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A cohort investigation of anaemia, treatment and the use of allogeneic blood transfusion in colorectal cancer surgery

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HIGHLIGHTS

- Exclusion of anaemia is underperformed during initial management of colorectal cancer.
- Anaemia is more frequently associated with larger diameter and right sided tumours.
- When identified, preoperative anaemia is undertreated.
- Reduction in severity of anaemia at surgery is associated with reduced transfusion requirements.

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ABSTRACT

Introduction: Preoperative identification and treatment of anaemia is advocated as part of Patient Blood Management due to the association of adverse outcome with the perioperative use of blood transfusion. This study aimed to establish the rate of anaemia identification, treatment and implications of this preoperative anaemia on ARBT use.

Methods: All patients who underwent elective surgery for colorectal cancer over 18 months at a single Tertiary Centre were reviewed. Electronic databases and patient casenotes were reviewed to yield required data.

Results: Complete data was available on 201 patients. 67% (n = 135) had haemoglobin tested at presentation. There was an inverse correlation between tumour size and initial haemoglobin ($P < 0.01$, $Rs = -0.3$). Initial haemoglobin levels were significantly lower in patients with right colonic tumours ($P < 0.01$). Patients who were anaemic preoperatively received a mean 0.91 units (95%CI 0–0.7) per patient which was significantly higher than non-anaemic patients (0.3 units [95%CI 0–1.3], $P < 0.01$). For every 1 g/dl preoperative haemoglobin increase, the likelihood of transfusion was reduced by approximately 40% (OR 0.57 [95%CI 0.458–0.708], $P < 0.01$). Laparoscopic surgery was associated with fewer anaemic patients transfused ($P < 0.01$).

Conclusion: Haemoglobin levels should be routinely checked at diagnosis of colorectal cancer, particularly those with large or right sided lesions. Early identification of anaemia allows initiation of treatment which may reduce transfusion risk even with modest haemoglobin rises. The correct treatment of this anaemia needs to be established.

1. Introduction

The administration of allogeneic red blood cell transfusions has been demonstrated to adversely impact upon host immune function [1]. Consequently, the perioperative use of allogeneic red blood cell transfusions in colorectal cancer surgery has been associated with adverse outcomes in the both the short term, with increased postoperative morbidity and mortality, and also longer term with

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impaired oncological outcomes [2].

The model of Patient Blood Management advocates instigation of measures to mitigate this need for ARBT [3]. These interventions can be considered in either the preoperative, intraoperative of postoperative phases of surgery and the preoperative management of anaemia has been highlighted as one particular area of focus [3]. This is particularly relevant in the context of CRC surgery due to the frequent association of anaemia with this disease [4].

Advances in CRC management such as the Bowel Cancer Screening Programme (BCSP) could reduce the prevalence of anaemia at diagnosis by identifying malignancy at an earlier stage [5]. Similarly, laparoscopic surgery (LS) may reduce the overall need for ARBT by minimising blood loss [6].

In light of these changes in current practice, this study aimed to identify the prevalence of anaemia and changes in haemoglobin levels across the course of surgical treatment of CRC in a National laparoscopic surgery training centre with an established BCSP. Furthermore, the study aimed to establish the rate of treatment and implications of this preoperative anaemia on ARBT use.

2. Methods

Patients who underwent elective surgery for resection of a primary colonic or rectal tumour between 1st January 2011 and 31st May 2012 were identified from the local National Bowel Cancer Audit Programme (NBOCAP) registry.

Two-hundred and twenty seven patients were considered for analysis. Sixteen were excluded for incomplete records, 6 for having undergone emergency surgery, and a further 4 for having had benign disease. Two-hundred and one patients were thus included in analysis.

Data was retrieved from patient casenotes and hospital electronic records and was reviewed at several time points. The first out-patients appointment (OPA) which prompted investigation resulting in the registered operation was defined as the presentation OPA. Blood test values taken at that appointment or on referral were used as the *"diagnosis"* value. The WHO definition of anaemia (Males, <13 g/dL; Females, <12 g/dL) was applied to all haemoglobin (HB) levels [7].

