Original Article

Cancer relapse in surgical patients who received perioperative transfusion of blood and blood products: A case-control study

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ABSTRACT

Background and Aims: Immunomodulatory consequences of allogeneic blood transfusion may outweigh the advantages of improved oxygen delivery and tissue perfusion, especially in patients with cancer. In colorectal cancer, there is evidence of cancer relapse in patients who received transfusion. This retrospective analysis was undertaken to evaluate the relationship between perioperative blood transfusion and cancer recurrence in patients undergoing oncosurgery. **Methods:** In this case-control study, we retrospectively analysed the case sheets of 194 patients who had perioperative transfusion and underwent cancer surgery from March to December 2013(Study group, Cases). They were compared with controls matched for cancer site and TNM staging who did not receive perioperative transfusions (Control Group, Controls). We intended to find out if the Study group had any increased risk of cancer relapse compared with the controls. Records from the institute cancer registry were analysed in 2018 to give a follow-up period of 5 years. Continuous variables were analysed using Student's T test and Mann Whitney U test for normally distributed and skewed data respectively. For Categorical data Fisher's exact test and Chi square test were applied. The risk for recurrence was estimated using odds ratio. **Results:** The recurrence rate in cases and controls was 53.09% and 19.59% respectively and the odds ratio, 4.647 (CI: 2.954, 7.309). In Cases, significant relapse was noted for carcinomas of ovary, colorectal, bladder, larynx, head of pancreas and liver. **Conclusion:** In surgical oncology patients, ABT is associated with greater rate of recurrence.

Key words: Blood transfusion, immunosuppression, perioperative period, recurrence, retrospective studies

INTRODUCTION

Perioperative allogeneic blood transfusion (ABT) is common in patients with cancer. ABT has an immune modulating effect. Nonspecific immunosuppression induced by transfusion might favour tumour growth.[1] Subsequent evidence suggests an adverse relationship between transfusion and survival after resection of colorectal cancer.[2] According to American Cancer Society, 'If cancer is found after treatment, or found after a period of time when the cancer could not be detected, it's called a cancer recurrence or relapse'. Hence, this study was done to evaluate the relationship between perioperative blood transfusion (PBT) and cancer recurrence in patients undergoing cancer surgeries.

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METHODS

After institutional review board approval, we retrospectively analysed the case sheets of 194 patients who had PBT and underwent cancer surgery from March to December 2013. PBT was defined as the receipt of any blood or blood product (packed red blood cells, whole blood, fresh frozen plasma or single-donor plasma) within 24h before or 48 h after surgery.[3] The decision to administer blood and blood products was at the discretion of anaesthesiologist intraoperatively and attending surgeon and anaesthesiologist postoperatively with no institutional standardised transfusion threshold. Patients with cancer undergoing primary surgical resection of the tumour were included in the study. Patients were excluded if they underwent prior surgical diagnosis of their current cancer through laparoscopy or laparotomy, were undergoing surgery for recurrent disease or with distant metastases. The retrospective analysis of the case sheets was done in 2018 to determine the disease status after 5 years of follow-up.

Clinicopathological variables recorded included body mass index, age, gender and duration of surgery, receipt of PBT and the number of transfused units, tumour stage and lymph node status. Tumour staging followed the 2009 American Joint Committee on Cancer/Union Internationale contre le cancer 7th edition TNM classification.

A total of 194 patients who had PBT and underwent cancer surgery from March to December 2013 (Study Group, Cases) were retrospectively compared against the same number of patients without any PBTs and who underwent cancer surgery during the same time period (Control Group, Controls), to determine whether the study group had any increased risk of cancer relapse compared with the patients in the control group. The control group included similar patients matched for cancer site and TNM staging (which was obtained from their clinical examination, biopsy results and imaging reports) as that of the study group. Records from the institute cancer registry were analysed in 2018 to determine the cancer relapse rates among the two groups.

For statistical analysis, the continuous variables [age, body mass index (BMI), duration of surgery] were summarised using mean and standard deviation. The categorical variables (relapse, group) were expressed in frequency and percentage. The association between two categorical variables was assessed using Chi-square or Fisher's exact test. The comparison between the cases and control on other continuous variables were tested using Student's *t*-test for normally distributed data; otherwise Mann–Whitney *U*-test was used. The odds for recurrence were estimated using odds ratio (OR) with 95% confidence interval (CI). A P value <0.05 was considered as significant, statistically. The site-wise sample size considered for the study was as follows –ovary: 100, colon: 110, liver: 12, lung: 12, larynx: 16, tongue: 16, buccalmucosa: 14, stomach: 20, breast: 10, oesophagus: 20, bladder: 24, kidney: 16 and head of pancreas 18.

