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Impact of Peri-Operative Blood Transfusion on Post-Operative Complications in Colorectal Surgery

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Abstract

Aim: Colorectal cancer (CRC) is commonly associated with anaemia often requiring perioperative blood transfusions (BT). There is significant evidence to show poor long term outcomes following BT in CRC surgery due to the immunomodulatory effects of BT. This study aims to analyse the impact of BT on post-operative surgical complications in CRC surgery.

Method: Data were collected retrospectively for patients undergoing emergency and elective colorectal cancer related surgery between January 2019 and December 2020 at Blacktown Hospital, Sydney. Data relating to transfusion and post-operative complications were collected through electronic medical records. R statistical software was utilised to calculate hazard ratio of common surgical complications in the blood transfusion group compared to the non-blood transfusion group.

Results: There were a total of 130 patients with 26 patients (20%) receiving BT. This study shows that BT is associated with an increased risk of post-operative complication in CRC surgeries [HR 3.74 (95% CI: 1.31-10.68; P=0.0073)], after adjusting for preoperative haemoglobin. In particular, this study shows a statistically significant higher rates of intra-abdominal collection [HR 12.98 (95% CI: 1.52-111.15; P=0.0114)]. and pneumonia [HR 21.65 (95% CI: 1.77-265.01; P=0.007994)] associated with blood transfusion.

Conclusion: This study shows that BT is associated with an increased risk of post-operative complication particularly intra-abdominal collection and pneumonia. However, a prospective randomised control trial is required to confirm these results.

Keywords: Bowel cancer; Colorectal surgery; Blood transfusion; Post-operative complication.

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Introduction

Colorectal Cancer (CRC) is one of the commonest cancers worldwide with approximately 1.9 million new CRC diagnoses in 2020 [1]. CRC is often related with anaemia which requires transfusion especially during perioperative period to enhance healing through improved oxygen delivery to tissues and avoid post-operative complications such as acute coronary syndromes. Anaemia in CRC can be due to various reasons including iron-deficiency anaemia from occult bleeding, increased hepcidin level from systemic inflammation, neoadjuvant treatment and intra-operative blood loss [2]. Studies have shown long term adverse effects related to peri-operative blood transfusion (BT) in terms of recurrence and metastasis in CRC surgery [3,4]. There is also some literature that shows an increase in post-operative complications in colorectal cancer surgery with perioperative blood transfusion, however the data is sparse and contradictory. BT is also a finite resource with no internationally validated guidelines for prescribing blood products hence there is significant variation in the rate of transfusion amongst surgeons and hospitals [5]. This study aims to evaluate the post-operative impacts related to peri-operative BT in order to bring more awareness of judicious use of blood products.

Methods

We conducted a retrospective study of all CRC resections at Blacktown Hospital, Sydney Australia between January 2019 and December 2020. Patient details, operative details, disease characteristics, perioperative haemoglobin, BT details and post-operative complications were collected from NSW Health electronic medical records. We included both elective and emergency operations including right hemicolectomy, left hemicolectomy, Hartmann's procedure, anterior resections, abdominoperineal resection and total and subtotal colectomies performed for colorectal malignancies. We excluded cases of bowel resection performed for non-malignant diseases in our study. Preoperative and post-operative BT was defined as transfusion of allogenic packed red blood cells within 30-days before or after the date of operation, respectively.

Primary end-points measured were post-operative complications such as seroma, hematoma, anastomotic leak, pneumonia, UTI, pulmonary emboli and post-operative bleeding. Our secondary end-point was 30-day mortality.

All statistical analysis calculation was performed in R (version 4.22) (R Core Team, 2022) with R studio software (version 2022.12.0+353) (RStudio Team, 2020) interface. Continuous variables were categorized and compared using chi-square test. All complication variables were analysed individually as dichotomous variables. Any variable reaching a P value of less than 0.25 was used for subsequent multivariable analysis using a stepwise Cox proportional hazard model. Hazard ratios and 95% confidence intervals were calculated for each variable. All P values less than 0.05 were considered to indicate a difference of statistical significance.

Results

There were a total of 130 patients who underwent CRC resection surgery between January 2019 and December 2020. Twenty-six patients (20%) required allogeneic peri-operative BT, with 10 patients receiving BT pre-operatively, 18 post-operatively and 5 patients receiving BT intra-operatively. Patient, disease and surgical characteristics of the perioperative BT vs the non-BT groups are presented in Table 1 for comparison.

The median age of patients in the BT group was 64.5 (IQR 55.75 -73.0) and non-BT group was 71.0 (IQR 63.5-82). There were 78 males (14 in the BT group) and 52 females (12 in the BT group).

There were 41 right colonic tumours (9 in the BT group), 10 transverse colon tumours (4 in BT group), 4 left colonic tumours (1 in the BT group), 20 sigmoid colon (5 in the BT group), 17 rectosigmoid tumours (4 in the BT group) and 31 rectal tumours (3 in the BT group). There were 6 patients with synchronous tumours with none in the BT group. American Joint Committee on Cancer (AJCC) staging distribution was: 15 stage I tumours (2 in the BT group), 41 stage II tumours (8 in the BT group), 48 stage III tumours (8 in the BT group) and 26 stage IV tumours (8 in the BT group). Nineteen patients received neoadjuvant chemotherapy including 2 patients in the BT group. Twenty-one patients received neoadjuvant radiation therapy including 3 patients in the BT group.

