Original Article

Avoiding unnecessary blood transfusions in women with profound anaemia

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Background: Blood transfusions may be associated with risks and the risk: benefit ratio is not always clear, even in the setting of haemorrhage.

Aims: To describe the management practices and outcomes in women with profound anaemia who refused blood transfusion.

Materials and Methods: Retrospective analysis over a 10-year time frame of severely anaemic women (Hb <50 g/L) with benign conditions who had requested not to receive a blood transfusion. Demographic data, clinical presentation, anaemia management practice and serious adverse events were collected from the medical record charts. Women were analysed in two groups: a gynaecologic (Gyn) and an obstetric (Ob) population.

Results: A total of 19 women (12 Gyn and 7 Ob) met the inclusion criteria with a mean age of 35.8 ± 10.2 years. The lowest mean Hb concentration was 41.3 ± 9.7 g/L (Gyn Group) and 36.0 ± 8.9 g/L (Ob Group) which increased, to 67.3 ± 14.3 g/L and 73.1 ± 6.9 g/L, respectively, by the time of hospital discharge. Anaemia management initially addressed the underlying etiology and was followed by intravenous iron (all cases) plus erythropoiesis stimulating agents, haemocoagulase and/or fluids. The mean length of hospital stay was 10.5 ± 4.4 and 13.7 ± 4.1 days for the Gyn and Ob groups, respectively. No deaths or other serious complications occurred.

Conclusion: These findings suggest that young and otherwise healthy women can tolerate profound anaemia (Hb <50 g/L) permitting corrective strategies to be successfully implemented without the need for blood transfusion.

Key words: anaemia, patient blood management, erythropoiesis stimulating agent, intravenous iron.

Introduction

Anaemia is an independent risk factor for adverse outcomes in patients undergoing cardiac and non-cardiac surgery.[1–3] Recent experimental studies have demonstrated that acute haemodilutional anaemia can result in a reduction in renal, cardiac and brain tissue oxygen, supporting the hypothesis that tissue hypoxia may be a significant mechanism of anaemia-induced organ injury.[4,5] Additionally, clinical studies have demonstrated that the risk of mortality and/or morbidity rises as the postoperative blood counts falls.[6,7]

For optimal patient blood management (PBM), the guiding principle is minimisation of blood loss during surgical procedures and optimisation of haemoglobin and haemopoiteic factors pre-operatively. Additionally, blood transfusions should only be prescribed when the clinician is satisfied that it is likely to offer a worthwhile benefit or that the risk of not transfusing is likely to be greater than the risk of transfusing. Whilst decision-making appears straightforward when a major haemorrhage is present, when bleeding is associated with profound thrombocytopenia or when disabling anaemia is associated with cancer chemotherapy the evidence base for these recommendations is incomplete or limited, and there are no rigorous data to guide the appropriate transfusion trigger. However, even today, transfusions are often the first intervention when Hb falls below 100 g/L in many operating rooms.[8]

Transfusions may be controversial, especially for Jehovah's Witnesses patients due to their religious beliefs, which do not permit the use of allergenic blood and related products. Denton Cooley demonstrated that open-heart surgery could be performed successfully without an allogeneic blood transfusion, illustrating that transfusions may not always be necessary and that tolerance to anaemia may be higher than often believed.[9]

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Cooley's success encouraged others to treat Jehovah's Witnesses in similar ways and stimulated the creation of bloodless surgery centres which started to use alternative management strategies to manage these patients.[10] Such strategies included meticulous surgical procedures and the use of intravenous (IV) iron and exogenous erythropoietin stimulating agents (ESAs) – both of which have been demonstrated to minimise transfusion requirements.[11,12]

At Soonchunhyang (SCH) University Seoul Hospital, The Bloodless Centre was established in 2000 to manage patients wishing to avoid blood transfusions. The SCH Bloodless Centre receives an average of 630 patient visits per year, 94% of whom are Jehovah's Witnesses. More than 2600 bloodless surgeries have been performed in this centre since its establishment and a total of 645 surgeries and 422 vaginal deliveries were performed in the Department of Obstetrics and Gynaecology between 2003 and 2012.

