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<b>Author(s)</b>	<b>Tran, HDD; Wong, GTC; Chee, YE; Irwin, MG</b>
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Review, US Spelling  
haematology

## Effectiveness and safety of erythropoiesis-stimulating agent use in the perioperative period

Effectiveness and safety of erythropoiesis-stimulating agent (ESA) use in the perioperative period

D. H. D. Tran *et al.*

Diane H-D Tran, Gordon T-C Wong, Yee Eot Chee & Michael G Irwin  
University of Hong Kong, Queen Mary Hospital, Department of Anaesthesiology, 102 Pokfulam Road, HK, Hong Kong gordon@hku.hk

University of Hong Kong, Department of Anaesthesiology, HK, Hong Kong

### Introduction:

Erythropoiesis-stimulating agents (ESAs) are widely used ~~to-in~~ treating anaemia associated with renal failure. They are also now used perioperatively to reduce the use of allogeneic blood transfusions (ABTs) in patients undergoing surgery with anticipated high blood loss. Although they can reduce the risks associated with ABT and improve quality of life, the use of ESAs is still associated with adverse effects.

### Areas covered:

A narrative review is provided on ESAs and a systematic review ~~was~~ has been conducted to examine the current evidence for the efficacy and safety of perioperative ESAs use. A search of PubMed and Medline databases ~~was~~ has been performed using a combination of search terms including erythropoietin, perioperative, surgical, safety and efficacy.

### Expert opinion:

Current evidence supports the use of perioperative ESAs to reduce the need for ABT. However, large studies assessing safety in anaemic patients with chronic renal disease have found adverse effects including cardiovascular, stroke and thromboembolic events. The dosing strategies used have been varied and short term in comparison, to adequately assess whether these adverse effects can be conferred onto the perioperative population. Future research needs to address the questions of optimal dosing strategies in order to maximise the positive effects ~~but also~~ and minimise adverse events.

**Keywords:** blood transfusion, erythropoiesis, erythropoietin, perioperative, surgery

### Abbreviations

ABT = allogeneic blood transfusions

ESAs = erythropoiesis stimulating agents

Hb = Haemoglobin

Hct = Haematocrit

IU = International Units

iv = intravenous

rHuEPO = recombinant human erythropoietin

sc = subcutaneous

## 1. Introduction

Major complex surgical procedures may be associated with substantial intraoperative and/or postoperative blood loss. A significant number of patients that develop anaemia from blood loss will require allogeneic blood transfusions (ABTs) and this is more likely if preoperative anaemia is present, a state that is not uncommon in certain surgical populations. Anaemia in itself can be harmful; in order to maintain systemic oxygen delivery, there is a compensatory increase in cardiac output. Even mild preoperative anaemia is independently associated with an increased risk of 30-day morbidity and mortality and postoperative complication rates in patients undergoing major non-cardiac surgery [1].

Although blood transfusion, in the context of either severe anaemia or life-threatening haemorrhage, can improve oxygen delivery to various organs, its use is associated with a number of well-recognized risks and complications. These include infectious risks, as well as transfusion reactions, transfusion errors, immunological reactions and immune modulation [2, 3]. The rise in hemoglobin (Hb) from blood transfusions are-is not consistently associated with improvement in oxygen delivery or oxygen consumption. This may be due to the significantly altered properties of the stored blood, including the depletion of 2,3-DPG which causes a left shift of the oxygen dissociation curve, thus impairing the oxygen-delivering ability of red blood cells [4].

The concerns regarding the adverse effects of ABT have prompted reviews of transfusion practices and the development of strategies to minimize the need. These include the implementation of restrictive transfusion protocols, use of pharmacological and non-pharmacological measures to reduce blood loss, preoperative autologous blood donation for transfusion, perioperative cell salvage, and stimulation of preoperative erythropoiesis <sup>5, 6</sup>.

This review will focus on erythropoiesis-stimulating agents (ESAs) as a component of this patient haematological strategy<sup>[CE2]</sup>. First, ~~it will provide~~ a narrative review on erythropoietin, including its history, formulations and regimens, is provided. Secondly, ~~it will examine, in a semi-quantitative manner,~~ the efficacy and safety of perioperative erythropoietin use is examined in a semiquantitative manner.

### 1.1 A Etiology of preoperative anaemia

In a US national audit of patients undergoing elective orthopaedic surgery, 35% of patients were found to have Hb levels < 13 g/dL at preadmission testing. ~~Many are were~~<sup>[CE3]</sup> women and anemia in approximately one-third of these ~~patients a had been~~ the result of iron deficiency, with the remaining being attributed to chronic inflammatory disease, chronic renal disease or unknown causes <sup>7</sup>.