Most common operations included in the study were 49 right hemicolectomies (22.4% in the BT group) and 50 anterior resections (10% in the BT group). Thirty-five patients underwent an emergency operation (of which 40% of patients were in the BT group).

Table 2 illustrates the post-operative complications rates between peri-operative BT and non-blood BT groups. Table 3 provides the risk ratios for post-operative complications associated with perioperative BT following multivariable analysis. This study demonstrates that peri-operative BT was associated with an increased risk of post-operative complications [HR 3.74 (95% CI: 1.31-10.68; P=0.0073)]. Particularly, BT was associated with an increased risk of post-operative pneumonia [HR 21.65 (95% CI: 1.77-265.01; P=0.008)] and intra-abdominal collection [HR 12.98 (95% CI: 1.52-111.15; P=0.011)]. Furthermore, results show that peri-operative BT was associated with an increase in surgical site infection [HR 1.91 (95% CI: 0.38-0.25, P=0.43)] and urinary tract infection [HR 3.16 (95% CI: 0.56-17.84, P=0.205)]. However these results are statistically not significant.

Table 1: Patient, disease and operative characteristics.

	Non-blood transfusion group	Blood transfusion group
Patient characteristics		
Gender		
Male	64	14
Female	40	12
Median age (IQR; SD)	64.5 (55.75-73.0; 14.29)	71.0 (63.5-82; 14.55)
Disease characteristics		
Location of tumour (%)		
Appendix and ileum	7 (6.0)	2 (7.7)
Right colon	25 (24.0)	7 (26.9)
Transverse colon	6 (5.8)	4 (15.4)

Left colon	3 (2.9)	1 (3.8)
Sigmoid colon	15 (14.4)	5 (19.2)
Rectosigmoid colon	13 (12.5)	4 (15.4)
Rectum	28 (26.9)	3 (11.5)
Anus	1 (1.0)	0 (0)
Synchronous tumour	6 (5.8)	0 (0)
AJCC tumour stage (%)		
I	13 (12.5)	2 (7.7)
II	33 (31.7)	8 (30.8)
III	40 (38.5)	8 (30.8)
IV	18 (17.3)	8 (30.8)
Neoadjuvant treatment		
Chemotherapy	17	2
Radiotherapy	18	3
Surgical characteristics		
Type of operation (%)		
Right hemicolectomy	38 (36.5)	11 (42.3)
Left hemicolectomy	3 (2.9)	1 (3.8)
Anterior resection	45 (43.3)	5 (19.2)
Abdominoperineal resection	7 (6.7)	2 (7.7)
Hartmann's procedure	4 (3.8)	3 (11.5)
Total or subtotal colectomy	5 (4.8)	3 (11.5)
Caecectomy	1 (1.0)	1 (3.8)
Appendicectomy	2 (1.9)	1 (3.8)
Nature of operation (%)		
Emergency	21 (20.2)	14 (53.8)
Elective	83 (79.8)	12 (46.2)
Open vs laparoscopy (%)		
Open	15 (14.4)	5 (19.2)
Laparoscopy	77 (74.0)	14 (53.8)
Hybrid	12 (11.5)	7 (26.9)
Median preoperative haemoglobin	129	102.5
Comorbidities (%)		
CVA/IHD	16 (15.4)	7 (26.9)
COPD	13 (12.5)	7 (26.9)
Smoker	48 (46.2)	9 (34.6)
ASA (%)		
I	8 (7.7)	1 (3.8)
II	51 (49.0)	6 (23.1)
III	41 (39.4)	12 (46.2)
IV	4 (3.8)	7 (26.9)

Table 2: Post-operative complication numbers in the blood transfusion and non-blood transfusion groups.

Complication	Non-blood transfusion group (Total patients = 104)	Blood transfusion group (Total patients = 26)
Surgical site infection	9	5
Seroma	1	0
Hematoma	5	3
Intra-abdominal collection	3	6
Pneumonia	1	4
PE	0	0
UTI	4	5
Post-op bleeding	5	5
Overall post-operative complication	19	14

Table 3: Hazard ratios of post-operative complication associated with peri-operative blood transfusion following multivariable analysis.