The second time point evaluated was the preadmission clinic (PAC) appointment when the patient was assessed for surgery. This occurred within the 7–14 days preceding surgery. Blood test values acquired at this visit were used clinically to reflect day of surgery values, and were regarded similarly in this review.

"Initial" HB levels were defined as the earliest available HB level, i.e. the "diagnosis" value when tested, and the PAC result when this was not available.

Tumour details were recorded as documented in the final histopathology report. The site of the tumour was classified as either "Right" (from caecum to distal transverse colon) or "Left" (from splenic flexure to anorectum). Tumour stage was noted per modified Dukes' [8] and TNM classifications [9]. Tumour size was recorded as the maximum tumour diameter in millimetres.

Details were obtained from the operation note, including the American Society of Anesthesiology grade (ASA), operative approach and description including documented blood loss. Blood transfusions including date and volume of administration were delineated from electronic transfusion logs and in patient charts and recorded from OPA until postoperative discharge. The transfusion policy employed by the clinical teams included a "trigger" of 7 g/dL in healthy individuals, or a target closer to 9 g/dL in those with significant cardiovascular or respiratory disease, in line with local policy.

Ethical approval was not sought for this review, but data collection was registered with the Clinical Audit and Evaluation office at Nottingham University Hospitals NHS Trust, audit reference 13-027C.

Statistical significance was defined as $P < 0.05$. Non-parametric

Table 1
Demographic details within groups.

	Group		*P* Value
	Entire cohort		
Gender (M:F)	201 (109:92)		–
Age years (IQR)	68.3 (61–77.3)		–
ASA (95%CI)	2.1 (1.99–2.21)		–
	Anaemic at diagnosis – untreated†	**Anaemic at diagnosis – treated oral iron†**	
Gender (M:F)	43 (23:20)	27(12:15)	0.624
Age years (IQR)	73 (63–79.8)	75 (68–82.8)	0.244
ASA (95%CI)	2.13(1.87–2.38)	2.35 (2.07–2.63)	0.202
Laparoscopic: Open	25:18	17:10	0.238
MCV fl (IQR)	83 (76.8–90)	80 (74.5–87)	0.24
	Anaemic at surgery	**Non-anaemic at surgery**	
Gender (M:F)	87 (41:46)	114 (68:46)	0.09
Age years (IQR)*	76 (67.5–81)	67 (59–73)	<0.01
ASA (95%CI)*	2.26 (2.09–2.43)	2.01 (1.87–2.15)	<0.05
Laparoscopic: Open	39:48	46:68	0.566
MCV fl (IQR)*	83.5 (76.5–90)	91 (86–93)	<0.01
	Laparoscopic surgery	**Open surgery**	
Gender (M:F)	84 (49:35)	117 (60:57)	0.39
Age years (IQR)	69 (62–78)	70.5 (61–76.3)	0.88
ASA (95%CI)	2.1 (1.93–2.27)	2.1 (1.96–2.25)	0.996
Anaemic at surgery(A:NA)	38:46	49:68	0.667
Converted procedures (converted:completed)	12:72	–	–
Tumour Size mm (IQR)	40 (30–50)	37.5 (25–51.25)	0.447
Tumour site (Right:Left)*	36:48	33:84	<0.05
T stage (95%CI)	2.82 (2.63–3)	2.89 (2.72–3.06)	0.687

NB† denotes exclusion of patients who did not have blood results at both diagnosis and surgery; IQR = Interquartile range; MCV = Mean Corpuscular Volume; NA = Not anaemic at surgery; A = Anaemic at surgery; – = Not applicable; *statistically significant.

