Journal of Blood Disorders & Transfusion - Open Access

Research Article
OPEN ACCESS Freely available online
doi:10.4172/2155-9864.1000101

Single Dose Preoperative Administration of Intravenous Iron Corrects Iron Deficiency Anaemia in Colorectal Cancer

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Abstract

Preoperative iron deficiency anaemia (IDA) is common and associated with poor postoperative outcomes. Standard treatment includes allogenic blood transfusion or oral iron supplementation, but new intravenous iron strategies have shown promise in the perioperative setting. We aim to assess the feasibility and effect of a single dose of intravenous iron in treating preoperative colorectal cancer related anaemia.

We performed an open labelled phase I uncontrolled trial. Patients with a diagnosis of colorectal cancer and biochemically proven IDA received intravenous iron a minimum of 14 days prior to surgery. Blood parameters including haemoglobin values were measured at pre-dose and preoperative time points.

Eight of the ten patients responded to intravenous iron supplementation with a mean preoperative rise in haemoglobin of 1.1 g/dl (p=0.036). Ferritin levels rose by a mean of 523.4ng/ml across the ten patients. No adverse events occurred in any of the trial patients.

This trial demonstrates that intravenous iron is both a feasible and effective treatment for IDA in anaemic colorectal cancer patients. However two patients did not respond to treatment, highlighting the need to identify biochemical markers which will accurately predict the underlying cause for anaemia and response to treatment.

Keywords: Anaemia; Intravenous; Iron; Colorectal; Cancer

Introduction

Preoperative iron deficiency anaemia (IDA) is common and is associated with increased need for allogenic blood transfusion and poor post operative outcomes [1,2]. Treatment of IDA is associated with a reduction in the need for blood transfusion in the perioperative period [3]. Treatment strategies include iron supplementation via either an enteral or parenteral route. The use of new intravenous formulations in the gynacological setting suggest that it may be as effective as oral iron but without the associated gastrointestinal side effects reported in some patients [4]. It has also been shown to be effective within a 14 day time period, suggesting that it could form a pragmatic part of an Enhanced Recovery after Surgery (ERAS) protocol while at the same time not delaying treatment targets. Intravenous iron has previously been shown to be effective in both solid organ and haematological malignancies, particularly when administered with erythropoeitic stimulating agents [5,6]. Repeat dosing of intravenous iron in colorectal cancer patients has been shown to be effective [7] but single dose administration that can form part of the preoperative work up has not been tested [8]. Patients suffering from colorectal malignancy are typically over fifty-five years of age, are commonly immunosuppressed due to the inflammatory nature of the cancer and may be undernourished. It may be more difficult for this group of patients to mount an erythropoeitic response in the face of supplemental iron therapy.

Furthermore, the type of anaemia manifest in colorectal cancer patients is typically assumed to be IDA however it is common for this group of patients to present with inflammatory related anaemia of chronic disease (ACD) [9]. The underlying cause of their anaemia is likely to dictate their response to treatment. The liver hormone hepcidin has recently been identified as central iron stores regulator [10] and it has been suggested that this may offer a more accurate representation of iron mobilisation from stores than current biochemical markers and could therefore predict response to treatment.

Aim

To assess the feasibility and effectiveness of a single dose of intravenous iron in treating preoperative colorectal cancer related anaemia.

Method

We performed an open labelled phase I uncontrolled trial, designed to determine the preoperative effect of intravenous iron. Ten patients with histologically proven colorectal cancer and biochemically diagnosed IDA were prospectively selected to receive preoperative Intravenous iron. IDA was defined as a haemoglobin (Hb)<13.0g/dL in males and a Hb<11.5g/dL in females, in combination with a serum ferritin level <20ng/ml, this was consistent with the local laboratory lower limit of normal range.