RESULTS

The study was done in 194 patients with cancer which included the following types: colorectal, ovarian, urinary bladder, stomach, oesophagus, head of pancreas, kidney, tongue, larynx, buccal mucosa, lung, liver and breast [Figure 1]. The descriptive statistics of the demographics (age, BMI, duration of surgery) for cases and controls are given in Table 1. No statistical significant difference between the two groups was observed in the demographic variables [Table 1]. Compared to control group, the relapse rates are higher for cases in all the sites [Table 2]. The recurrence rate for all cancers put together in cases and controls is 53.09% and 19.59% respectively, OR 4.65 (CI: 2.95, 7.31), [P = 0.001]. In our study, significant relapse in terms of P value was noted for carcinomas of ovary (P value: 0.001), colorectal (P value: 0.004), urinary bladder (P value: 0.013), larynx (P value: 0.021), head of pancreas (P value: 0.046) and liver (P value: 0.046) cases and it was not significant for others [Table 2]. The estimated odds ratio was found to be higher for all cancer sites, colon 3.15 (CI: 1.430,6.931), lung

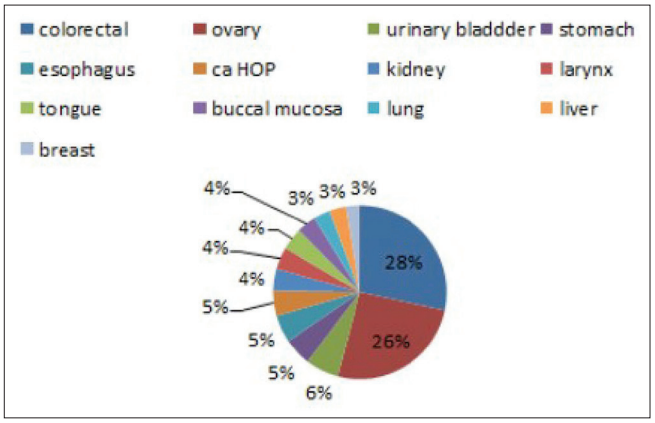

Figure 1: Study population

Table 1: Site wise comparison of case and control with respect to Age, BMI & Duration of Surgery

Site	Group	Age			BMI			Duration of Surgery		
		Case	Control	*P*	Case	Control	*P*	Case	Control	*P*
Colon	Mean	53.22	54.05	0.669	23.82	22.77	0.084	155.75	150.78	0.225
	SD	10.35	10.13		3.46	2.83		21.60	21.07	
Lung	Mean	50.33	57.00	0.233	20.55	23.73	*0.006	388.33	385.17	0.989
	SD	7.84	10.20		1.53	1.66		30.79	50.03	
Ovary	Mean	51.24	52.60	0.550	23.91	23.70	0.764	160.54	158.18	0.592
	SD	11.30	11.37		3.60	3.51		20.84	23.02	
Liver	Mean	51.50	51.00	0.940	24.33	23.67	0.766	523.33	515.00	0.657
	SD	10.41	11.83		4.96	2.04		34.01	28.81	
Larynx	Mean	47.13	49.88	0.612	24.25	21.64	0.091	300.63	326.25	0.078
	SD	9.55	11.54		3.29	2.40		32.34	20.13	
Tongue	Mean	49.38	54.38	0.302	26.00	23.39	0.130	285.63	306.25	0.146
	SD	11.15	7.05		2.33	4.00		24.70	28.75	
BM	Mean	51.71	43.71	0.190	21.94	23.73	0.319	199.29	202.86	0.743
	SD	11.18	10.34		1.82	4.19		20.50	19.33	
Stomach	Mean	50.30	49.80	0.931	23.59	24.90	0.409	430.50	415.50	0.174
	SD	12.73	12.87		3.69	3.22		24.32	23.03	
Oesophagus	Mean	54.20	47.70	0.158	24.98	25.61	0.720	512.00	501.00	0.245
	SD	10.13	9.59		4.02	3.74		19.89	21.06	
Breast	Mean	36.00	46.20	0.124	23.84	24.26	0.696	117.00	112.00	0.455
	SD	7.38	11.03		1.68	1.59		12.04	7.58	
Bladder	Mean	60.92	55.67	0.124	25.27	24.36	0.427	393.75	402.92	0.369
	SD	6.78	9.14		2.50	2.67		30.61	16.16	
Kidney	Mean	55.75	48.00	0.142	21.29	25.78	*0.005	397.50	395.63	0.869
	SD	6.78	12.34		2.51	2.73		25.09	19.17	
Head of Pancreas	Mean	47.67	51.89	0.421	22.57	26.00	*0.023	549.44	545.00	0.741
	SD	9.08	12.37		2.06	3.54		26.51	29.58	
Overall	Mean	51.88	10.73	0.810	24.75	14.84	0.321	262.93	142.13	0.916
	SD	52.14	10.84		23.67	3.25		261.41	141.93	