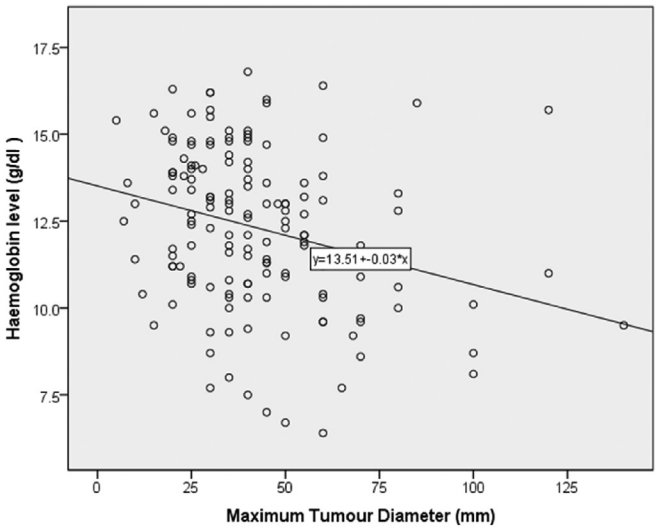

Fig. 1. Scatter-graph illustrating the inverse correlation of tumour size and initial haemoglobin levels.

data was compared using Wilcoxon signed rank test for paired data, Mann-U Whitney for independent variables, and Kruskal–Wallis test when group numbers exceeded two. Categorical data was evaluated using Chi-squared test. Continuous non-parametric data was evaluated with Spearman's rank test to assess correlation. Binary logistic regression was used to investigate the effect of HB levels on transfusion status whilst accounting for confounders. Statistical analyses were performed using SPSS® version 21 (SPSS, Chicago, Illinois, USA).

3. Results

Demographic data for the entire cohort and specific subgroups analysed are illustrated in Table 1. At diagnosis, only 67% (n = 135) patients had HB tested, with a median value of 13.65 g/dl [IQR 11.88–14.9] for males and 12.60 g/dl [IQR 10.95–13.2] for females. At this point, 54% ($n = 73$) of patients were anaemic. Twenty-seven anaemic patients received oral iron (OI), and a further 3 patients received intravenous iron.

The median time from OPA to Surgery was 50 days (IQR 26–94). The change in HB levels over this period was significant for patients with results available from both time-points ($P < 0.05$). The median fall for males was 0.20 g/dl [IQR-0.9 to 0.25] and 0.15 g/dl [IQR -1 to 0.4] for females.

In those prescribed OI who did not receive ARBT in this period, the median HB was 13.10 g/dL [IQR 11.55–14.4] at diagnosis with a non-significant median rise of 0.10 g/dl [IQR-0.3 to 1.1] ($P = 0.107$). This was significantly higher than the corresponding overall change in untreated anaemic patients ($P < 0.05$, untreated change −0.20 g/dl, IQR-0.3–1.5). Median treatment duration was 56 days [QR 37–126].

There was no association between initial HB levels and Dukes' Stage or TNM Stage of disease ($P = 0.09$), However, increasing T-stage was associated with decreasing initial HB levels ($P < 0.05$) and there was a significant inverse correlation between tumour size and initial HB levels ($R_S = -0.3$, $P < 0.01$, see Fig. 1). Consequently, tumour size ($P < 0.01$) and T-stage ($P < 0.05$) were higher in those patients who were anaemic on initial HB.

Initial HB levels were significantly lower in patients with tumours located in the right colon ($P < 0.01$) which corresponded to a significant difference in the prevalence of gender specific anaemia of 67% vs 36% for right and left respectively ($P < 0.01$). There was no