Patients undergoing major surgery with anticipated high blood loss often have co-morbidities, underlying chronic disease processes as well as being of advanced age. Aging is increasingly being identified as a proinflammatory state. The anemia of chronic disease is multifactorial but is thought to be immune-driven. Cytokines induce changes<sup>[CE4]</sup> in iron homeostasis, ~~impaired the~~ proliferation of erythroid progenitor cells, and reduce circulating levels of erythropoietin and the life-span of red blood cells. Increase uptake of iron by cells of the reticuloendothelial systems causes a diversion of iron away from the circulation. Erythropoiesis can be directly affected by the

infiltration into bone marrow of microorganisms as well as tumour cells [8]. Ongoing occult blood losses from gastrointestinal or urogenital cancers may also contribute.

## 2. Erythropoietin and erythropoiesis-stimulating agents

Erythropoietin is the primary regulator of erythropoiesis. It is a glycoprotein hormone naturally produced and secreted primarily by renal tubular cells with a minor hepatic contribution. Production is stimulated by tissue hypoxia or severe haemorrhagic stress, and erythropoietin binds to specific receptors on erythroid progenitor cells in the bone marrow. The ultimate effect is to increase erythropoiesis in an attempt to maintain oxygen delivery to vital organs.

In 1977, human erythropoietin was successfully purified and characterized from the urine of patients with aplastic anaemia. In 1985, two groups of investigators independently cloned the human erythropoietin gene, identifying the corresponding nucleotide sequences [9]. Erythropoietin for clinical use is now produced by recombinant DNA technology. The first human trials using recombinant human erythropoietin (rHuEPO), which is identical to the naturally occurring erythropoietin, examined its effectiveness in correcting anaemia of chronic renal disease. These initial results demonstrated that rHuEPO could increase the haemoglobinHb level, thus removing the need for regular blood transfusion and improving the quality of life in patients requiring dialysis [10]. The trial results were so impressive that rHuEPO was approved for human use in patients with chronic renal failure by the Food and Drug Administration (FDA) in June 1989 [9, 11].

Erythropoietin stimulating agents (ESAs) are given by injection to stimulate red cell production and to treat anaemia. Clinical trials have demonstrated a dose-response relationship between erythropoietin and red blood cell expansion [12]. They are commercially available in several forms. The first-generation ESAs such as Epoetin- $\alpha$ -alfa and epoetin- $\beta$ -beta are recombinant erythropoietin analogues, each consisting of 165 amino acids but differ only in their glycosylation. Darbepoetin- $\alpha$ -alfa, a second-generation ESA, is a hyperglycosylated derivative of Epoetin. It has

a longer half-life and, therefore, may be administered less frequently than Epoetin. Although these rHuEPOs act on the same erythropoietin receptor, there are some variations on the degree of glycosylation which is responsible for the differences in pharmacokinetics and pharmacodynamics between them. The newer third-generation ESAs are chemically synthesized, continuous erythrocyte receptor activators (CERA), with an even longer half-life than darbepoietin [13, 14].

The FDA has now extended approval of these agents for the treatment of anaemia resulting from a number of causes. These include chronic kidney failure, chemotherapy and certain treatments for Human Immunodeficiency Virus (HIV). It is also used to reduce the number of blood transfusions during and after major surgery and in patients who refuse to have an allogeneic blood transfusion (ABT) for religious reasons such as Jehovah's Witness. The rHuEPO used for these indications has been described as a 'promising blood-saving technique' [15]. Preoperative rHuEPO gained regulatory approval in 1996 to reduce the need for ABT in anaemic patients (pre-treatment Hb of 10 g/dL to 13 g/dL) undergoing major surgery [16]. It has been (along with iron, vitamin B12 and folic acid) recommended (along with iron, vitamin B12 and folic acid) as a specific medication 'that should be used instead of blood transfusion', if the clinical condition of the patient permits sufficient time to promote erythropoiesis [11]. The rHuEPO has also been approved for use in patients undergoing autologous donation in Japan, Europe and Canada since 1993, 1994 and 1996, respectively, and for perioperative adjuvant therapy without autologous donation in Canada and the United States since 1996 [17].

Other situations relevant to the perioperative period where ESAs have been used, is to treat the anaemia associated with critically ill patients in the intensive care unit. Despite earlier trials suggesting a small decrease in ABT after administration of ESAs, a more recent multicenter trial, conducted after the more widespread use of restrictive transfusion triggers, did not show a significant reduction in ABT use [18]. Trials have also been conducted in cardiac patients with acute ST elevation myocardial infarction with the aim of reducing infarct size and improving

cardiovascular outcomes. Although these have produced positive outcomes in animal studies, so far there have not been any conclusive studies to confirm these effects in the human population [19].