Even though blood transfusion has life-saving benefits in major haemorrhage, evidence of the negative impact of blood transfusions is increasing.[13–15] We conducted this retrospective analysis to offer insight into the impact and tolerance for severe anaemia.

Materials and Methods

All women admitted to the inpatient Obstetric and Gynaecologic Clinic of the SCH bloodless Centre between March 2003 and December 2012 were the basis of this retrospective study. Prior to any data collection, our local institutional ethics committee approved the conduct of the study.

All women with benign conditions, Hb < 50 g/L and refusing a blood transfusion, for any reason, formed in the study dataset. Data for eligible patients were then extracted to a case report form and included demographic details, clinical presentation, medical or surgical interventions, anaemia management strategies and all recorded adverse events and case outcome. The mean value and standard deviation for age, nadir Hb, Hb on discharge and length of hospital stay were calculated, and all statistics were performed using the Excel STD program.

The nadir Hb was defined as the lowest value recorded after admission, and the length of hospital stay was defined as the number of days from admission to discharge irrespective of the reason for admission. Whilst usually observed on the second or third day postoperatively, profound anaemia may have been observed on any day during the admission. The presenting diagnosis was considered as the main cause of anaemia for this analysis.

Surgical management or intervention was categorised as either prior to anaemia management or post-anaemia management (depending whether anaemia was corrected before intervention or post). Women were divided into two cohorts, those admitted for gynaecologic reasons (Gyn Group) or pregnant women (Ob Group).

Transfusion alternative management was grouped by haematinic agents including IV iron, recombinant human erythropoietin (rhEPO) or darbepoetin alpha (DBP), haemocoagulase and/or gonadotropin releasing hormone agonist (GnRH agonist).

Medical management was performed according to our standardised protocol for severely anaemic patients. This includes the use of IV iron and subcutaneous rhEPO (200 IU/kg, three times a week or 40 000 IU, once a week) or DBP (240 μg, once a week). Also, based on individual cases, haemocoagulase was used to control bleeding. Further, a GnRH agonist was used to suppress oestrogen production if assessed as necessary by the treating clinician.

Results

A total of 19 women who had Hb levels <50 g/L at any time during admission were included in this analysis. Of these, 12 were admitted due to gynaecologic (Gyn) reasons and seven due to obstetric (Ob) reasons. The mean age was 35.8 ± 10.2 years old and all denied blood transfusion due to religious reasons.

The lowest mean lowest Hb during the observation period was 39.3 ± 9.5 g/L and increased to 69.5 ± 12.2 g/L on discharge. All women received IV iron (mean total dose 2195 ± 1218 mg iron), 68% received rhEPO (mean total dose 70 000 ± 51 186 IU) and 16% received DBP (mean total dose 1160 ± 1316 μg). Eight women within this group presented with heavy vaginal bleeding; five received medical treatment to normalise anaemia followed by correction of the underlying cause, two required immediate intervention followed by anaemia management and the last case required only anaemia correction. The additional three women in this cohort developed profound anaemia due to postoperative bleeding. Anaemia management included IV iron in all cases and concomitant ESA therapy in nine of the 12 cases (75%). No woman receive a blood transfusion. The mean discharge Hb was 67.3 ± 14.3 g/L (51.0–100.0 g/L), and the mean hospital stay was 10.5 ± 4.4 days (5–21 days). Data are presented in full, by case, in Table 1.

For the second cohort, who were admitted for obstetric reasons, the mean age was 32.4 ± 5.9 (23–41) years and the lowest mean Hb concentration was 36.0 ± 8.9 g/L (26.0–48.0 g/L). Of the seven women in this group, two were admitted after vaginal delivery with one requiring a uterine artery embolisation and the other a primary repair of a vaginal laceration. The other five women had anaemia post caesarean section although only one required an emergency hysterectomy. Anaemia management included IV iron and ESA in all cases. No women received a blood transfusion. At discharge, the mean Hb was 73.1 ± 6.9 g/L (62.0–82.0 g/L) and the mean length of hospital stay was 13.7 ± 4.1 (8–20) days. Data for all women in this cohort are presented in Table 2.

