PRE-OPERATIVE ANAEMIA MANAGEMENT WITH INTRAVENOUS IRON

A SYSTEMATIC REVIEW

Submitted by

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STATEMENT OF DECLARATION

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ABSTRACT

BACKGROUND

Iron deficiency anaemia (IDA) is a common condition in patients presenting for surgery and is found in up to 75% of non-cardiac surgical patients. Pre-operative haemoglobin (Hb) is a strong predictor of transfusion requirement and it should, as part of a comprehensive blood conservation approach, be optimised whenever possible. Treatment options for iron deficiency anaemia include oral and intravenous iron or red blood cell transfusion. That both, anaemia and red blood cell (RBC) transfusion expose the patient to unnecessary risks is supported by an ever-increasing body of evidence. Consequently, allogeneic RBC transfusion should be avoided whenever possible and alternative treatment modalities which optimize the patient's own red cell mass should be exhausted. However, anxiety over the short and long term effects of intravenous iron have limited its more widespread use. Newer dextran-free compounds, however, provide a safer treatment option.

OBJECTIVE

The objective of this systematic review was to critically appraise, synthesise and present the best available evidence related to the effectiveness and economic aspects of intravenous iron administration on the correction of iron deficiency anaemia in the peri-operative period.

DATA SOURCES

A comprehensive search was undertaken on major electronic databases from 2001 to 2012. The search was conducted in English, German, Italian and Dutch.

REVIEW METHODS

Randomized controlled trials, quasi-randomized controlled trials and quasi-experimental studies were included in the review. Critical appraisal and data extraction were undertaken using the Joanna Briggs Institute critical appraisal instrument and the standard data extraction form for evidence of effectiveness. Anaemia correction was as defined by study authors

RESULTS

The quantitative component of the review identified two randomized controlled trials for inclusion. One study of 76 patients with menorrhagia evaluated the effectiveness of pre-operative intravenous (IV) iron compared with oral iron in anaemic patients scheduled for surgery – the nature of which was not reported, aiming for a 1 g/L haemoglobin increase preoperatively. The intravenous iron group had greater increases in the Hb level than the oral iron group (3.0 vs. 0.8 g/dl, respectively; $p < 0.0001$). One other study evaluated the effectiveness of pre-operative intravenous (IV) iron compared with placebo in patients with bowel cancer scheduled for resectional surgery, looking at haemoglobin changes between recruitment and day of admission. A small subgroup of these patients was anaemic but no difference was demonstrated in haemoglobin changes between the groups. One additional RCT was found examining the effectiveness of IV iron in cardiac surgical patients, but full text examination and appraisal revealed that the majority of patients enrolled in these studies were not anaemic.

The search for the economic component of the review revealed no randomized controlled trials examining the cost effectiveness of preoperative correction of iron deficiency anaemia with intravenous iron

CONCLUSIONS

Our review found insufficient data to make firm conclusions about the efficacy of pre-operative intravenous iron administration for the correction of anaemia based on clinical trial settings. Neither could we establish firm conclusions on the potential cost savings due to intravenous iron supplementation.

IMPLICATIONS FOR PRACTICE

There is inadequate RCT evidence at present to guide clinical practice.

IMPLICATIONS FOR RESEARCH

Our study found insufficient data to make firm conclusions about the efficacy, safety and cost effectiveness of pre-operative intravenous iron administration for the correction of anaemia pre-operatively. Adequately powered RCTs are required that evaluate and report the efficacy, safety and potential cost savings of intravenous iron administration as a treatment modality for iron deficiency anaemia.

KEYWORDS

Pre-operative anaemia, iron deficiency, intravenous iron, oral iron, blood transfusion, adverse effects, cost-benefit, cost effectiveness, cost-utility.

CHAPTER 1: INTRODUCTION

Most countries from around the world are facing significant demographic changes over the next two decades (1). These changes come as the result of a dramatic increase in the older population and a decrease of the young due to an ongoing decline in birth rates in the western world. More complex surgery in the elderly in addition to many serious medical conditions requiring transfusion is likely to lead to an increase in demand for blood products. The shrinking pool of donors compounds the problem and demand threatens to outstrip a safe supply of a high quality product. This looming shortfall has to be addressed urgently to guarantee the sustainability of the blood supply. Known and unknown infection risks from blood transfusions, an inventory at risk and ever-increasing cost should be the driver for change (2). This has also been recognized and endorsed by the World Health Organization (World Health Alliance Resolution A63.R12) supporting the need for Patient Blood Management (PBM) (3). Some countries have taken action to advocate a more efficient and appropriate blood utilization (4), but uptake of clinical practice change remains slow (5).

The transfusion of red blood cells (RBC) for the correction of anaemia is a widely accepted treatment modality and a very common occurrence in the peri-operative period. In the USA 16 million units of blood are collected each year. Only 20 % of all transfusions are given in haemorrhagic shock to the hemodynamically unstable patient and may be potentially lifesaving (6). However most RBC are prescribed to stable patients according to empirical guidelines. Unfortunately the decision to transfuse is also often left to the most junior medical staff.

According to available evidence an enormous variability in transfusion practice exists (7) and many of these transfusion events can be considered inappropriate. The potential for reduction of RBC transfusions is substantial. By donating blood to “save lives”, donors place a valuable resource into the clinicians’ hands with the assumption that it will be dealt with responsibly. This responsibility should be taken into account each time we prescribe blood products. No other treatment modality comes under so little scrutiny.

Guidelines appear to be frequently ignored or underutilised and many clinicians revert to transfusion practices based on individual beliefs (8). This frequently includes a minimum transfusion of two units, where one might have been sufficient to provide the desired effect. Despite an increasing body of evidence that peri-operative allogeneic transfusion contributes to worse outcomes, such as, increased lengths of stay (LOS), increased infection rates, increased occurrence of transfusion related lung injury (TRALI), transfusion related circulatory overload (TACO) and the number of deaths, this form of anaemia management continues (9, 10). Many of these transfusion events could be avoided if more attention was spent on optimising pre-operative haemoglobin values and the patients iron status.