*P<0.05

5.0 (CI: 0.34, 72.77), ovary 4.03 (CI: 1.71, 9.49), tongue 7.0 (CI: 0.57, 86.32), buccal mucosa 4.5 (CI:0.34,60.15),stomach6.0(CI:0.53,67.65),oesophagus 6.0 (CI: 0.81, 44.35), urinary bladder 10.0 (CI: 1.44, 69.26), kidney 7.0 (CI: 0.57, 86.32), head of pancreas 10.0 (CI: 0.86,117.02). OR was statistically significant only for colon (P = 0.004), ovary (P = 0.001), urinary bladder (P = 0.020), [Table 3].

DISCUSSION

In the present study, cases and controls has been taken in the ratio 1: 1. High risk for relapse was observed in cases compared to control in all types of cancers. The odds ratio has shown statistical significance for ovary, colorectal, bladder and overall cancers and marginal significance for oesophagus and head of pancreas cancers at 5% level of significance. Even though all other sites are having higher odds ratio, they are not statistically significant (P value >0.05) may be due to the small sample size. Hence, we infer that in surgical oncology patients, ABTs are associated with greater rate of recurrence.

PBT is used to ensure optimal tissue oxygenation in patients undergoing surgery. ABT has an immune modulating effect which enhances cancer metastasis and recurrence.[4,5] The demonstrated mechanisms in transfusion-related immune modulation are a decrease in interleukin 2 secretion, natural killer cell activity, macrophage function, CD4/CD8 ratios and delayed hypersensitivity responses.[6] Although transfusion aims at increasing the delivery of oxygen to the tissues, the physiological changes during RBC storage could limit this goal.[7]

In colorectal cancer, there is evidence of cancer relapse in patients who received PBT.[8] In other types of cancer, conclusive evidence is not available.[9-16] The most probable reason for recurrence could be the immunosuppressive effect of surgery and anaesthesia, aggravated by administration of blood products. Tumour manipulation during surgical resection, volatile anaesthetics, opioids, stress response to surgery, inflammatory response to injury, hyperglycaemia and hypothermia cause a significant imbalance in defence responses, which may facilitate distal seeding of

Table 2: Site wise case-control analysis with respect to relapse

Site	Group	Relapse		*P*	Relapse Rate (%)
		No [Number] (%)	Yes [Number] (%)		
All sites	Case	91 (23.5)	103 (26.5)	0.001	53.09
	Control	156 (40.2)	38 (9.8)		19.59
Colon	Case	24 (21.81)	31 (28.18)	*0.004	56.4
	Control	39 (35.45)	16 (14.55)		29.1
Lung	Case	3 (25)	3 (25)	0.545	50.0
	Control	5 (41.67)	1 (8.33)		16.7
Ovary	Case	22 (22)	28 (28)	*0.001	56.0
	Control	38 (38)	12 (12)		24.0
Liver	Case	3 (25)	3 (25)	*0.046	50.0
	Control	6 (50)	0 (0)		0.0
Larynx	Case	4 (25)	4 (25)	*0.021	50.0
	Control	8 (50)	0 (0)		0.0
Tongue	Case	4 (25)	4 (25)	0.106	50.0
	Control	7 (43.75)	1 (6.25)		12.5
BM	Case	4 (28.57)	3 (21.43)	0.237	42.9
	Control	6 (42.86)	1 (7.14)		14.3
Stomach	Case	6 (30)	4 (20)	0.121	40.0
	Control	9 (45)	1 (5)		10.0
Oesophagus	Case	4 (20)	6 (30)	0.068	60.0
	Control	8 (40)	2 (10)		20.0
Breast	Case	5 (50)	0 (0)	-	-
	Control	5 (50)	0 (0)		-
Bladder	Case	4 (16.7)	8 (33.3)	*0.013	66.7
	Control	10 (41.7)	2 (8.3)		16.7
Kidney	Case	4 (25)	4 (25)	0.106	50.0
	Control	7 (43.7)	1 (6.3)		12.5
Head of Pancreas	Case	4 (22.2)	5 (27.8)	*0.046	55.6
	Control	8 (44.4)	1 (5.6)		11.1