The therapeutic effect of ESAs involves counteracting the antiproliferative effects of cytokines along with the stimulation of iron uptake and heme biosynthesis in erythroid progenitor cells (see [Section 1.1](#)).

There are many approved as well as off-label uses of ESAs. The nature of the anaemia they are treating and these range from chronic use such as to treat the anaemia of chronic renal failure as well as episodic use which would include its use to treat the anaemia of critical illness and

### 3. Regimes of perioperative rHuEPO use

Preoperative administration of rHuEPO is effective in treating anaemia by increasing the erythrocyte mass and autologous donation volumes while maintaining a higher haematocrit (Hct) [20]. Consequently, it can be administered to assist with autologous donation or prior to elective surgery in patients who do not predonate. The beneficial effect of rHuEPO among patients participating in preoperative autologous blood donation programmes and for the preoperative preparation of patients has been previously reported. Early clinical trials of rHuEPO therapy in the setting of autologous donation provided further important information regarding clinical safety, rHuEPO dose, and erythropoietin response. Later trials of perioperative rHuEPO therapy without autologous donation then provided data on efficacy (reduced allogeneic blood exposure) that led to approval of rHuEPO in patients undergoing surgery. Factors that influence the response to rHuEPO include the dose and timing of treatment, combined administration of iron and baseline Hbhaemoglobin concentration [21, 22].

#### 3.1 Dose and timing of treatment



The effect of rHuEPO is rapid. Within 2 to 3 days, a sustained rise in the reticulocyte index is seen and the ~~Hct~~haematocrit begins to increase. The equivalent of one unit of blood is produced by day 7, and the equivalent of 5 units is produced by day 28 [20]. Although several different preoperative regimens have been described, the regimen approved by the US FDA consists of four subcutaneous (s.c.) injections of epoetin- $\alpha$ -alfa, 600 U/kg of body weight, administered at 3, 2 and ~~one~~ week before surgery and again on the day of surgery [23]. Weekly doses of rHuEPO are as effective as daily administration but are less expensive. Initiating therapy with a single weekly dose would seem logical, especially if therapy is commenced well before surgery [20].

The minimal effective rHuEPO dose required to reduce ABT rate in surgical patients is unknown, especially when administered together with iron, and this is reflected in the huge range of dose regimes employed by different studies. Protocols used vary from a single large dose of rHuEPO given ~~one~~ day preoperatively [24] and a subsequent smaller dose administered at the time of surgery [25], to multiple doses given at weekly intervals over a period of 3 to 4 weeks preoperatively [26, 27, 28]. Some protocols extend into the post-operative period, while ~~st~~ daily regimes administered ~~from~~ up to 10 days preoperatively have also been used [29, 30, 31, 32, 33, 34, 35, 36]. The individual single dose was higher in patients undergoing weekly treatment compared to those undergoing daily treatments, with the majority of those on weekly treatment having 40,000 IU/~~per~~ week and those on daily treatments receiving between 10,000 IU and 21,000 IU/daily. Some were based on weight, while others were a set dose irrespective of any other factors. Total dose is generally higher and the duration of treatment shorter in patients treated daily compared with those treated weekly.

### 3.2 Route of administration

Both the intravenous (i.v.) and ~~subcutaneous~~ (s.c.) routes can be used to deliver rHuEPO to patients with renal impairment. The circulating half-life of rHuEPO is 6 to 8 hours, with significant inter-individual variations in plasma levels [20]. Clinical studies have demonstrated that the s.c. route



offers a few advantages over *i.v.* [9, 37, 38]. Both *i.v.* ~~Intravenous~~ and *s.c.* administrations of rHuEPO show substantial differences in their pharmacokinetics. Levels remain elevated longer after *s.c.* (48 ~~hours~~) than after *i.v.* administration (18 – 24 ~~hours~~), although peak levels are not as high. The sustained serum levels associated with *s.c.* dosing are more physiological and, therefore, more effectively stimulate erythropoiesis [9, 20]. This pharmacokinetic difference may explain why the majority of studies chose a rHuEPO dosing strategy using the *s.c.* method. It is difficult then to evaluate the relative efficacy of either *i.v.* or *s.c.* methods.

### 3.3 Co-administration of iron

Iron deficiency is considered to be the most important cause of an inadequate response to ESAs.