Iron deficiency anaemia (IDA) is a common condition. It is the most common nutritional deficiency worldwide, affecting more than 2 billion people. All age groups are affected with women being more prevalent. Mental and physical performance is compromised and productivity loss is significant (11). Age, socio-economic circumstances, poor nutrition, certain medication, and physiological processes, for example pregnancy, with a substantial increase in iron demand, can result in anaemia. Many pathological states also commonly lead to severe

iron depletion. These include inflammatory bowel disease, colo-rectal cancer (both often associated with chronic intestinal blood loss) and menorrhagia. In patients presenting for surgery iron deficiency (with or without anaemia), is found in up to 39% of non-cardiac surgical patient (12). In certain subgroups of patient, for example bowel surgery patients the occurrence of preoperative anaemia has been found to be as high as 75 %. For all anaemic patients this leads frequently to an increased number of cardiac complications, increased number of days in hospital, more allogeneic transfusion events and more deaths. A more recent publication in 227,425 patients undergoing major non-cardiac surgery, of whom 69,229 (30.44%) had preoperative anaemia, confirmed that even mild forms of anaemia increase 30 days mortality (13). These findings imply that preoperative anaemia screening and correction should become an integral part of the preoperative assessment and management process. This management process however requires time and personnel in addition to medication, consumables and chair time, in the case of intravenous drug administration. The need for the identification and management of the condition has to be understood by all clinicians and a multidisciplinary approach is imperative.

The costs of blood products are a significant burden for health systems globally. The “real” cost is often difficult to establish and varies substantially. Societal changes will increase the pressure on a supply chain, already facing shortfalls from time to time. In many countries transfusion related costs are not apparent, neither to the consumer, the prescriber or even the health care provider, like in Australia. The provision of a free but potentially harmful product does not provide a platform for initiatives to facilitate change and clearly illustrates the need for reform.

This need is recognized however, and experts from around the world have designed comprehensive patient blood management (PBM) programs. The programs, consisting of a three pillar strategy, include the entire perioperative period and illustrate effective approaches to optimise patient care. Patients presenting for major surgery, particularly from certain risk groups, will benefit the most and should be assessed ideally at least 4 weeks prior to their surgery (14). This would allow clinicians to interpret blood results and provide a window of opportunity to act. In addition, unless urgent, surgery should also be considered to be delayed, to investigate the cause of the anaemia (15). If it is not possible to undertake this prior to surgery, the investigations have to be performed at a later stage. This requires meticulous documentation and communication.

With the common occurrence of iron deficiency anaemia, it appears to be one of the key aspects and the starting point of PBM. Various treatment modalities exist. Oral iron replacement can be effective but is in many instances poorly tolerated, ineffective or detrimental to the underlying disease process (16,17). There is increasing evidence that in select patient groups presenting for elective surgery, but also in urgent cases, a more contemporary approach with intravenous iron might benefit the patient and can result in improved outcomes and a reduction of RBC transfusion.

The economic benefits of pre-operative anaemia correction are difficult to assess. Multiple transfusion cost assessments exist but differ significantly between countries. However, it is certain that market forces in combination with constant additional testing for emerging new pathogens will lead to an increase in cost. This should be an important and additional driver for evidence based practice change. Transfusion of blood products has already been identified as one of the

most expensive treatment modalities, swallowing up to 5% of health care expenditure (18). Following economic principles scarcity will contribute to cost increases.

Cost of transfusion and transfusion related morbidity has to be balanced against the cost of a robust pre-operative anaemia management. The Canadian ONTraC program placed a network of nurse transfusion coordinators in 23 hospitals. These hospitals accounted for 65% of allogeneic red blood cell transfusions. Most hospitals reduced their red cell consumption significantly allowing for estimated potential annual cost savings of 14.6 Million dollars (19).

A preliminary search of the JIB library, Medline, the Cochrane Library of Medicine, Embase, and Health Business Elite found no existing systematic reviews of effectiveness evidence and economic evidence on intravenous iron administration on the correction of iron deficiency anaemia in the pre-operative period.

Therefore this systematic review critically appraised, synthesised and presented the best available evidence related to the effectiveness and economic cost-benefit ratio of intravenous iron administration on the correction of pre-operative iron deficiency anaemia.

CHAPTER 2: THE SYSTEMATIC REVIEW PROTOCOL

2.1 REVIEW OBJECTIVE

The quantitative objective was to identify the effectiveness of intravenous iron administration on the correction of iron deficiency and anaemia in the pre-operative setting.

More specifically, the objectives were to identify the effectiveness of iron infusion on the rate of red blood cell (RBC) transfusion and incidence of transfusion related comorbidities such as postoperative infection, immunological morbidity and mortality. In addition changes in functional capacity that could impact on quality of life.

The economic objective of this review was to identify the cost aspects of anaemia management.

More specifically, the objectives were to identify the evidence of cost benefits on pre-operative anaemia correction and the potential for cost savings on blood products and the indirect cost savings on transfusion related adverse effects.

2.2 REVIEW QUESTION

Does pre-operative anaemia management with intravenous iron increase haemoglobin effectively?

2.3 Criteria for considering studies for this review

2.3.1 TYPES OF STUDIES

The quantitative component of the review considered any experimental study design including randomised controlled trials, non-randomised controlled trials, quasi-experimental, before and after studies, for inclusion.

The economic component of the review considered cost effectiveness, cost-utility, and cost-benefit studies for inclusion.

2.3.2 TYPES OF PARTICIPANTS

The quantitative component and also the economic component of the review considered studies that include adult patients presenting for major surgery, regardless of gender, ethnicity, diagnosis and co-morbidities with pre-operative anaemia.

2.3.3 TYPES OF INTERVENTION(S)/PHENOMENA OF INTEREST

The quantitative component of the review considered studies that evaluated the management of anaemia with iron infusions compared to oral iron treatment alone, oral iron in combination with erythropoietin, erythropoietin alone or haemoglobin correction with blood transfusion. This included the dosage of iron, the frequency of its administration and the time frame of treatment prior to surgery. In addition it is of interest to assess how the intervention was employed, the personnel involved and the time spent to complete management.

