting the results of this cohort of patients as a basis for further research.

Certainly parenteral iron is considered as an attractive option for the treatment of IDA and is likely to be even more popular due to the introduction of new intravenous iron preparations (Table 2), which allow relatively high doses of iron to be administered rapidly in a single treatment. Recent reports demonstrate the feasibility of rapid iron polymaltose infusion over 90 minutes [33,34]. However, a test-dose of iron polymaltose (100 mg) should be first administered over 30 minutes. Moreover, the new intravenous iron preparations represent a medical revolution in the effective, rapid and safe repletion of iron stores in the management of IDA and therefore should be considered in the new guidelines of management of IDA in different clinical scenarios [24,34]. This will create an effective and attractive solution in the management of IDA in different populations.

In summary, this study aligns and provides further supporting evidence for the ongoing debate regarding the peri-operative module of the Australian National Blood Authorities Patient Blood Management Guidelines [35]. In this sense, the NATA recommends screening of all elective orthopaedic surgical patients with full blood count 4 weeks prior to surgery with a target Hb, before elective surgery, to be within the normal range, according to the WHO criteria [20]. Further investigations are recommended to evaluate anaemia for nutritional deficiencies, and/or chronic renal insufficiency. NATA also recommends that nutritional deficiencies should be treated and substituted. Erythropoiesis-stimulating agents may be used for anaemic patients in whom nutritional deficiencies have been ruled out, corrected, or both [20].

Thus, a standard global guideline for management of preoperative anaemia should be implemented by the experts in the field and at the same time should be flexible to address patients and health professionals' requirements as well as considering the local health system accessibility for the best possible outcome.

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