Erythropoietin-stimulated erythropoiesis is independent of age and gender, and the variability in response among patients is most likely attributable to iron-restricted erythropoiesis [17]. Absolute iron deficiency, where total body iron stores are depleted, or functional iron deficiency can occur. The latter, with normal ferritin levels but low transferrin saturation, is a state which occurs when increased erythron iron requirements exceed the available supply of iron. This inability to mobilize iron stores rapidly enough develops under conditions of intense erythropoiesis such as during treatment with ESAs, and in these cases, supplementary iron may improve the response to ESAs [39]. Iron deficiency may blunt the response to EPO<sub>[CE6]</sub> or delay recovery from postoperative anaemia [40]. The maximal effect of rHuEPO injections is usually only achieved when patients' iron stores are adequate [41].

It has been demonstrated that the use of *i.v.* iron, with or without rHuEPO, reduced the need for ~~allogeneic blood transfusion~~ ABTs, but stimulation of erythropoiesis seemed to be more pronounced among patients also receiving rHuEPO. For these reasons, it has been recommended that rHuEPO therapy is supported by supplementary iron either orally or intravenously. Oral iron is usually effective but *i.v.* supplementation should be considered for patients with low iron stores, those with

a poor initial response to rHuEPO therapy or those who demonstrate increasing evidence of iron deficiency with treatment [20]. Infusion of iron should take place two to three times weekly for 3 to 4 weeks. This treatment can be administered to all patients to prevent iron-deficiency during erythropoiesis [42]. While the majority of studies combined treatment with iron, patients were predominantly treated with oral iron rather than i.v.

However, the use of iron supplementation in anaemia is associated with potentially deleterious effects and is therefore controversial. Iron is an essential nutrient for proliferating organisms and has been linked to increased risk of developing bacteraemia. It is also associated with the formation of oxidative free radicals which can cause tissue damage and may also have immune modulation immunomodulatory effects [CE7] [43].

#### 4. Evidence for the efficacy of ESA use

A search was performed using PubMed and Ovid MEDLINE to identify all articles with erythropoietin as a text word. All the titles and abstracts found were examined for studies evaluating the use of, as well as safety and efficacy of ESA erythropoiesis stimulating agents in the perioperative setting. Studies were included if they were published in English between January 1993 and June 2013. Only randomized trials were included in this part of the review. Studies involving children and preoperative autologous blood donation were excluded. Of the 14 published studies included (see Table 1), the largest number of trials was in orthopaedic surgery, particularly joint replacement procedures, with the remaining trials in gastrointestinal cancer surgery [29, 30, 31, 32, 33] and cardiac surgery. All were randomized and included eight double-blind, two single-blind and four open-label studies. The majority of primary outcomes in these trials were the need for intraoperative blood transfusion, mean number of units of blood transfused, Hb haemoglobin concentrations, Hct haematocrit levels and reticulocyte counts. Others included length of hospital stay and deep venous thrombosis (DVT) detected.

On the whole, there were variations in dosage regimes and length of treatment duration between the different types of surgery. The studies looking at orthopaedic surgery generally had a weekly or daily treatment protocol that involved longer treatment duration and enrolled a larger number of patients than either cardiac or colorectal cancer surgery. In all the studies, either a minimal Hbhaemoglobin or Hcthaematoerit was required for inclusion. Where Hbhaemoglobin was part of the inclusion criteria, this ranged from ~~above~~  $\geq 8.5$  g/dL to 10 g/dL to ~~below~~ mainly  $\leq 13.5$  g/dL. Two studies did set higher Hbhaemoglobin levels at 14.5 g/dL [43] and 16 g/dL [34] and for those that used Hcthaematoerit, this was set at above 42 [28, 36]. Most benefit was found in patients with a baseline Hbhaemoglobin of between 10 and 13 g/dL. Where stated, all studies excluded patients with uncontrolled hypertension and history of thromboembolism.

There were few standard transfusion triggers and often relied on clinical judgement of both surgeons and anaesthetists and subjective symptoms reported by patients, while ~~est~~ several adopted a clinical measure such as Hbhaemoglobin level, but this ranged from 7.5 g/dL to 11 g/dL. A restrictive transfusion trigger has been shown ~~to be~~ unlikely to be associated with an increased incidence of silent myocardial ischaemia or longer hospital stay, but may result in a significant reduction in ABT rate.

Three of the included studies undertaken in patients undergoing orthopaedic procedures and one in colorectal cancer surgery randomized patients into ~~3~~ three groups; ~~2~~ two treatment groups along with a control group [33]. The ~~2~~ two treatment groups differed in dosage of rHuEPO used ~~—~~; a higher and lower dose was studied.