The economic component of this review considered studies that evaluate the costs and benefits (cost- effectiveness, cost-utility, or cost-benefit) of iron infusions compared to oral iron treatment or haemoglobin correction with blood transfusion for the treatment of pre-operative anaemia.

2.3.4 TYPES OF OUTCOME MEASURES

The quantitative component of this review considered studies that included (but not limited to) the following outcome measures:

- The number of patients treated with intravenous iron that increase haemoglobin effectively as defined by the study authors
- The rate of red blood cell (RBC) transfusion measured as proportion of patients transfused with allogeneic RBC and the average number of units transfused.
- The length of stay in hospital (LOS)
- Rate of readmission within 30 days of discharge
- The incidence of transfusion related co- morbidities measured as infection rates, the occurrence of transfusion related lung injury (TRALI), transfusion related circulatory overload (TACO) and the number of deaths.
- The impact of intravenous iron administration on functional outcomes
- The economic component of the review will consider (but not limited to) the following outcome measures:
- The reduction in costs for units of allogeneic blood avoided
- The reduction in cost associated with a reduction in length of stay in hospital LOS
- The reduction in transfusion laboratory cost and nursing time
- The increase in cost for iron administered and nursing time

2.4 REVIEW METHODS

2.4.1 SEARCH STRATEGY

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilised in this review. An initial limited search of MEDLINE was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms was then undertaken across

all included databases. Thirdly, the reference list of all identified reports and articles were searched for additional studies. Studies published in English, German, Italian and Dutch were considered for inclusion in this review. Awareness of transfusion and anaemia related outcomes have been addressed mainly over the last 10 years. Therefore studies published from 2001 until December 2012 will be considered for inclusion in this review.

The databases searched included:

- PubMed
- EMBASE
- The Cochrane Library
- Health Business Elite database
- NHS Economic Evaluation Database (NHS EED)
- Health Economic Evaluation Database (HEED)
- The search for unpublished studies included: MedNar and Proquest Dissertation and Thesis.

2.4.2 ASSESSMENT OF METHODOLOGICAL QUALITY

Quantitative papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

Economic papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using

standardised critical appraisal instruments from the Joanna Briggs Institute Analysis of Cost, Technology and Utilisation Assessment and Review Instrument (JBI-ACTUARI) (Appendix I). Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

2.4.3 DATA EXTRACTION

Quantitative data was extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix II). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Economic data was extracted from papers included in the review using the standardised data extraction tool from JBI-ACTUARI (Appendix II). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

2.4.4 DATA SYNTHESIS

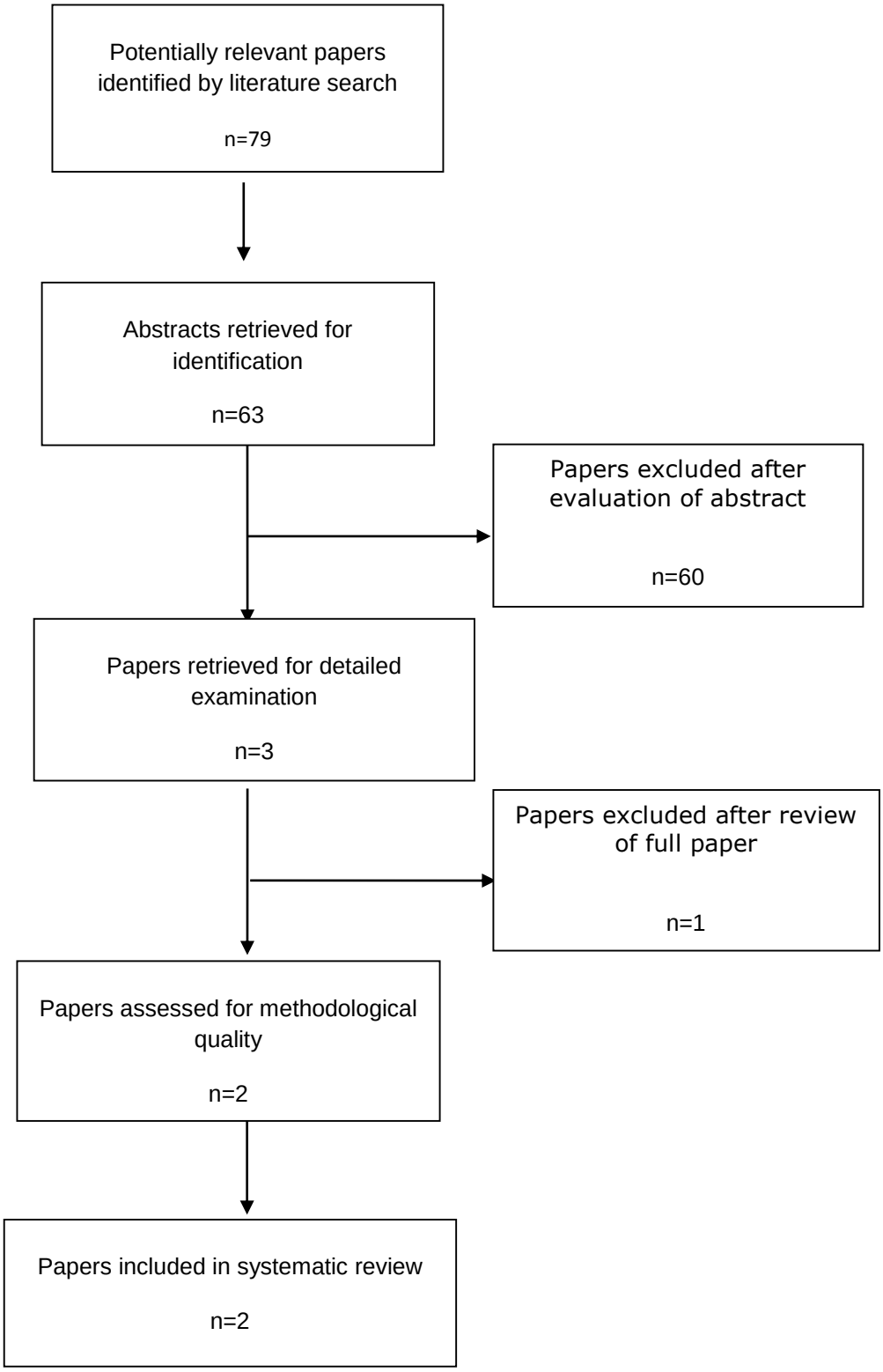
This review set out to conduct both meta-analyses of the findings of effectiveness studies using MAStARI and pooling of economic findings using ACTUARI. Because of the number of studies found, this was not possible and the findings are therefore presented in tabular or narrative form.

