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Original Research Article

Prevalence and predictors of hypercoagulability detected by rotational thromboelastometry in peritoneal malignancy patients undergoing cytoreductive surgery

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ABSTRACT

Background: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is an established treatment for peritoneal malignancy. A hypercoagulable state in these patients and the associated risk of venous thromboembolism (VTE), remains the most common cause of 30-day mortality. This study aimed to evaluate the prevalence and perioperative factors associated with baseline hypercoagulability detected by rotational thromboelastometry (ROTEM), a point-of-care haemostatic assay, in peritoneal malignancy patients.
Methods: A retrospective cohort study was performed in a peritoneal malignancy unit on patients undergoing CRS between 2019 and 2023, who underwent preoperative ROTEM testing. Patients were divided into group A (hypercoagulable) and Group B (normal coagulation). Baseline characteristics, pathology results, operative details and post operative outcomes were reviewed. Univariate and multivariate analysis were used to identify factors associated with baseline hypercoagulability.
Results: The 70 patients were included, 23 patients in group A (32.9%) and 47 patients in group B (67.1%). Group A had a lower preoperative haemoglobin ($p<0.001$), higher platelet count ($p<0.001$) and median peritoneal carcinomatosis index (33 vs 10, $p=0.003$). Appendiceal primary was associated with hypercoagulability (47.8% vs 23.4%, $p=0.039$). Group A required more intraoperative transfusion with red blood cells ($p=0.014$) but not platelets ($p=0.6$) or cryoprecipitate ($p=0.8$). Although group A had a higher incidence of VTE events (30.4% vs 23.4%) this was not statistically significant.
Conclusions: Baseline hypercoagulability exists in one-third of patients with peritoneal malignancy and was associated with increased tumour burden and appendiceal primary. The increasing use of ROTEM is a valuable tool for perioperative management of complex peritoneal malignancy patients.

Keywords: TEM, Thromboelastography, Peritoneal neoplasms, Peritoneal carcinomatosis, Cytoreduction surgical procedures, HIPEC

INTRODUCTION

Malignancy and major abdominal surgery are well known causes for a hypercoagulable state and subsequently risk factors for VTE including deep venous thrombosis (DVT) and pulmonary embolus (PE). It follows that patients undergoing surgery for cancer are at particularly high risk of thrombotic events. They are twice as likely to develop a DVT and four times more likely to develop a fatal PE when compared to non-cancer patients

undertaking similar operations.[1,2] As such, VTE remains the most common cause of death at 30 days post-surgery in cancer patients.[1]

CRS with or without HIPEC is firmly established as the optimal surgical treatment for peritoneal carcinomatosis, which arises due to a variety of primary tumours including the appendix, colon, ovaries, stomach or pancreas. In appropriately selected patients, CRS significantly improves survival and quality of life compared to the alternative palliative treatments. However, CRS and HIPEC involve extensive surgery and carries morbidity and mortality risks, reported at 24% and 2% respectively.[3] Previous studies have demonstrated risk for VTE post CRS for patients with peritoneal disease as high as 30-50% without appropriate VTE prophylaxis.[4] There is also significant mortality associated with post operative VTE in these patients, reported as a 20-fold increased risk.[5] Clearly, VTE represents a major concern in patients undergoing CRS.

ROTEM is a modern, point of care viscoelastic haemostatic assay which measures multiple properties of haemostasis from initiation of coagulation cascade to fibrinolysis. It has been used to guide haemostatic resuscitation in cardiac surgery, liver transplant as well as major trauma.[6] Compared to conventional coagulation studies, ROTEM has an unparalleled rapid turnaround time and can detect hypercoagulable states, hyperfibrinolysis and mixed coagulation states.[7] Previous studies have demonstrated insufficiencies of conventional coagulation tests specifically in CRS with HIPEC.[8] The existing literature has focused on post operative changes in coagulation profiles after CRS and HIPEC, but there exists a paucity of information on pre-existing or 'baseline' hypercoagulability in these patients.[9-12] The aim of this study was to evaluate the prevalence, preoperative risk factors and outcomes of baseline hypercoagulability detected by ROTEM in peritoneal carcinomatosis patients undergoing CRS.

METHODS

Study design

We conducted a retrospective cohort study in the peritoneal malignancy unit at St George hospital, Sydney on all patients undergoing CRS between 2019 and 2023 who underwent ROTEM testing immediately prior to the induction of anaesthesia. This study was designed to align with strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.

Participants

The inclusion criteria were adult patients (aged 18 years or older), with a diagnosed peritoneal malignancy undergoing elective laparotomy for CRS. Exclusion criteria were patients with known coagulation disorders or those on anticoagulant therapy. All patients adhered to standard perioperative care including perioperative VTE prophylaxis and liberal use of imaging to diagnose thromboembolic events.

Data collection

ROTEM data extraction was performed in the previously described manner.[13] Hypercoagulability on ROTEM test was defined as decreased clotting time (CT; CT-intem <100s, CT-extem <38s, CFT-intem <30s), decreased clot formation time (CFT; CFT-intem <30s, CFT-extem <34s) or increased maximum clot formation (MCF; MCF-intem >72 mm, MCF-extem >72 mm).[7] Patients were subsequently divided into two groups based on this result: Group A (hypercoagulable) and B (normal coagulation).