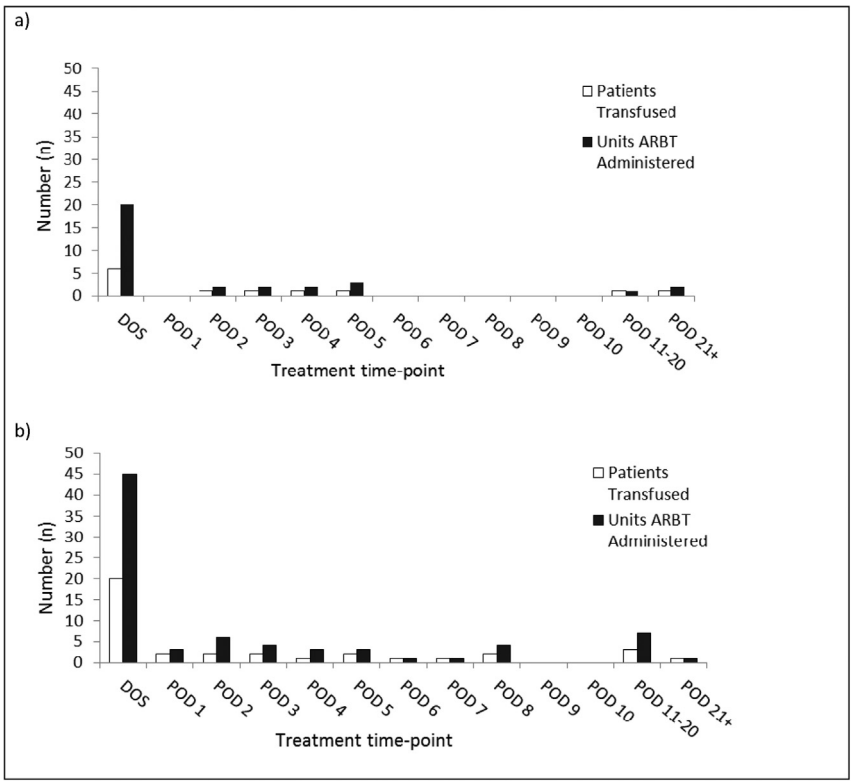

Fig. 2. Bar graphs illustrating the treatment time point at which patients received Allogeneic Red Blood cell Transfusion (ARBT) and the number or ARBT units administered for non-anaemic (a) & anaemic patients (b).Where: DOS = day of surgery, POD = Postoperative day.

Table 2
Odds and risk ratio variation in comparison to baseline risk with haemoglobin levels above 13 g/dl.

Haemoglobin level (g/dl)	Odds ratio (95%CI)	Risk ratio (95% CI)	*P* Value
>13	Standard		<0.01[a]
12.1–13	1.219 (0.29–5.17)	1.2 (0.32–4.53)	
11.1–12	3.25 (0.9–11.74)	2.23 (1.05–4.75)	
10–11	5.474 (1.7–17.67)	4 (1.52–10.53)	
<10	19.5 (6.16–61–78)	8.4 (3.65–19.36)	

[a] Denotes statistical significance for overall significance of association and also linear trend.

association between Dukes' stage ($P = 0.762$) or TNM stage with location ($P = 0.77$). No association was found between transfusion rates and tumour location ($P = 0.343$).

Overall, 56% of patients ($n = 114$) were not anaemic at surgery. Of these, 8% ($n = 9$) received ARBT from surgical admission until discharge receiving a total of 32 units. This equated to a mean of 0.3 units [95%CI 0–1.3] per patient in this group.

In the 87 anaemic patients at surgery, 30% ($n = 26$) had not had HB measured at OPA. Of all those anaemic at surgery, 32% ($n = 28$) received ARBT from admission to discharge. Seventy-eight units were administered to this group, a mean 0.91 units [95%CI 0–0.7] per patient. The transfusion rate was significantly higher in the anaemic group ($P < 0.01$) as was the mean transfusion volume ($P < 0.01$). Fig. 2 illustrates the point in surgical treatment when ARBT were administered for each group, and the number of patients transfused.

Regression analysis demonstrated that with every 1 g/dL increase in HB, the likelihood of transfusion was reduced in the order of 40% (OR 0.57 [95%CI 0.458–0.708], $P < 0.01$). The magnitude of this was not materially altered when accounting for confounders including ASA, mode of operative access, age and gender (adjusted OR 0.58 [95%CI 0.444–0.754], $P < 0.01$).

Table 2 illustrates the odds ratio (OR) and risk ratio (RR) of transfusion in relation to HB levels at surgery, whilst Fig. 3 demonstrates the increasing percentage of patients who received ARBT in relation to decreasing HB levels at Surgery.

Twenty-seven patients were anaemic at OPA with available blood results from OPA and Surgery and received OI over this period. There were 43 untreated anaemic patients with corresponding values, one of which was excluded from this analysis due to a diagnosis of myeloma causing relapsing and remitting anaemia.