CHAPTER 3: RESULTS

3.1 DESCRIPTION OF STUDY IDENTIFICATION

79 potentially relevant papers were identified in databases searches. Title and abstract were examined for 63 papers. Three full text papers were retrieved for comprehensive examination. One paper was excluded after full text examination. Two studies were selected for critical appraisal. However, one of the two included studies allowed only the inclusion of a subgroup result. The reason for this was that the subgroup fulfilled all review inclusion criteria, but the majority of patients studied did not. A flow chart has been included to reflect the study selection process (Figure 1). A table was developed outlining the characteristics of the included studies and the interventions and outcomes described is included as Appendix 4.

Figure 1: Identification and selection of studies



3.2 DESCRIPTION OF INCLUDED STUDIES

The first included study by Kim et al (20) was an open-label, prospective, randomized, multicentre trial conducted at three hospitals (including a tertiary referral centre) in Seoul, Korea. Patient enrolled were women with menorrhagia, where the condition resulted in IDA and haemoglobin levels of <9 g/dl. Patients were randomized to receive either intravenous iron sucrose or oral iron protein succinylate, starting 3 weeks prior to scheduled surgery. Based on a 2-tailed α of 0.05, it was determined that 36 patients per group were required to detect a 1-g/dl Hb difference in the primary outcome variable with a power of 80%.

No severe adverse effects were observed in the study period. 76 patients were randomised and 30 completed the study in the IV iron arm and 26 in the oral arm. Thirty (76.7 %) patients reached the target Hb in the IV iron group compared with twenty (11.5 %) in the oral iron group RR, 95% CI ($p< 0.0001$). Hb and ferritin were also significantly higher in the IV group at the end of the study. The intravenous iron group had a greater increases in the Hb level than the oral iron group (3.0 vs. 0.8 g/dl, respectively; $p < 0.0001$) associated with an increase in the ferritin level (170.1 vs. 4.1 µg /l; $p < 0.0001$). This was a well conducted study in a patient cohort with significant iron deficiency anaemia. The other phenomena of interest for this review, the rate of red blood cell (RBC) transfusion, the average number of units transfused, the length of stay in hospital, the rate of readmission within 30 days of discharge, the incidence of transfusion related co- morbidities, the number of deaths and the impact of intravenous iron administration on functional outcomes were not reported in this study.

The second (partially) included study by Edwards et al (21) was a single centre study in patients with suspected bowel cancer scheduled to undergo a bowel resection. The study was powered at 80% to detect a 0.5 g/dl haemoglobin change between recruitment and the day of admission. In addition the haemoglobin value on the day of hospital discharge was recorded. All patients of a particular period, fulfilling the inclusion criteria, were enrolled and allocated to a treatment (IV iron) group or a placebo group. No significant difference was found for the primary outcome parameter between the groups and mean changes in haemoglobin vale between recruitment and at presentation for surgery were -019 g/dl for the IV iron group and -0.50 g/dl for the placebo group. IQR, 95%CI (p=0.355).

Only 18 subjects (9 in each arm) out of a total of 62 participants were anaemic. The subgroup results could be included in this review, as the patients demonstrated the inclusion criteria for this review. The analysis of the anaemic subgroup did not show any outcome differences. Mean change from recruitment to pre-operative value was −0·46 g/dl (−0·79, −0·12) in the IV iron group compared with −0·11 g/dl (−0·63, 0·41) in the placebo group (p=0.223). There was no separate analysis or reporting of the discharge haemoglobin in the anaemic subgroup. In addition no differences were demonstrated in any of the secondary outcome measures haematocrit, mean cell Hb (MCH), reticulocytes, serum iron, ferritin and transferrin saturation.

The other phenomena of interest for this review, the rate of red blood cell (RBC) transfusion, the average number of units transfused, the length of stay in hospital, the rate of readmission within 30 days of discharge, the incidence of transfusion

related co- morbidities, the number of deaths and the impact of intravenous iron administration on functional outcomes were not reported in this study.

3.3 METHODOLOGICAL QUALITY

MASTARI

The two included studies were RCT"s (20) (21) and both studies were truly randomized based on a computer-generated randomization sequence stratified according to pre-recruitment Hb. Both studies attempted to determine sample size by using power analysis.

The detailed assessment is illustrated in Appendix 4.

ACTUARI

No studies were found and therefore assessed with this assessment tool.

CHAPTER 4: DISCUSSION AND CONCLUSION

4.1 KEY FINDINGS

Anaemia management is promoted heavily in the current literature as a key element of a comprehensive blood management approach. Multiple treatment options including IV iron are available. This study represents the first systematic review into the efficacy and cost effectiveness of pre-operative IV iron administration for the correction of pre-operative anaemia.

Our review resulted in two key findings. First, the high level evidence currently available is based on a small number of patients (74 in total) reported in two separate RCTs (Kim et al. and Edwards et al.). Both studies investigated the effectiveness of administering pre-operative IV iron. The second key finding in respect to the economic component of the review was that no randomized controlled trial was found that examined the cost effectiveness, or otherwise, of pre-operative correction of iron deficiency anaemia using IV iron.