Table 1 Clinical presentation and management of the gynaecology cases

Case number	Age (years)	Diagnosis	Lowest Hb (g/L)	Hospital stay (days)	Medical treatment	Other treatment
1	49	Adenomyosis	17	21	5100 mg IV iron, 2640 μg DBP, GnRH-a	TLH†
2	51	Endometrial hyperplasia	47	13	1400 mg IV iron, 120 μg DBP	D&C Progestogen-releasing IUD†
3	47	Submucosal myoma	47	10	3000 mg IV iron, 56 000 IU EPO	Hysteroscopic myomectomy†
4	44	Endometrial hyperplasia	46	10	2000 mg IV iron, 40 000 IU EPO	D&C†
5	38	Cervical myoma	44	12	2200 mg IV iron, 56 000 IU EPO	Hysteroscopic myomectomy†
6	46	Uterine myoma	43	5	1200 mg IV iron	UAE, D&C
7	24	Vaginal laceration	27	15	1200 mg IV iron, 120 000 IU EPO	Vaginal repair
8	15	Dysfunctional uterine bleeding	43	6	800 mg IV iron	
9	42	Postoperative (myomectomy) bleeding	49	8	1800 mg IV iron, 30 000 IU EPO	UAE
10	42	Postoperative (hysterectomy) bleeding	46	9	1800 mg IV iron, 40 000 IU EPO	
11	36	Postoperative (myomectomy) bleeding	47	10	1800 mg IV iron	
12	20	Ovarian cyst rupture	49	7	1300 mg IV iron, 56 000 IU EPO	Laparoscopic cystectomy

†The operation or procedure was performed post correction of anaemia.
D&C, dilatation and curettage; DBP, darbepoetin alpha; EPO, erythropoietin; IUD, intrauterine device; IV iron, intravenous iron; TLH, total laparoscopic hysterectomy; UAE, uterine artery embolisation.

Signs and symptoms of acute anaemia including hypotension, dizziness and sinus tachycardia were observed in all cases. However, there were no deaths or other serious complications of profound anaemia such as myocardial infarction, congestive heart failure, arrhythmia (except sinus tachycardia) or infection. No case of Sheehan's syndrome was observed within the obstetric group.

All women were discharged in a stable condition and follow-up visits were performed after at least two weeks. At this visit, all women reported symptomatic improvement and the Hb level was >100 g/L in the 11 women where repeat haematological assessments were conducted. For the other eight women, although no repeat Hb was available, they did not experience additional complications or require additional medical review.

Discussion

Blood-borne illnesses and accumulating cumulating data on the negative consequences of transfusions have prompted consideration by the medical profession to minimise or avoid unnecessary blood transfusions. The number of units transfused should also be carefully assessed as increasing mortality rates correlate with the number of RBC units transfused.[16] Acute reactions pose significant issues secondary to administrative errors and the UK surveillance system recently reported an adverse event rate attributed to incorrect transfusion that was 10 times higher than the rate attributed to infectious disease transmission.[17,18]

Another important consideration in today's society is cost. While blood has been historically considered 'cheap' or even free, studies reviewing all of the true costs suggest quite the opposite[19], with a mean cost of administering a single unit of RBCs within the hospital valued as high as AUD700.[20]

Jehovah's Witnesses are a group who refuse to accept blood transfusions and hence this group of patients have required the development of transfusion avoidance practices. In 2003, Varela *et al.*[21] conducted a retrospective cohort study of 556 patients and concluded that Jehovah's Witnesses do not have a significantly increased risk of death after major trauma (although not receiving transfusions) when compared with other religious groups. Several other studies have supported this finding when patients undergo cardiac, neurologic, urologic, orthopaedic, and major gynaecologic and obstetric surgery, even after controlling for preoperative factors.[22–28]

This study describes our experience over a 10-year period for the management of profound anaemia in otherwise healthy women who refused transfusion. We noted that severe anaemia, as low as 50 g/L, could be tolerated and with the appropriate intervention to cease blood loss combined with IV iron and, in most cases ESA therapy, we were able to provide the women the building blocks to correct their anaemia using physiological processes. This was achieved without