Complication	HR (95% confidence interval)	P value
Any complication	3.74 (1.31-10.68)	0.0073
Pneumonia	21.65 (1.77-265.01)	0.007994
Intra-abdominal collection	12.98 (1.52-111.15)	0.0114
Surgical site infection	1.91 (0.38-0.25)	0.43
Seroma	0.00 (0.00-10)	1
Haematoma	0.49 (0.06-4.09)	0.51
Urinary Tract Infection	3.16 (0.56-17.84)	0.205
Post-operative bleeding	3.00 (0.59-15.27)	0.212
30-days mortality	4.12 (0.25-68.16)	0.34

Discussion

The results of this study demonstrates an association between perioperative BT and increased post-operative complication following surgery for CRC (HR=3.74; 95% CI: 1.31-10.68, P<0.0073). Our study shows statistically significant increase in pneumonia (HR=21.65; 95% CI: 1.77-265.01, P<0.008) and intra-abdominal collection (HR=12.98; 95% CI: 1.52-111.15, P<0.011) with peri-operative BT in CRC surgery following multivariable analysis. In addition, this study highlights the increase in surgical site infection (SSI) and urinary tract infection (UTI) associated with peri-operative BT, however these results were statistically not significant. This is the only Australian study investigating the post-operative complication associated with blood transfusion with significant results that advocates for more considerate use of blood products.

The results produced in this study are supported by a few other international studies. A recent study by McSorley et al. provided similar conclusions to our study [6]. They demonstrated that BT was associated with higher post-operative complications, anastomotic leak, Clavien-Dindo grade 3-5 complications and longer median length of stay in a propensity score matched cohort [6]. The increase in post-operative complications can be associated with

the immunomodulatory effects caused by BT. The allogenic red cell transfusion suppresses a myriad of immune cells including T cells, natural killer cells, macrophages and monocytes [7,9]. These cells have a significant impact on wound and anastomosis healing and preventing post-operative infections. The immunomodulation is thought to be caused by three mechanisms: 1. Allogenic white blood cells (WBCs) which cause immune downregulation in the recipient; 2. Soluble biological response modifiers that are gradually released into the supernatant fluid during packed red blood cells storage in a time dependent fashion; 3. HLA peptides and other soluble mediators that circulate the plasma of the stored blood [10]. There is significant interest in the role of WBCs in triggering the immunomodulation following BT; however, studies exploring the effect of WBCs and the use of WBC-reduced blood products on post-operative infections have been conflicting [11,12]. Furthermore, peri-operative BT is also shown to cause a significant decrease in serum albumin levels in the post-operative days [1,5]. contributing to decreased healing capacity in addition to immunomodulation [6].

The long-term impacts of perioperative BT during colorectal resection surgery for colon cancer contributed by the systemic inflammatory reaction from the surgical trauma and immunomodulation is well established. A report by Wu et al. showed that 3-year and 5-year disease-free-survival (DFS) rates in the transfusion group was 71.4% and 66.7% compared with 83.5% and 80.3% in the non-BT groups. [13] Similarly, they reported that 3-year and 5-year overall survival (OS) rate in the transfusion group respectively were 83.4% and 74.4% compared with 95.2% and 91.5% in the non-BT group [13]. A meta-analysis published by Pang et al. reported that perioperative BT decreased OS significantly [4]. They further showed that OS was significantly lower following large volume of transfusion (>3 units of packed red blood cells (pRBC)) compared to less than or equal to 3 units of blood transfusion. Similarly, studies have also shown similar effects from BT in other malignant diseases such as ovarian cancer and head and neck cancers [14,15].

Despite the statistically significant impacts of perioperative BT shown in this study and other retrospective studies, it is also important to consider the confounding factors that may increase the risk of complications post-operatively. Our study closely accounted for the pre-operative haemoglobin levels during statistical analysis. There is myriad of other patient and surgical factors that contribute to increased post-operative complications. A meta-analysis conducted by Xu and colleagues identified a set of eight risk factors, such as obesity (OR=1.59), diabetes (OR=1.34), male sex (OR=1.24) and others including perioperative blood transfusion (OR=2.23) which increase the risk of surgical site infection following CRC surgery [12]. Therefore, the correlation demonstrated in this study needs further validation with randomised control trials, specifically in CRC surgery, to confirm this association.

Our results show statistically significant results for surgical complications and specifically for pneumonia and intra-abdominal collections. The HR for other complications including surgical site infection, urinary tract infection, post-operative bleeding and 30-day mortality are not statistically significant due to higher P value and 95% confidence interval crossing the null ratio of 1. The confidence intervals for intra-abdominal collection and pneumonia are also wide. These implications on the statistical analysis is largely contributed due to the lower number of patient population, particularly in the BT group (n=26). Furthermore, inadequate patient number in the BT group precluded further subgroup analysis including the effect of the timing of BT administration. The retrospective nature of this study further contributes to the limitations of this study with variable patient characteristics between the two group. Therefore, additional prospective randomised control studies are required to further confirm the results produced in this study.

Conclusion

In conclusion, this study demonstrates an association with blood transfusion and increased risk of post-operative complication in colorectal surgery. However, further prospective randomised control studies are required to further confirm the results of this study. In addition, clinicians need to be considerate in utilising blood products peri-operatively and attempt to optimise patient and surgical factors to prevent clinically significant anaemia in colorectal surgeries.

Declarations

Author contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Aswin Shanmugalingam, Phelopatir Anthony, Mike Wu and Arthur CH Ng. The first draft of the manuscript was written by Aswin Shanmugalingam and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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