Of the two identified RCTs evaluating the efficacy of pre-operative IV iron administration in patients presenting with anaemia, the study by Kim et al. demonstrated significant advantages in the administration of IV iron for the correction of iron deficiency anaemia prior to surgery for women with menorrhagia. Haemoglobin increased by 3.0 g/dl in the IV iron group compared to 0.8 g/dl in the oral iron group. Ferritin also increased significantly in the IV iron group, 170.1 vs 4.1 µg/L. The study by Edwards et al. allowed the inclusion of an anaemic subgroup for analysis in this review. In contrary to the results in Kim's study, these patients presenting for bowel resections did not benefit from the

administration of IV iron. However the difference of the trial design and reporting of outcomes of the two studies prevented a meta-analysis.

An additional RCT (22) that examined the efficacy of IV iron in the pre-operative cardio-surgical setting was found. However, full text examination and appraisal revealed that the majority of patients enrolled in this study were not anaemic, therefore not fulfilling the inclusion criteria for this review.

The limited amount of high level evidence is surprising, as reviewing the literature on anaemia and iron deficiency in the pre-operative setting confirmed that iron deficiency anaemia (IDA) is a very common and serious condition.

4.1.1 THE BURDEN OF ANAEMIA

As the most common global nutritional deficiency, the burden on society resulting from anaemia is immense. Anaemia related symptoms such as fatigue, impaired cognitive function, poor exercise tolerance lessen quality of life and lead to huge productivity losses (23).

The prevalence of IDA varies, depending on sources, definitions and patient cohorts (24-26). Iron deficiency, with or without anaemia, is found in up to 75% patients presenting for surgery (25). A growing body of evidence suggests that this has serious consequences for the peri-operative period. IDA frequently leads to an increased number of cardiac complications, increased number of days in hospital and a greater number of allogeneic transfusion events (8). Pre-operative anaemia was also shown to independently increase peri-operative mortality (12). A more recent publication involving 227,425 patients, of whom 69,229 (30.44%) had pre-operative anaemia, confirmed the high incidence and concluded that even mild forms of anaemia increase 30 days mortality (13).

Anaemia is commonly aggravated in the postoperative period. Intra-operative blood loss, wound drainage, hemodilution and frequent venepuncture for testing are all contributing factors. In addition, pre-existing iron depletion prevents effective peri-operative erythropoiesis impairing post-operative functional recovery (27).

4.1.2 IMPACT ON BLOOD USAGE AND UTILIZATION

When it comes to the surgical setting, which is the particular focus of this review, the presence of anaemia often results in RBC transfusion. This continues to be a widely accepted treatment modality despite the clear and well described potential adverse effects and outcomes. Donated blood is often claimed and perceived to be “safe”, prompting many clinicians to transfuse as a default position. Old dogmas prevail and the decision to transfuse is not only taken lightly but also often triggers a minimum transfusion of 2 units (10). This is especially important, as there appears to be a significant dose dependent effect of transfusion related adverse effects. It needs to be emphasised that not only total avoidance but also minimisation of exposure to blood would potentially prevent harm and benefit the patient (28).

By donating blood to “save lives”, donors place a valuable resource into the clinicians’ hands with the assumption that it will be dealt with responsibly. This responsibility should be taken into account each time we prescribe blood products. It can however be noted that prescribing a blood transfusion is a process which remains too easy, is rarely discussed and often left to the inexperienced medical officer. A common lack of documentation and/or consent accentuates the lack of scrutiny applied to the process of transfusion. The

transfusion event is poorly monitored, is often unjustified, and due to various different funding models sometimes comes at no cost for the health care provider (e.g. Australia). These factors combined make it unlikely that clinical practice will change.

4.1.3 RISK GROUPS AND IDENTIFICATION

This review highlights that many patients who present for surgery are at risk of iron deficiency. This subsequently exposes them to a number of potential complications and a higher transfusion risks. This risk increases with the type and extent of the surgery, but also with the underlying disease process. Certain types of patients stand out and should make the clinician cautious. Patients with gastro-intestinal malignancies show the highest prevalence of IDA. Chronic and longstanding blood loss results in iron loss and iron store depletion. Inflammatory bowel disease exposes patients to similar risks. Women with menorrhagia often suffer from heavy menstrual bleeding for many years leading to gradual iron depletion. In these, generally otherwise healthy women, the condition is often well tolerated for a very long time and women frequently present with severe IDA to emergency departments when the tipping point is reached. Patients scheduled for cardiac or orthopaedic surgeries commonly combine many disadvantages. Advanced age, significant comorbidities such as congestive heart failure, ischemic heart disease, osteoarthritis and renal disease often compound the problem and ID and IDA becomes multifactorial. An inflammatory state as a result of the chronic disease process leads to hepcidin increases and down regulation of iron absorption and utilisation (29). Certain medication may also further impair absorption (eg proton pump inhibitors, antacids) and other drugs can contribute to blood loss (aspirin, clopidogrel, warfarin, NSAIDs.) threatening iron

metabolism and iron balance. As many of the described findings are treatable and/or preventable it is obvious that pre-operative anaemia screening, detection and correction, particularly in patient groups at risk of IDA, should become an integral part of the pre-operative assessment and management process. Iron deficiency with or without anaemia is not a physiological state. It must therefore be considered a “disease process”. In medical practice we are required to treat disease and as such, anaemia correction deserves much more attention. This makes it all the more surprising that our study found such a limited numbers of related studies.

4.1.4 APPROACH TO CHANGE

It is clear, however, that high level evidence alone will not guarantee knowledge translation. Conducting audits and providing feedback can be a powerful intervention and provide the adequate tool in achieving the desired change in clinical practice (30). This was reiterated very recently by a panel of experts at the International Consensus Conference on Transfusion and Outcomes (ICCTO) held in April 2009 in Phoenix (31,32) . The panel concluded that there is little evidence to support a beneficial effect from the greatest number of transfusions currently being given to patients.

Experts and authorities from around the world, including the WHO, have recognised the need for change and the importance of more appropriate treatment approaches (5) (33). This can be facilitated through the implementation of PBM programs. It is crucial, however, that awareness is created and that PBM programs are driven by a local team underpinned by government support. Recognising the importance of such change, accreditation, education and audit

should consequently be linked in with PBM, and be compulsory. Even short educational sessions improved transfusion practice in the peri-operative setting (34). Physicians who understand transfusion indications and are receptive to input from colleagues apply a significantly higher quality transfusion practice (35). Education, therefore, in addition to a willingness to accept “expert advice” is fundamental.