Table 2 Clinical presentation and management of seven obstetric women

Case number	Age (years)	Diagnosis	Lowest Hb (g/L)	Hospital stay (days)	Medical treatment	Other treatment
1	30	Postpartum bleeding -uterine atony-	27	20	4400 mg IV iron, 720 μg DBP	UAE
2	23	Postpartum bleeding –laceration-	32	14	800 mg IV iron, 5600 IU EPO	Cervical and vaginal repair
3	32	Postpartum(CS) bleeding:uterine atony-	39	12	2200 mg IV iron, 72 000 IU EPO	TAH
4	33	Postpartum bleeding CS for placenta praevia	26	17	2600 mg IV iron, 224 000 IU EPO	
5	41	Postpartum(CS) bleeding CS for placenta praevia	33	15	4300 mg IV iron, 56 000 IU EPO	
6	30	Postpartum(CS) bleeding CS for placenta praevia	48	10	2200 mg IV iron, 44 000 IU EPO	
7	38	Postpartum(CS) bleeding CS for placenta praevia/accreta	47	8	1600 mg IV iron, 64 000 IU EPO	

CS, caesarean section; DBP, darbepoetin alpha; EPO, erythropoietin; IV iron, intravenous iron; TAH, total abdominal hysterectomy; UAE, uterine artery embolisation.

jeopardising the woman's health, as demonstrated in the clinical outcomes with all women remaining well and alive after management while death or other serious complications, such as myocardial infarction, congestive heart failure, arrhythmia except sinus tachycardia, infection and/or Sheehan's syndrome were absent.

The data regarding the level of anaemia to which physiological changes can compensate are inconclusive. Some studies suggest that cardiac output rises when the Hb level is in the range of 90–100 g/L,[29] while other data suggest that the Hb level must be below 70 or 80 g/L for these changes to occur.[30,31] Compensation likely begins at different Hb levels depending on age, comorbidity, volume status and medication.[32]

In our study, the women received adequate fluid, haemocoagulase, ESAs and IV iron immediately on diagnosis of profound anaemia to initiate prompt correction without blood transfusion. ESAs administration might have contributed to more rapid improvement of key haematological parameters (from day 2) with an approximate 30 g/L increase in Hb concentration by 12 days and iron administration likely permitted effective erythropoiesis and contributed to the effectiveness of rhEPO therapy.[33–35]

Although the use of ESAs therapy has been reported to have potential adverse effects including thromboembolic and cardiovascular events,[36,37] we did not observe any significant adverse events using ESAs. This is likely because the Hb values were not 'pushed' to supra-physiological levels, and use was in women with their iron stores appropriately replenished enabling erythropoiesis. These data support rhEPO has a role in the treatment of critically ill Jehovah's Witnesses experiencing significant blood loss as an alternative to blood product administration.[35,38,39]

Haemocoagulase has been prescribed widely in Korea for patients with acute bleeding, and every woman in this study was given intravenous haemocoagulase to help control bleeding.

Haemocoagulase is a mixture of purified enzymes isolated from the venom of Bothrops jaracaca. Haemocoagulase has two different enzymatic activities, one which promotes blood coagulation by converting prothrombin to thrombin and the other which causes a direct transformation of fibrinogen to fibrin monomer.[40,41] All women in this study were administered intravenous haemocoagulase to assist in achieving haemostasis.

The development of alternative red blood cell substitutes to aid in the management may also offer additional alternatives to transfusions in the future, potentially avoiding some of the issues related directly to the allogeneic nature of transfusions.

Finally, it is important to acknowledge that the women in this study were relatively young (mean age 37.8 years old) and healthy without any other co-morbid diseases. Therefore, wider extrapolation of these approaches to other patient groups will require further consideration.

In conclusion, our findings support that conservative management without blood transfusions is feasible post diagnosis of 'profound anaemia', even when concentrations fall below 50 g/L, in relatively young and otherwise healthy obstetric and gynaecologic cases. The period of tolerability for this anaemic state permits correction using IV iron (as the fundamental building block of erythropoiesis), short-term ESA use (to further stimulate production of RBC's), haemocoagulase (to promote coagulation) and fluids. With this strategy, it is possible to enable rapid and sustained improvement in

haematological parameters without serious morbidity related to hypoxia in such women.

Large randomised studies are warranted to confirm these results and support that the above practices may also be applied to other patient groups.

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