A minimum of 14 days prior to surgery each patient received a single administration of intravenous iron dextran (Cosmofer). Iron dosage was calculated using the manufacturer's established protocol based on Body Mass Index and baseline Hb measurement (max dose 1.5g). Haemoglobin and Ferritin measurements were recorded immediately prior to iron administration and on the day before operation. Patients initially received a 25mg test dose over 15

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Received August 21, 2010; **Accepted** October 01, 2010; **Published** October 03, 2010

Citation: Simpson JAD, Ng SL, Brookes MJ, Acheson AG, (2010) Single Dose Preoperative Administration of Intravenous Iron Corrects Iron Deficiency Anaemia in Colorectal Cancer. J Blood Disord Transfus 1:101. doi:10.4172/2155-9864.1000101

Patient	Baseline Haemoglobin (g/dL)	Preoperative Haemoglobin (g/dL)	Change in Haemoglobin (g/dL)	Dose of Cosmofer (mg)	Location of Tumour	Histopathology (TNM classification)	Length of Stay (days)	Perioperative transfusion rate (No. Of units)	30 day post-operative morbidity	30 day post-operative mortality
1	9.9	10.2	0.3	1295	Left colon	$T_2N_1M_0$	16	1	Respiratory acidosis and atrial flutter	No
2	7.1	10.4	3.3	1500	Transverse colon	$T_4N_2M_0$	13	2	N/A	No
3	9.7	12	2.3	1200	Right colon	$T_3N_0M_0$	6	0	N/A	No
4*	12.6	13.3	0.7	800	Rectum	$T_2N_1M_0$	10	0	N/A	No
5	11	10.4	-0.6	1300	Right colon	$T_4N_0M_0$	7	0	N/A	No
6	10	10.3	0.3	900	Right colon	$T_4N_2M_1$	6	1	N/A	No
7	12	12.7	0.7	800	Right colon	$T_3N_0M_0$	6	0	N/A	No
8	12.1	11.8	-0.3	900	Transverse colon	TVA with high grade dysplasia	13	0	Multi-organ failure secondary to SBO	Yes
9	8.1	9.6	1.5	1360	Rectum	$T_{is}N_0M_0$	1	0	N/A	No
10	8.6	11.4	2.8	880	Right colon	$T_4N_0M_0$	11	1	N/A	No
Mean	10.1	11.2	1.1	1093.5			8.9			

Table 1: Patient baseline, preoperative and change in haemoglobin values, Intravenous iron dose, Location and stage of tumour, Length of hospital stay, Transfusion rate, 30 day postoperative morbidity and mortality. TVA (Tubulovillous adenoma), SBO (Small bowel obstruction), *denotes patient receiving preoperative chemotherapy.

minutes, following this the infusion was stopped and temperature, blood pressure and pulse were recorded every 15 minutes for the next 60 minutes. If no adverse reaction was detected the remaining infusion commenced at a rate of 200mg over 60 minutes and was then increased to 300mg/hour. Temperature, blood pressure and pulse were recorded every 30 minutes. The intravenous cannula was flushed with normal saline prior to removal. The primary outcome measure was preoperative change in haemoglobin concentration, secondary outcomes included length of hospital stay, transfusion requirements and postoperative morbidity and mortality. Wilcoxon signed rank test was to used to compare baseline and preoperative haemoglobin values.

Results

Nine males and one female were recruited with a mean age of 73.5 (SD +/- 9.1) years. The calculated dose of intravenous iron, tumour stage and location, and primary and secondary endpoints are detailed in Table 1. Only one patient received preoperative chemoradiotherapy and none of the patients required a preoperative blood transfusion following administration of intravenous iron.

The mean baseline Haemoglobin was 10.1g/dL (range 7.1-12.6g/dL). Following IV iron administration a significant mean rise of 1.1g/dL (range -0.8-3.8g/dL) in Haemoglobin was seen over an average time period of 27 days (p=0.0359). Resulting in a mean preoperative Hb of 11.2g/dL (range 9.6-13.3g/dL) (Figure 1a). Out of the ten patients, two did not respond to intravenous iron. Patients 5 and 8 showed a drop in haemoglobin level over the course of treatment by 0.6 and 0.3g/dL respectively. Ferritin levels rose by a mean of 523.4ng/ml across the ten patients as illustrated in (Figure 1b).