4.1.5 MODELS OF PRACTICE

Pregnancy, however, is one of the key areas where this has been explored. Pregnant women are a well-recognised risk group for developing ID and IDA. In the context of this review, the existing evidence from this patient cohort could not be included because the condition is not considered “pre-operative” per se. However, 30 % of women deliver by caesarean section (CS), a surgical procedure with an average blood loss of 400 ml. In addition to this, even normal vaginal delivery (NVD) is often associated with significant blood loss.

Several studies have shown significant benefits from the administration of IV iron compared to oral iron supplementation (36) (37). Changes in Hb allowed women to be better prepared for delivery. This also enabled women to tolerate and recovery better from blood loss associated with labour , which in 13 % of women is moderate to severe (38). Restoration of iron stores often alleviates ID associated symptoms. These benefits are also felt in the post-partum period by reducing the incidence of post-partum depression and prolonging breast feeding episodes (39) (40). Therefore, despite the lack of evidence in the “surgical” population some of the results from obstetric patients can offer insight and may be translated.

4.1.6 INTERIM SOLUTIONS

In the absence of multiple RCTs in the literature providing guidance, one has to appreciate that prospective and retrospective cohort studies have described IV iron as an effective intervention (41) (42) (43) (44). Due to a high risk of serious adverse events associated with infusions of iron dextran, physicians have been cautious about IV intervention and have frequently substituted it with the transfusion of red blood cells to correct any pre-operative anaemia. In some clinical settings it has been demonstrated however, that IV iron appears to be beneficial, particularly in iron deficient patients, with or without anaemia.

4.1.7 RISKS OF IV IRON

Older types of IV iron such as high molecular iron dextran carried the risk of anaphylactic reactions and raised serious concern among medical personnel. However, newer types of low molecular weight or dextran free IV irons, offer a much improved safety profile resulting in significantly lower incidences of adverse effects. These adverse effects are relatively rare and often mild. Common adverse effects are injection site reactions, headaches, nausea and hypertension.

In recent years, this has led to the expansion of licensed indications for iron sucrose and ferric carboxymaltose for example. It is surprising therefore that this treatment has not been studied extensively and there is not enough data from RCTs to support this approach. Accumulating observational data appears promising but randomised trials are needed to evaluate efficacy and cost effectiveness. In addition to dose requirements, trials are needed to determine the ideal time of administration and to identify the patient groups most in need of this intervention.

The majority of surgery is undertaken in an elective setting. Clinicians should strive for optimal patient outcomes in an attempt to minimise morbidity and mortality (15). The development of patient blood management guidelines should assist in addressing anaemia in order to minimise patient exposure to allogeneic blood, to enhance patient recovery and contribute to overall cost savings within health sectors, already under enormous financial strain (45). Divided into three pillars, reflecting the pre-, intra- and post-operative phase, the pre-operative period should focus on the detection and correction of anaemia and iron deficiency. One could argue, that no patient with anaemia booked for elective surgery should enter the operating room. It is however crucial to identify patients with the appropriate test, communicate this well amongst involved specialities, and decide on the right strategy and treatment modality in order to achieve the best possible improvement in iron status and haemoglobin values. (25).

4.1.8 ECONOMIC IMPLICATIONS

The search for the economic component of the review revealed no randomized controlled trials examining the cost effectiveness of the preoperative correction of iron deficiency anaemia with IV iron. Considering the enormous health care expenditure for the provision of blood and blood products this is another interesting finding. In Australia for example the total cost to government to cover the demands for these products reached almost a total of $ 1 billion in 2010/11 (46). In many instances, transfusion of red blood cells remains the default position for the correction of pre-operative anaemia. As mentioned above, the risks of transfusions are well demonstrated and acknowledged. Murphy established a direct link between transfusion of patients undergoing cardiac surgery and infection rates. Transfusion avoidance by anaemia correction could

have resulted in a 40% overall reduction in hospital cost (9). The rising costs and looming shortage and availability of RBC's add to the multiple disadvantages of allogeneic transfusions.

Analysing the cost of transfusion in the surgical setting should involve all steps required at a hospital level, called activity based cost. This is crucial in order to reflect the true cost of blood but is very complex. Due to fundamental differences in health jurisdictions, these cost factors are not universally applicable, but it is possible to establish identifying principles. Irrespective of the health system examined, it is highly likely that the real cost of blood has been underestimated in the past (18). Many jurisdictions are already employing implementation of tools that identify activity for blood usage and this will certainly assist in rigorous cost analysis.

Blood management has been on the agenda for some time. It is therefore surprising that, despite a vast amount of publications and multiple guidelines available, knowledge translation is lacking and many transfusion events remain inappropriate.

Unmanaged anaemia leads to a significant increase in transfusion. A Canadian program demonstrated successfully improved clinical outcomes and cost savings by managing patients appropriately in the pre-operative period (8). A recent publication on the implementation of a local blood management algorithm in major orthopaedic surgery illustrated that cost-savings can be achieved (47). In a RCT setting oral iron supplementation has been shown to reduce transfusion incidence resulting in significant cost savings (48). Depending on the time frame

prior to surgery and the severity of the anaemia and/or iron depletion, IV iron administration appears to be an even more effective approach (41, 43, 49).

It is important to remember that the main target of patient care is patient outcome. Patient blood management should be standard care for all patients in the surgical setting. Even if total transfusion avoidance is not feasible for all patients, overall reductions are achievable. Endorsing appropriate transfusion approaches in combination with pre-operative optimization should result in improved patient well-being, and cost savings are likely to be a logical flow on effect.

4.2 IMPLICATIONS FOR PRACTICE

The available evidence suggests that IV iron is a promising and effective treatment in the management of preoperative anaemia but the evidence is limited to small trials investigating very few patients. There is no data currently available on whether this intervention is cost effective

4.3 IMPLICATIONS FOR RESEARCH

An adequately powered RCT is needed to determine whether preoperative intravenous iron administration corrects anaemia efficiently and is cost effective.