Of the untreated patients, 21% ($n = 9$) received a total of 23 units ARBT between Diagnosis and the day before surgery. This compared to 11% ($n = 3$) of the treated patients, who received 9 units between OPA and the day prior to surgery. Neither the mean units transfused ($P = 0.41$) nor transfusion rate ($P = 0.35$) differed between groups.

Forty percent of untreated anaemic patients ($n = 17$) received ARBT from the start of Surgery until discharge, at a mean of 1.1 units [95%CI 0.59–1.6] per patient in the group. This equated to an overall transfusion rate from OPA to discharge of 47%, and a mean 1.67 units (95%CI 0.99–2.3) per patient.

In comparison, 37% of anaemic patients treated with OI ($n = 10$) received ARBT from the start of Surgery until discharge, a mean of 1.04 units [95%CI 0.18–1.89] per patient in the group. The overall transfusion rate for this group was 37%, with a mean transfusion rate of 1.4 units [95%CI 0.39–2.3], which was not different from those untreated ($P = 0.6$).

No difference was noted in patient HB levels between those who underwent laparoscopic or open procedures ($P = 0.643$). Despite this, LS was associated with fewer patients transfused (laparoscopic 9/84; open 28/117, $P < 0.01$).

4. Discussion

This study aimed to investigate key aspects of anaemia, treatment and ARBT use in patients undergoing colorectal cancer surgery. The study was undertaken at a centre with established laparoscopic practice and CRC screening which started 3 years before the study period. The findings are therefore relevant to modern practice. Given the close matching to previous data regarding patient demographics [10] and tumour details [11] the findings should be transferable to the wider population.

The first key observation was the low proportion of HB levels measured at presentation. Only 2/3 of patients had an HB level measured at presentation. It is most likely that these patients were selected based on symptomatology of anaemia, which may account for the higher prevalence of anaemia than previous series [4].

As part of PBM, a suspected diagnosis of CRC should prompt clinicians to actively exclude anaemia. As large tumours, advanced T-stage and right sided lesions were associated with anaemia, this highlights a particular need to measure HB levels in these high risk patients.

It would appear that HB levels do continue to fall in the preoperative period, which highlights a further need for early

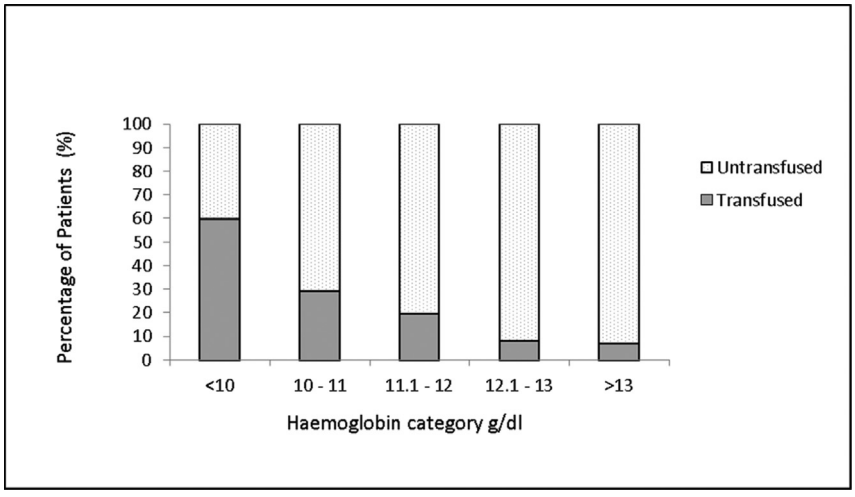

Fig. 3. A stacked bar graph illustrating the change in proportion of patients receiving an allogeneic red blood cell transfusion in relation to the haemoglobin level at surgery.

identification and treatment of anaemia. The magnitude of this decline, though small, was potentially underestimated in this study. In an attempt to review the natural history of HB changes preoperatively, patients who received ARBT were excluded from that analysis. However, it is highly likely that patients who require preoperative ARBT for anaemia would probably have higher inherent tumour blood loss, or a longer history of haemorrhage with associated greater depletions in iron stores. As a result, such an exclusion would remove the subset of patients who may have demonstrated larger HB decreases if left untreated.