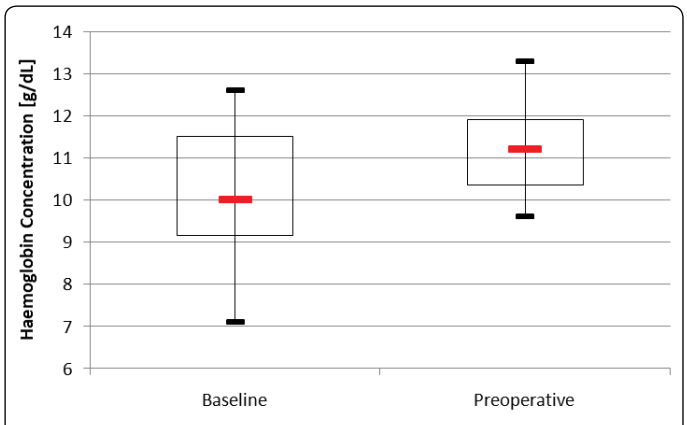

Figure 1a: A box plot demonstrating minimum, maximum, median and inter-quartile values for haemoglobin concentration as measured before dosing with intravenous iron and immediately preoperatively.

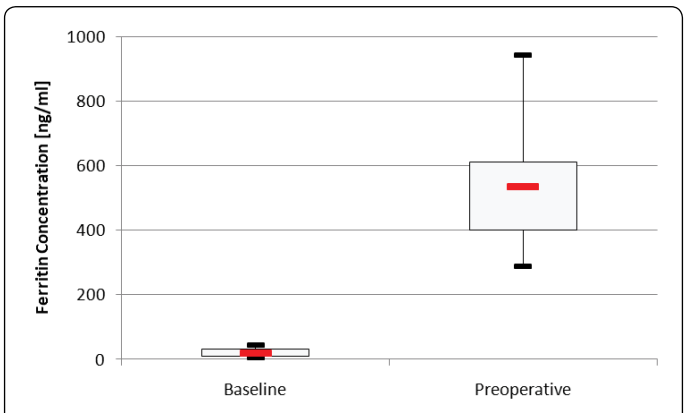

Figure 1b: A box plot demonstrating minimum, maximum, median and inter-quartile values for serum ferritin concentrations as measured before dosing with intravenous iron and immediately preoperatively.

Comparison of the baseline haemoglobin with the respective change in haemoglobin post dosing for each patient demonstrates an inverse relationship (Figure 1c). No adverse events occurred in any of the trial patients as a result of receiving intravenous iron. The median length of postoperative hospital stay was 8.5 days and a total of five units of red blood cells were transfused in four of the ten patients. All transfusion products were given intraoperatively. None of the patients received alternative transfusion products or erythropoietin supplementation. Two patients developed postoperative complications: one experienced a respiratory acidosis and associated atrial flutter but made a full recovery prior to discharge. The second patient developed multi organ failure following acute onset small bowel obstruction and died on the thirteenth postoperative day.

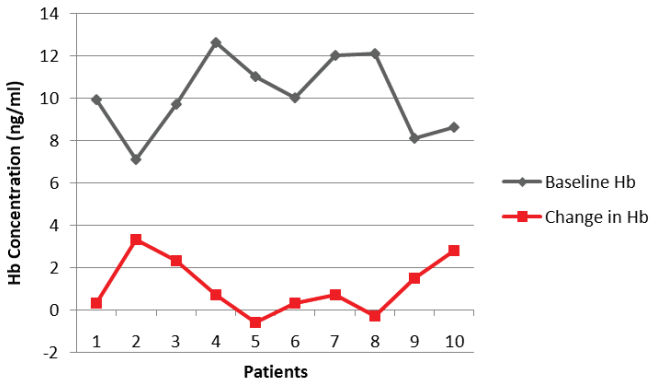

Figure 1c: The inverse relationship between baseline Hb and change in Hb values is clearly illustrated by the mirror image generated when the two data sets are plotted in this line graph.