4.4 LIMITATIONS

The search was limited to the last 11 years and the four languages spoken by the author. However, studies on patient blood management, restrictive transfusion approach and anaemia management have been particularly topical in those years. It is unlikely that the addition of more languages or an extended search period would have revealed further information.

4.5 CONCLUSIONS

There is a significant gap in the literature. Our study found insufficient data to make firm conclusions about the efficacy of pre-operative intravenous iron administration for the correction of anaemia based on clinical trial settings. We were also unable to establish firm conclusions in respect to the potential cost savings due to intravenous iron supplementation.

Aside from the risk posed to the individual patient, continuation of commonly observed transfusion practices will result in significant consequences to our health system as a whole. To accommodate the future challenges, prevention - by improving and preserving the patient's red cell mass and thereby reducing the number of allogeneic red cell transfusions - must be an important goal. Anaemia management is at the core of this approach.

4.6 CONFLICT OF INTEREST

none

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APPENDIX 1: CRITICAL APPRAISAL INSTRUMENT

Reviewer _____ Date _____

Author _____Year _____ Record Number _____

	Yes	No	Unclear
1. Was the assignment to treatment groups truly random?	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐
7. Were groups treated identically other than for the named interventions?	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐

9. Were outcomes measured in a reliable way? ☐ ☐ ☐

10. Was appropriate statistical analysis used? ☐ ☐ ☐

Overall appraisal: Include Exclude Seek further info.

Comments (Including reasons for exclusion)

APPENDIX 2: DATA EXTRACTION INSTRUMENT

Author Record Number

Journal

Year

Reviewer

Method _____

Setting _____

Participants _____

Number of Participants

Group A Group B

Interventions

Intervention A _____

Intervention B _____

Outcome Measures

Outcome Description	Scale/Measure

Results

Dichotomous Data:

Kim et al.

Achieving target haemoglobin of 10 g/dL

Results of treatment

Outcome	IV iron n=30	oral iron n= 26	p value
Success	23	3	<0.0001
Failure	7	23	

Continuous Data

Kim et al.

Results of treatment

Outcome	IV iron Group Mean & SD	Oral iron Group Mean & SD	p value
Preoperative Hb, g/dl	7.58 ± 1.2	7.8 ± 1.1	<0.0001
Postoperative Hb, g/dl	10.5 ± 1.4	8.6 ± 1.4	
Preoperative ferritin, µg/l	81.7 ± 272.1	5.9 ± 5.0	<0.0001
Postoperative ferritin, µg/l	231.4 ± 561.7	9.7 ± 10.3	

Primary outcome variables in the anaemic subgroup

Outcome	IV iron Mean(interquartile range)	placebo Mean	p value
Recruitment Hb, g/dl	11.8 (2.0)	12.4 (2.0)	0.627
Before surgery Hb, g/dl	11.2 (3.0)	12.5 (4.0)	0.427
Mean change recruitment to preop. g/dl	-0.46(-079,-0.12)	-0.11(-0.63,0.41)	0.223

APPENDIX 3: DETAILED SEARCH STRATEGY

MAStARI

PubMed

("surgical procedures, operative"[MeSH Terms] AND "preoperative care"[MeSH Terms]) AND ("iron/deficiency"[MeSH Terms] OR "anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms]) AND ("blood transfusion"[MeSH Terms] OR ("hematinics/administration and dosage"[MeSH Terms] OR "hematinics/therapeutic use"[MeSH Terms]) OR ("erythropoietin/administration and dosage"[MeSH Terms] OR "erythropoietin/therapeutic use"[MeSH Terms]) OR ("iron/administration and dosage"[MeSH Terms] OR "iron/therapeutic use"[MeSH Terms]) OR ("iron compounds/administration and dosage"[MeSH Terms] OR "iron compounds/therapeutic use"[MeSH Terms]) OR ("infusions, intravenous"[MeSH Terms] AND "iron"[MeSH Terms])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])("surgical procedures, operative"[MeSH Terms] AND "preoperative care"[MeSH Terms]) AND ("iron/deficiency"[MeSH Terms] OR "anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms]) AND ("blood transfusion"[MeSH Terms] OR ("hematinics/administration and dosage"[MeSH Terms] OR "hematinics/therapeutic use"[MeSH Terms]) OR ("erythropoietin/administration and dosage"[MeSH Terms] OR "erythropoietin/therapeutic use"[MeSH Terms]) OR ("iron/administration and dosage"[MeSH Terms] OR "iron/therapeutic use"[MeSH Terms]) OR ("iron compounds/administration and dosage"[MeSH Terms] OR "iron compounds/therapeutic use"[MeSH Terms]) OR ("infusions, intravenous"[MeSH

Terms] AND "iron"[MeSH Terms])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])

Database: Embase <1980 to 2012 Week 35>

Search Strategy:

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1 exp Surgical Procedures, Operative/ (2924635)

2 exp Preoperative Care/ (32993)

3 Iron deficiency/ (7861)

4 anemia/ (94470)

5 Anemia, Iron-Deficiency/ (11933)

6 exp Blood Transfusion/ or Hematinics/ad, tu [Administration & Dosage, Therapeutic Use] (110562)

7 Erythropoietin/ad, tu [Administration & Dosage, Therapeutic Use] (655)

8 Iron/ad, tu [Administration & Dosage, Therapeutic Use] (1851)

9 exp Iron Compounds/ad, tu [Administration & Dosage, Therapeutic Use] (77)

10 Infusions, Intravenous/ (310622)

11 Iron/ (98811)

12 anemia/dm, dt, pc, rh, th [Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy] (18509)

13 iron deficiency anemia/dm, dt, pc, rh, th [Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy] (5041)

14 1 and 2 (32993)

15 3 or 4 or 5 (109211)

16 10 and 11 (1175)

17 6 or 7 or 8 or 9 or 16 (113583)