Preoperative administration of rHuEPO was shown to reduce allogeneic blood exposure in individuals undergoing elective surgical procedures associated with significant blood loss such as joint replacement, cardiac and oncological surgery in all except three studies [29, 30, 31]. All the studies showing a negative correlation with ABT rate were in patients undergoing colorectal surgery. In all those studies which showed a significant reduction of ABT associated with rHuEPO

use, there was also a significant reduction in the mean number of units transfused in the treatment groups. In all papers that evaluated this as the primary outcome, there was also a significant increase in reticulocyte count and Hcthaematoerit.

~~In~~ Among the ~~4~~four studies that had ~~2~~two treatment groups as well as a control group, ~~3~~three of ~~thesestudies~~ showed a significant reduction in ABT in both treatment groups. In one of these studies, there was more reduction in ABT in the lower~~\_~~dose group compared to the higher dose ~~28~~. The remaining one study~~of the~~ ~~4~~, despite showing a reduction of ABT use in both treatment groups, was only significant with the higher dose of rHuEPO ~~33~~.

#### 4.1 Colorectal cancer surgery

There were ~~5~~five randomized trials looking at the use of rHuEPO in colorectal cancer surgery. Of these, three studies ~~29,30,31~~ did not show a significant difference in blood transfusion rates between treatment group and control. One of these three studies did, however, show a significant reduction in the mean number of units transfused in the treatment group ~~31~~. In comparison, the two other studies ~~32, 33~~ showed a significant reduction in transfusion rates in the rHuEPO group as well as increased Hbhaemoglobin levels. The study that had ~~2~~two treatment groups with a high~~\_~~dose and low~~\_~~dose regime ~~only~~ showed a significant reduction in ABT in those treated with a higher dose of EPO ~~33~~.

The rHuEPORecombinant human erythropoietin needs to be given in combination with iron, and this is particularly important in patients undergoing cancer surgery who may be iron~~\_~~deficient, although it has been suggested that the benefit of supplemental iron may be less in oncology patients due to the decreased ability ~~for~~of erythropoiesis which could be related to other factors associated with malignancy. All studies involved the co-administration of iron and in all but one~~43~~ this was done as oral supplementation. The studies that used i.v. iron showed a significant reduction in ABT in the treatment group. It appears that oncology patients respond better to i.v. than to oral

iron supplementation in chemotherapy-induced anaemia treated with rHuEPO. <sup>[CE8]</sup> This is thought to be due to an absolute iron deficiency ~~due to~~ because of continuous external losses ~~externally~~ but and also due to decreased gastrointestinal absorption and iron sequestration caused by increased expression of hepcidin that can occur in oncology patients, as well as poor compliance <sup>[8, 44]</sup>. ~~Due~~ Owing to the shorter duration of treatment prior to surgery necessitated by the urgency of these procedures, the duration of iron treatment ~~was has~~ also been short.

The low transfusion trigger was set at a Hbhaemoglobin level of 7.5 g/dL and the iron deficiency in almost all patients in one of the studies may have contributed to the generally low transfusion frequency leading to a negative result <sup>[30]</sup>. Another possibility for the negative results in this group was that rHuEPO was not adequately effective in stimulating haematopoiesis in patients with tumour-induced anaemia and colorectal cancer <sup>[29]</sup>. The nature of cancer surgery means that any unnecessary delay would be unethical which normally means that there is a shorter preoperative time and, therefore, a shorter period of time to initiate rHuEPO treatment. In light of this, the treatment start date in these studies ranged from 4 to 10 days prior to surgery. A daily treatment regime was used in all study protocols. This, in part, may also have contributed to the heterogeneity of the results. <sup>[CE9]</sup> ~~The differences~~ with between the 2-two studies which showed a reduction of blood transfusion with ESA treatment is that the overall dosage of ESA administered over the treatment period was higher ~~→~~; one study had the dosage of ESA for 10 days daily and the other for 7 days daily preoperatively <sup>[24, 36, 43]</sup>.

## 4.2 Cardiac surgery

Despite all study protocols being different with regards to dosage, interval of dosing and length of time of treatment duration, they all showed a significant reduction in ABT in the treatment group as well as significant reduction in mean units of blood transfused.

## 4.3 Orthopaedic surgery

All these studies used relatively large sample sizes, ranging from 194 patients in one study to 695 patients in another 26. All showed a significant reduction in ABT in the ESA treatment group with several also showing a significant reduction in mean units of blood transfused in the ESA group. Three studies utilized two treatment groups with a lower and higher dose of ESA and all showed a significant reduction in ABT in both ESA treatment groups. Dosage regimes varied from single dose to daily and weekly regimes. Total duration of treatment ranged from one single dose to 4 weeks.