Discussion

This open label prospective study demonstrates that preoperative single dose administration of intravenous iron is both feasible and efficacious in anaemic colorectal cancer patients. The use of intravenous iron produced a mean 1.1g rise in haemoglobin over two preoperative weeks. These results support those previously reported by Munoz et al who demonstrated improvement in haemoglobin concentration in 30 colorectal cancer patients receiving preoperative iron sucrose (200 mg/ twice a week; 4-8 sessions) [7]. In contrast [11] concluded, that there is no support for intravenous iron sucrose as a preoperative adjunct in colorectal adenocarcinoma to increase haemoglobin levels. However, concerns regarding the study design and the ability to justify these conclusions have been raised [12]. It is crucial to establish the haemoglobin and iron status in order to determine the efficacy of intravenous iron. In Edwards study only nine patients in each group had a below normal haemoglobin, and in these patients receiving intravenous iron the mean ferritin was 100.5ng/ml with a mean transferrin saturation of 11.0%. The parameters listed in the iron intervention group represent a phenotype more consistent with functional iron deficiency or reticuloendothelial blockade [3]. Current British Society of Gastroenterology guidelines recommend using a ferritin of <50ng/ml to define iron deficiency in the face of co-existing disease, [13] thus suggesting that very few of the patients recruited were actually iron deficient and unlikely to respond to any form of iron supplementation. Furthermore, recommendation for dosing intravenous iron sucrose is based on individual patient's BMI and differential between actual and target haemoglobin values rather than same dose administration, as used in this study. The study underestimates the importance of adequately identifying iron deficiency, which is likely to confound results.

Interestingly the change in haemoglobin concentration following administration of intravenous iron was inversely proportional to the starting concentration. Although we did not measure erythropoietin levels during the study this may in part explain the observed relationship. De Klerk et al. [14] have previously demonstrated an inverse relationship between Hb levels and serum erythropoietin titres in an *in vitro* model of anaemia. Furthermore, a number of studies have demonstrated improved response in Hb concentration when intravenous iron and erythropoietin are given in combination compared to when either is given alone, particularly in chemotherapy and chronic renal disease related anaemia [6,15]. Therefore those patients with more severe IDA are likely to have the highest serum erythropoietin levels, following administration of intravenous iron this leads to improved utilisation of these building blocks by the bone marrow and ultimately a greater rise in Hb concentration.

However, a recent Cochrane review of the pre and peri-operative use of erythropoietin supplementation in colorectal cancer patients concluded that there was no robust evidence to support its use in this group and that in particular it had no effect on reducing allogenic blood transfusion [16]. Although this systematic review did not highlight an increase in mortality or thrombotic events in the intervention groups, there have been a number of trials that have reported an increase in thrombotic events, decreased survival and poor tumour control following administration of erythropoeisis stimulating agents in cancer patients, particularly if it is given in conjunction with chemotherapy regimens [17,18].

It is also important to note that two patients in this trial failed to respond to intravenous iron therapy. Excessive ongoing blood loss was considered because this may have blunted the effect of intravenous iron. Rectal blood loss was not directly quantified but clinical review in the pre-operative period, by both the study team and the patient's medical team, did not find excessive per rectal bleeding in either patient. This raises the possibility that they may be suffering from a functional iron deficiency where the problem is not reduced iron stores but the inability to make available and utilise iron. The relatively recent discovery of the liver hormone, hepcidin, and its role in iron homeostasis may lead to the development of a chemical biomarker which will allow clinicians to predict response to iron therapy in the future. Early studies have indicated a relationship between hepcidin expression and anaemia associated with both solid organ and haematological tumours [19,20], but a connection between hepcidin expression and inflammatory induced anaemia in colorectal cancer is yet to be established. However, it has been suggested that hepcidin has a role to play in the oncogenic signalling pathways of colorectal cancer [21].

It is clear that preoperative anaemia is associated with the need for allogenic blood transfusion and poor post operative outcomes [1,2]. Although this study confirms that intravenous iron did not result in any adverse events and could be used to treat preoperative anaemia in this small group of non-symptomatic colorectal cancer patients, whether this can improve postoperative complications or reduce the need for peri-operative blood transfusion rates remain to be seen. Indeed we hope that this study informs the design of larger randomised controlled trials to determine the effect of intravenous iron on postoperative endpoints including length of stay, postoperative mortality and morbidity.

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