18 14 and 15 and 17 (120)

19 12 or 13 (23150)

20 14 and 19 (134)

21 18 or 20 (166)

22 exp "Costs and Cost Analysis"/ (225568)

23 economics.mp. or economics/ (242587)

24 22 or 23 (420714)

25 21 and 24 (15)

26 limit 21 to (evidence based medicine or consensus development or meta analysis or outcomes research or "systematic review") (5)

27 limit 21 to (clinical trial or randomized controlled trial or controlled clinical trial or multicentre study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) (44)

28 26 or 27 (46)

ACTUARI

PubMed

("economics"[MeSH Subheading] OR "costs and cost analysis"[MeSH Terms] AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])) AND (("surgical procedures, operative"[MeSH Terms] AND "preoperative care"[MeSH Terms]) AND ("iron/deficiency"[MeSH Terms] OR "anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms]) AND ("blood transfusion"[MeSH Terms] OR ("hematinics/administration and dosage"[MeSH Terms] OR "hematinics/therapeutic use"[MeSH Terms]) OR ("erythropoietin/administration and dosage"[MeSH Terms] OR "erythropoietin/therapeutic use"[MeSH Terms]) OR ("iron/administration and dosage"[MeSH Terms] OR "iron/therapeutic use"[MeSH Terms]) OR ("iron compounds/administration and dosage"[MeSH Terms] OR "iron compounds/therapeutic use"[MeSH Terms]) OR ("infusions, intravenous"[MeSH Terms] AND "iron"[MeSH Terms])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])) AND ("2003/02/14"[PDat] : "2013/02/10"[PDat] AND English[lang])

APPENDIX 4: INCLUDED STUDIES

MASTARI

Number of studies included and excluded

Number of studies included	Number of studies excluded
2	0

Randomised Control Trial / Pseudo-randomised Trial

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Kim, Y. H., Chung, H. H., Kang, S. B., Kim, S. C., Kim, Y. T., 2009	Y	N	N	N	U	Y	Y	Y	Y	Y
Edwards, T. J., Noble, E. J., Durran, A., Mellor, N., Hosie, K. B., 2009	Y	Y	Y	Y	U	Y	Y	Y	Y	Y
%	100	50	50	50	0	100	100	100	100	100

Author/year/country	Kim, Y. H., Chung, H. H., Kang, S. B., Kim, S. C., Kim, Y. T.\2009\Korea
Study	Safety and usefulness of intravenous iron sucrose in the management of preoperative anaemia in patients with menorrhagia
Method	RCT
Participants	Seventy-six patients with haemoglobin levels < 9.0 g/dl who were scheduled to undergo surgical treatment
Intervention	randomized to receive either intravenous iron sucrose or oral iron
Outcomes	to detect a 1-g/dl Hb difference adverse effects compliance
Risk of bias/allocation concealment	premature cessation of the oral iron arm, relatively small number, some protocol violations that limited the clinical and laboratory data were possible
Level of evidence	II
Notes	Intravenous iron was superior to oral iron in this study. The target haemoglobin was achieved in a significantly higher percentage of patients after intravenous iron administration. There was also a significant difference in the magnitude of haemoglobin increase and the ferritin levels in the iv group. No serious adverse events were recorded in either group.

Author/year/country	Edwards, T. J., Noble, E. J., Durran, A., Mellor, N., Hosie, K. B. /2009/ UK
Study	Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery
Method	RCT, prospective, blinded, placebo-controlled
Participants	62 adult patients to undergo bowel resection for suspected colorectal cancer
Intervention	intravenous placebo vs intravenous iron sucrose
Outcomes	The primary outcome measure was change in Hb concentration between recruitment and day of admission. Secondary outcomes were transfusion rate, changes in serum iron markers over the same time period, length of hospital stay and adverse perioperative events.
Risk of bias/allocation concealment	Excluding patients with previous transfusion and on oral iron, patients with potential profound anaemia, majority of patients randomised were not iron deficient or anaemic
Level of evidence	II
Notes	Only 9/34 patients with anaemia in the intravenous group and 9/26 patients with anaemia in the oral group. This allows the assumption that in most cases treatment with iron was not going to be successful, irrelevant of the route of administration

ACTUARI

Number of studies included and excluded

Number of studies included	Number of studies excluded
0	0

APPENDIX 5: EXCLUDED STUDIES

Author/year/country	Garrido-Martin, P., Nassar-Mansur, M. I., de la Llana-Ducros, R., Virgos-Aller, T. M., Fortunez, P. M., Avalos-Pinto, R., Jimenez-Sosa, A., Martinez-Sanz, R. /2012/ Spain
Study	The effect of intravenous and oral iron administration on perioperative anaemia and transfusion requirements in patients undergoing elective cardiac surgery: a randomized clinical trial
Method	RCT, prospective, double-blind, placebo-controlled, observational clinical trial
Participants	159 adult patients presenting for cardiac surgery
Intervention	Three groups, all treated pre-and postoperatively Group I intravenous iron sucrose. GII oral iron. GIII Placebo
Outcomes	Increase in Haemoglobin: Transfusion requirements
Risk of bias/allocation concealment	Study underpowered to show a difference, patient selection included all patients in the study period irrespective of the iron status
Level of evidence	II
Notes	There is no information on the number of patients with iron deficiency or anaemia.

APPENDIX 6 SEARCH RESULTS

Beattie, W. S., Karkouti, K., Wijeysundera, D. N., Tait, G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology.2009; 110(3): 574-81.

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Gilliss, B. M., Looney, M. R., Gropper, M. A. Reducing noninfectious risks of blood transfusion. Anesthesiology.2011; 115(3): 635-49.

Gombotz, H. Patient blood management is key before elective surgery. Lancet.2011; 378: 1362-3.

Goodnough, L. T., Shander, A., Spivak, J. L., Waters, J. H., Friedman, A. J., Carson, J. L., Keating, E. M., Maddox, T., Spence, R.. Detection, evaluation, and management of anemia in the elective surgical patient. Anesth Analg.2005; 101(6): 1858-61.

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