## 5. Safety of erythropoietin in perioperative use

The majority of studies involving the use of perioperative erythropoietin in patients undergoing surgery were targeted at efficacy which was reflected in the primary end points being reduction in ABT or change in other haematological parameters. Perioperative administration of ESAs to surgical patients is thought to have few adverse side effects, because it is a short-term treatment and contra-indicated for patients with co-morbidities that may predispose to these side-effects. These include uncontrolled arterial hypertension, previous acute myocardial infarction or stroke, unstable angina and severe carotid stenosis and are usually cited as exclusion criteria in these studies. Doses used in perioperative treatment tend to be lower than that which have been used conventionally in the past and also for a shorter duration of time. Due-Owing to the nature of expected surgical blood loss, the rise in Hb is not sustained.

Trials did report adverse effects in their sample populations including ~~deep venous thrombosis (DVT)~~, hypertension, infection, anastomotic breakdown and death. However, due to the low incidence of such events in the studies, no clear correlation with rHuEPO treatment could be made.

The rHuEPO was also withheld in patients who developed any of these adverse events during the study period. A concern for EPO use is the development of thrombotic complications associated with the higher Hcthaematoerit resulting from EPO therapy. Thrombotic and vascular events, including myocardial infarction, angina, deep vein thrombosis, superficial phlebitis, and peripheral

arterial thrombosis are associated with rapid increases in the Hbhaemoglobin level and the Hcthaematocrit and are of special concern in patients who are managed with EPO. None of the studies clearly stated whether anticoagulation prophylaxis was routinely used in their sample population.

The safety effects of rHuEPO have been more extensively studied in other non-surgical patient populations. Three large randomized controlled trials, the Normal Haematocrit Study [45], the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) Trial [46] and The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [47] [46] involved patients with anaemia and chronic kidney disease. These studies showed that the use of ESAs to achieve a higher Hbhaemoglobin level rather than partial correction of anaemia, which is the most common use of ESAs in this population, was associated with significantly increased adverse events including non fatal and fatal myocardial infarction, non-fatal and fatal stroke, death and thromboembolic events. In fact, the results were so conclusive that 2-two of the studies were halted early. In these studies, the dose of ESA was adjusted and increased if the target Hb was not achieved during monitoring. A review of these studies suggested that the increased incidence of adverse events may be related to the rapidity of increase in Hbhaemoglobin concentration and an overshoot of target concentration which may have been due to aggressive dosing. Another possibility was that these adverse effects may be due to some other consequence of ESAs such as trophic effects on vascular endothelial or smooth muscle cells [48].

Studies of the use of ESAs in critically ill patients showed that the proportion of patients who experienced thrombotic events was significantly greater with rHuEPO than placebo. However, the risk for-of thrombotic events was significantly increased in patients who did not receive heparin at baseline but not among patients who did receive heparin at baseline [18].

In a large multicentere trial of 680 surgical patients scheduled for elective spine surgery, blood transfusion and patient outcomes were compared for ESA and placebo-treated cohorts. These



patients did not receive anticoagulation prophylaxis for thrombotic adverse events. This study documented a higher incidence of deep vein thrombosis of 4.7% in the study group ~~was 4.7%~~ compared to 2.1% in control ~~2.1%~~, with the upper confidence limit for the between-group difference being 5.4%. This exceeded the predefined boundary of 4% that was required to demonstrate noninferiority <sup>49</sup>.

In a small-scale, double-blind, placebo-controlled study involving 30 healthy male volunteers who were given rHuEPO, there was a moderate stimulation of thrombopoiesis and this has been suggested to be increased by 15%. However, rHuEPO was also thought to cause increased platelet reactivity and a thrombogenic effect on the newly synthesized platelets, which may lead to increased thrombotic events <sup>12</sup>.

Hypertension is commonly associated with long-term rHuEPO therapy in patients with chronic renal failure. Although there seems to be a low risk of precipitating hypertension during short-course preoperative rHuEPO therapy, there have been reports of individual patients without prior history developing hypertension during such treatment. Despite the finding of hypertension in some of the patients in these studies, there was no clear correlation with rHuEPO therapy.

There is uncertainty about the potential side effects of erythropoietin analogues in anemic patients ~~people with anaemia~~ who are receiving treatment for cancer. The European Medicines Agency 'has recently reviewed the safety of erythropoietin analogues based on new data from both published and unpublished studies. These studies suggest an increased risk of serious cardiovascular complications in people with chronic renal failure and a possible effect on tumour progression in people with cancer' <sup>13</sup>. However, the risk/benefit of ESAs has recently been questioned based ~~upon~~ individual reports and meta-analyses showing that these agents are associated with an increased risk of mortality when chronically administered to patients with advanced/metastatic cancers <sup>50</sup>. Erythropoietin receptors are found on several malignant lines and can increase tumour recurrence rates.