The PBM principal of early identification of anaemia [3] appears essential given the apparent relationship between HB levels at Surgery and ARBT requirement. Anaemia at the point of surgery was found to be associated with an increased ARBT rate and increased number of units required. As severity of anaemia increased, so too did the proportion of patients who required ARBT.

This is further exemplified within Table 2, which demonstrated that normality need not be reached to reduce the use of ARBT, but that improvement of preoperative HB levels could reduce the number of patients who would need ARBT. This is substantiated by the finding that for every 1 g/dl rise in preoperative HB, the need for ARBT was reduced by approximately 40%. Ideally an HB level in excess of 12 g/dl appears to reduce the risk of ARBT to a level more comparable with non-anaemic patients.

It could be argued the increased ARBT use is secondary to the increased age and ASA of the anaemic group. Although it is possible that the clinical threshold for administration of ARBT would have been lower within this group, the relationship between HB levels and transfusion use remained stable when cofounders such as ASA and age of patient were accounted for, implying a key role for preoperative HB levels. Furthermore, transfusion rates were not different between procedures for Left and Right sided malignancy, indicating operative factors were also of lesser importance.

It is therefore relevant that under half of anaemic patients received some form of iron supplementation at diagnosis. The clinical effect of OI would initially appear to be minimal due to a non-significant rise in HB of only 0.1 g/dl from diagnosis to surgery in non-transfused anaemic patients. Such an observation parallels previous studies reviewing the role of OI in preoperative CRC patients, which indicated that OI does not increase HB in this context, but merely reduces the natural decline in HB in the preoperative period [12].

Despite the apparent lack of efficacy of OI, two key limitations must be acknowledged. It can only be assumed that these patients were iron deficient based on the clinical context and reduced Mean Corpuscular Volume (MCV) values, yet MCV is recognised to have limitations in the diagnosis of iron deficiency [13]. Also no record of dosing or adherence to medication treatment protocols was available. Studies have demonstrated high variability in compliance and absorption of OI which may have affected the efficacy [14]. Secondly, although the difference in HB change with OI was non-significant over the preoperative time period, the difference was significant when compared to a "control" group of untreated anaemic patients, potentially implying a larger treatment effect.

Fig. 3 illustrates striking differences in ARBT use with variations in preoperative HB levels at increments of 1 g/dl-a factor of 10 greater than the observed treatment effect of OI. This could indicate that more efficacious iron treatments are required in order to increase HB levels to this degree. Intravenous iron has been trialled in this setting with limited success at low dose [15] but with associated HB rises in excess of 1 g/dL at higher doses [16,17].

In the current study, it would appear that laparoscopic surgery does have a clinical impact upon ARBT use. Notably, transfusion rates were significantly lower in laparoscopic cases across the entire cohort and also in the anaemic subgroup, yet was not noted in the non-anaemic patients. This would indicate that the degree to which operative losses are reduced by minimal access surgery was of particular clinical relevance in anaemic patients who were particularly vulnerable to further losses.

This difference was unlikely to be secondary to the higher proportion of open surgical cases for left sided lesions. Although it is conceivable that left sided operations are associated with higher intraoperative losses which could prompt increased ARBT use, the fact that the transfusion rate was similar between those undergoing surgery for left and right sided malignancy would discredit this confounding link.

In conclusion anaemia is common in CRC surgical patients, particularly in those with large or right sided malignancy. Early identification of anaemia is important to allow attempted treatment which is important as HB levels continue to fall from the point of diagnosis to surgery if untreated and, preoperative anaemia is associated with increased ARBT requirement. Furthermore, small increases in HB levels can have potentially dramatic effects upon this requirement, hence further investigation into the optimal treatment strategy for anaemia is needed.

Ethical approval

Ethical approval was not sought for this review, but data collection was registered with the Clinical Audit and Evaluation office at Nottingham University Hospitals NHS Trust, audit reference 13-027C.

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Author contribution

Study Concept: BK, AA, AM, JAS
Study Design: BK, AM
Data Collection: BK, CS, SB
Data Analysis: All
Data Interpretation: All

Conflicts of interest

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Guarantor

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Consent

Not applicable for this publication.

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