*P<0.05

Table 3: Site wise odds ratio for case compared to control

Site	*P*	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper
All sites	0.001	4.647	2.954	7.309
Colon	*0.004	3.148	1.430	6.931
Lung	0.239	5.000	0.344	72.767
Ovary	*0.001	4.030	1.712	9.488
Tongue	0.129	7.000	0.568	86.321
BM	0.256	4.500	0.337	60.151
Stomach	0.147	6.000	0.532	67.649
Oesophagus	0.079	6.000	0.812	44.351
Bladder	*0.020	10.000	1.444	69.262
Kidney	0.129	7.000	0.568	86.321
Head of Pancreas	0.067	10.000	0.855	117.017

*P<0.05

circulating cells and the growth of micrometastases into established clinical metastases.[17]

The circumstances under which PBT was given are likely to influence cancer recurrence. Preoperative nutrition, functional status and anaemia, degree of resectability, type and duration of anaesthesia, amount of blood loss, stress response and the presence of postoperative complications are some of these factors. It is difficult to understand the potential impacts of many of these important confounding factors on cancer recurrence from retrospective studies. The decision to transfuse should not be driven only by the haemoglobin concentration, and no single criterion can be used as an indication for transfusion. Clinical status of the patient should be of utmost consideration.

The recurrence or relapse of the cancer involves the surgical factors as well. Standard surgical procedure was done for the preoperatively staged malignancy. We have sub-specialised and the same surgeon operated the same cases. *En bloc* resection of the tumour including the draining lymph nodes was resected in all cases. The number of lymph nodes sampled was histopathologically assessed and was found to be comparable with American Joint Committee for Cancer standards.

This study has several limitations, the most important of which is it is a retrospective design, which means the results warrant further confirmation in well-defined prospective and randomised clinical trials. The

second limitation was that we could not control for the variables of the number of units transfused, type of blood products given, preoperative haemoglobin levels, preoperative albumin value, intraoperative estimated blood loss, patient comorbidity or performance status which can act as confounding variables. Third, PBT was at the discretion of the anaesthesiologist/surgeon and because of the retrospective nature of the study, it is impossible to ascertain the exact reasons and indications for it, which also introduces a major bias to the conclusion. The small sample size for most of the sites resulted in higher odds ratio, also forms another limitation of the study.

Even though it is not clear from the study that a specific threshold can be recommended, it is important to stick to the current blood transfusion studies and avoid any unnecessary transfusions. Leukodepleted red blood cells (RBCs) and fresh blood are preferred if substitutes to ABT are not easily available. Meticulous selection of surgical cases, improving preoperative nutritional status, anaesthetic techniques that prevent tumour progression and surgical techniques that minimise blood loss are to be adopted.

Many substitutes exist for ABT. Autologous transfusion techniques including preoperative autologous donation, acute normovolaemic haemodilution, intraoperative and postoperative cell salvage and reinfusion are life-saving in high blood loss surgeries. The efficacy of these can be augmented by supplemental iron or erythropoietin. Tranexamic acid reduces bleeding and is safe and inexpensive. Further studies are needed to prove the safety and efficacy of artificial blood substitutes. Detailed discussion about these is beyond the scope of this article.

Patient blood management strategies to minimise ABTshould be undertaken, and focus should be more on the substitutes to it, and large prospective studies are required.

CONCLUSION

In surgical oncology patients, ABTs are associated with greater rate of cancer recurrence.

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Conflicts of interest

There are no conflicts of interest.

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