Although the positive short-term effects of ESA therapy ~~with ESAs~~ on the correction of anaemia and avoidance of blood transfusions are well documented, few data are available on possible effects on the course of underlying disease, particularly since ESAs can exert additional biological effects including interference with the signal transduction cascade of cytokines.

## 6. Conclusions

Minimizing ~~allogeneic blood transfusion~~ ABT should be a high priority of any health-care delivery system. Transfusions associated with perioperative care represent a significant proportion of blood consumed. The concept of patient blood management has recently been described and was adopted by the World Health Organization in 2010 as a principle to improve transfusion safety. It refers to pre-empting and significantly reducing the need for transfusion by addressing anaemia, blood loss and hypoxia as modifiable risk factors. It comprises three main factors: detection and correction of preoperative anaemia, minimizing perioperative blood loss and optimizing the patient's physiological tolerance to anaemia [50]. It can play a significant role in negating preoperative anaemia and augmenting the quantity of blood available for autologous transfusion.

The effect of ESAs on transfusion requirements in cancer surgery patients remains uncertain, although, in patients who underwent orthopaedic surgery, treatment with preoperative ESA reduced both the use and rate of blood transfusion. It is clear that the use of perioperative rHuEPO does reduce the number of transfusions, reduce the mean number of transfusions given, increase the reticulocyte count and increase Hbhaemoglobin levels. At present, there is no clear optimal strategy with respect to dose, timing and length of treatment. The subcutaneous s.c. route is commonly used and has pharmacokinetic advantages. Perioperative rHuEPO therapy seems to be associated with a low incidence of complications, although larger studies are necessary to define this more clearly. There is an apparent risk of deep vein thrombosis but the risk can be ameliorated with the judicious use of anticoagulation.

Despite being theoretically attractive, the uptake of perioperative rHuEPO use has been slow. One reason for the limited use of preoperative rHuEPO in clinical practice may be the impracticality of the dosing schedule as recommended by efficacy trials, particularly with a required lead-time of 4 weeks. Another reason may be the high-cost of the recommended dosage. Complications from ~~ABT~~allogeneic blood transfusion can be serious and expensive but are not necessarily linearly related to the numbers of units transfused and, consequently, the cost savings gained from averting a disaster are difficult to quantify. Other effects such as immune suppression are even less tangible. The 'true' cost-effectiveness of EPO treatment is thus difficult to calculate and may be a hindrance to more widespread adoption.

## 7. Expert opinion

There is evidence that the perioperative use of ESAs can reduce the need for ~~ABT~~allogeneic blood transfusions in patients undergoing major surgery with ~~high~~ anticipated high blood loss. With the current drive to improve transfusion safety by modifying risk factors such as anaemia, blood loss and hypoxia, the targeting of anaemic patients preoperatively and the use of ESAs to stimulate erythropoiesis have been shown to have beneficial effects. The increase in haematological parameters may improve a patient's status in order to optimise post-operative rehabilitation, which can in turn lead to reduced hospital stay and improved quality of life.

Currently, the use of perioperative ESAs in surgery with anticipated high blood loss does not appear to be widely adopted. While the evidence exists for the use of rHuEPO in the perioperative setting, it has yet to be quantified whether other types of ESAs may also be effective. Development ~~in~~ of the newer ESAs with their more favourable pharmacokinetic profiles may mean decreased frequency of administration and may therefore improve the practicalities of incorporating ESAs into a perioperative programme.

Many of the studies were in small numbers of patients and it is difficult to adequately assess efficacy as an end-point. Safety of ESAs have mainly come from the large-scale studies in anaemic

patients with chronic renal disease which have shown an increased risk of non-fatal and fatal myocardial infarction, non-fatal and fatal stroke, death and thromboembolic events. It is unclear though whether these results can be extrapolated to the perioperative population. There are many differences between these ~~2~~-two groups of patients; the higher levels of Hb are not maintained as significant blood loss is expected intraoperatively in the perioperative group and the duration ~~is~~-of treatment is much shorter with much lower cumulative doses. The elective surgical population will also have a better functional and physiological baseline.

Well-designed prospective ~~randomized controlled trial~~RCTs on a larger scale are needed to address dose, type of ESA, timing and duration of administration in order for optimal dosing strategies to be formulated. The adverse event reporting could also be more accurate.

Once an optimal dosing strategy can be agreed, it would be useful to undertake cost-effectiveness studies; there are not only the costs associated with the treatment drug itself, ~~but also there are~~ administration and screening costs, but these may be ameliorated by the cost savings of reduction in hospital stay as well as improvement in quality of life.

An important area for future research may be to explore further the pleiotropic effects of ESAs as well as to investigate the effects of ESAs at the cellular level as possible mechanisms to exert their adverse effects.

Given the awareness of risks and complications associated with ~~ABT~~allogeneic blood transfusions, the use of perioperative ESA in surgery with anticipated high blood loss, is an important consideration.

#### Article highlights.

Benefits of perioperative ~~erythropoiesis stimulating agents~~ (ESAs) include an increase in ~~Hct~~haematocrit and reticulocyte counts which lead to a reduction in ~~ABT~~allogeneic blood transfusions.

Reduction in ~~ABT~~allogeneic blood transfusion has~~ve~~ been consistently shown in randomized trials of patients undergoing orthopaedic and cardiac surgery.

Use of perioperative ESAs in cancer patients has~~ve~~ not consistently demonstrated a reduction in ~~ABT~~allogeneic blood transfusion use.

Iron deficiency can reduce the efficacy of ESAs.

The optimal dosing strategies for perioperative use have not yet been defined.

ESA use in chronic renal failure patients with anaemia have shown an increase in adverse events when aiming for normalization of Hb levels rather than partial correction.

Adverse events associated with short-term perioperative use have not yet been quantified.

This box summarizes key points contained in the article.

### Declaration of interest

The authors have no competing interests to declare [r10] and have received no funding in preparation of the manuscript.

Table 1. Summary of the clinic trials included in this review.

Type of surgery	Type of blinding	No. of patients	Start Hb	ESA used	Treatment duration prior to surgery	Total duration treatment	Administration frequency	Fe used	
Orthopaedic – bilateral knee replacements) [25]	Open	108	Hb > 10	EPO B s.c.	Once during surgery	Single dose	Single dose	iv. Fe sucrose	1 unit 69 g/l between
Orthopaedic – primary or revision hip [34]	Double	320	Hb 11 – 16	EPO s.c.	10 days	14 days	Daily	Oral Fe sulfate	Clinic practi volun intrac 9/dL opera
Orthopaedic – all elective major [26]	Open	695	Hb 10 – 13	EPO A s.c.	21 days	22 days	Weekly	Oral Fe	Hb <
Orthopaedic – major elective [35]	Double	200		EPO s.c. (3 groups)	10 days	15 days	Daily	Oral Fe	Discr surge 0.27
Orthopaedic – total hip arthroplasty [27]	Double	201	Hb 9.8 – 13.7	EPO A s.c. (3 gps)	4 weeks	4 weeks	Weekly	Oral Fe	Discr surge

Orthopaedic – knee and ankle [28]	Open	194	Hct < 42%	EPO B s.c.se (3 gps)	3 – 4 weeks	3 – 4 weeks	Weekly	Oral Fe	Discontinue surge Hb <
Cancer – GI gastrointestinal tract [32]	Double	63	Hb 8.5 – 13	EPO A s.c.se	7 days	14 days	Daily	iv-i.v. Fe	Hb <
Cancer – colorectal surgery [33]	Open	204	Hb 9 – 12	EPO A s.c.se (3 gps)	10 days	12 days	Daily	Oral Fe	Period loss > heart Other mL. Hb, 1 poor featur g/dL
Cancer – colorectal [29]	Double	30	Hb 9 – 13	EPO s.c.se	10 days	13 days	Every 2 days	Oral Fe	≤ 9 g
Cancer – right hemicolectomy [30]	Double	109	Hb 8.5 – 13.5	EPO B s.c.se	5 – 10 days	10 – 15 days	Daily	Oral Fe	Hb <
Cancer – colorectal [31]	Double	81	Hb <= 8.5	EPO A s.c.se	4 days	8 days	Daily	Oral Fe	Discontinue anaes
Cardiac – valvular [24]	Single	74	Hb < 12 F and Hb < 13	EPO iv	16 – 24 hr prior to surgery	Single dose	Single dose	iv-i.v. Fe sucrose	Hb < CPB after opera

Cardiac – off pump CABG 43	Single	320	M Hb < 14.5	EPO s.c.se	2 days	5 days	Daily	-	Hb <
Cardiac – open heart 36	Double	76	Hct < 0.45	EPO B i.v.	14 days	14 days	5 doses	Oral Fe sulfate	CPB: posto 8.5 g 0.26

ABT: Allogeneic blood transfusion; CABG: Coronary artery bypass graft; CPB: Cardiopulmonary bypass; EPO A: Epoetin- $\alpha$ -alfa; EPO B: Epoetin- $\beta$ -beta; ESA: Erythropoiesis-stimulating agents; Fe: Iron; Hb: Haemoglobin; Hct: Haemocrit; HD: High dose; i.v.: Intravenous; LD: Low dose; s.c.: Subcutaneous.

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