Electronic and paper medical records were used to gather baseline characteristics including gender, age at operation and primary tumour site. Preoperative blood tests, performed a day prior to surgery, were recorded including carcinoembryonic antigen (CEA), CA125, CA 19.9, creatinine, albumin, haemoglobin (hb), platelet count and international normalised ratio (INR). Operative factors were recorded including whether it was an initial or repeat CRS, operative peritoneal cancer index (PCI) and HIPEC regimen. Outcomes included the volume of intraoperative blood products, operating time, estimated blood loss, development of post operative DVT and PE, and length of hospital stay.

Statistical analysis

Analyses were undertaken using SPSS, version 29 (SPSS Inc., Chicago, Ill, USA). Categorical variables were described using number and percentages. Pearson's Chi-square test or Fisher's exact test, when appropriate, were used to compare groups. Continuous variables were described using mean and standard deviation or median and interquartile range when skewed. Differences between groups were compared using independent t test. When skewed, Mann Whitney U test was used. Statistical significance was set at $p<0.05$. Stepwise binomial logistic regression was performed to compare patients with baseline hypercoagulable and normal coagulation state including key baseline variables and variables with significant difference on univariate analysis.

Ethics approval was obtained through the local health district and assessed as low/negligible risk (2023/ETH02752).

RESULTS

A total of 70 patients were included, with a mean age of 58 years and 44 (63%) were female (Table 1). The overall median operative PCI was 13 and mean operating time was 9.5 hours. Median length of stay was 21 days. 18 patients (26%) developed a DVT or PE post operatively. Based on ROTEM results, there were 23 patients in group A (32.9%) and 47 patients in group B (67.1%). Characteristics of these groups are reported in Table 2.

On univariate analysis, group A had higher median operative PCI (33/39 vs 10/39, p=0.003), lower preoperative haemoglobin (p<0.001), higher platelet count (p=0.001) and higher INR (p=0.007), albeit median platelet count and INR were within normal range (Table 2). Primary tumour type was more likely to be appendiceal in Group A than B (47.8% vs 23.4%, p=0.039). Group A required significantly more intraoperative transfusion with packed red blood cells (PRBC) (6.8 vs 3.7, p=0.014) but not platelets (p=0.6), plasma (p=0.9)/ cryoprecipitate (p=0.8) and had a significantly longer length of stay (37 vs 20 days, p=0.01). Although group A had higher incidence of venous thromboembolic events (30.4% vs 23.4%), this did not reach statistical significance. Interestingly, half of all patients who suffered VTE (9/18) had appendiceal primary tumour which was significantly higher compared to other tumour primaries (p=0.049). Multivariable analysis with binomial logistic regression demonstrated PCI remained statistically significant when controlling for key variables (p=0.007). There was 6.2% (95% CI=1.017-1.110) increased risk of baseline hyper-coagulability for every point increase in PCI. In the multivariable model lower Hb also remained statistically significant (OR=0.949, 95% CI=0.913-0.986, p=0.007) as did higher baseline platelet count (OR=1.027, 95% CI=1.001-1.053, p=0041) in group A. Units of intraoperative PRBC transfusion did not remain significant when controlling for Hb (OR=1.059, 95% CI=0.933-1.201, p=0.057). Length of stay did not remain significant when controlling for PCI (OR 1.021, 95% CI=0.994-1.048, p=0.123).

Table 1: Clinical characteristics of entire cohort of patients undergoing CRS (n=70).

Characteristics	
Female, N (%)	44 (62.9)
Age in years, mean±SD	58±12
Primary tumour site N (%)	
Appendix	22 (31.4)
Colorectal	22 (31.4)
Gynaecological	15 (21.4)
Mesothelioma	5 (7.1)
Gastric	3 (4.3)
Gallbladder	1 (1.4)
Pancreatic	1 (1.4)
Adenocarcinoma unclear origin	1 (1.4)
Preoperative blood results	
CEA, (ng/ml), median (IQR)	4 (11)
CA 19.9 (kU/l), median (IQR)	19 (41)
CA 125 (kU/l), median (IQR)	23 (69)
Creatinine (mmol/mol), median (IQR)	68 (23)
Albumin (g/l), mean±SD	36±6
Haemoglobin (g/l), mean±SD	120±18
Platelets (x10^9/l), median (IQR)	279 (149)
INR, mean±SD	1±0.1
Operative factors	
First CRS, N (%)	50 (71.4)
Operative PCI, median±IQR	13 (28)
HIPEC regimen, N (%)	
Mitomycin	38 (54.3)
Cisplatin	11 (15.7)
Carboplatin	4 (5.7)
Oxaliplatin	5 (7.1)
Mitomycin and cisplatin	6 (8.6)
No HIPEC	6 (8.6)
Operating time in hours, mean±SD	9.5±2.4
Estimated blood loss (ml), median (IQR)	1150 (725)
Units of packed red blood cells, mean±SD	5±5
Units of plasma, mean±SD	1.7±2.6
Units of platelets, mean±SD	0.3±0.7
Units of cryoprecipitate, mean±SD	7.7±6.2
Post operative parameters	
Length of stay in days, median (IQR)	21 (24)
Post-operative DVT or PE, N (%)	18 (25.7)
Post-operative DVT or PE in appendix primary, N (%)	9 (50)

Table 2: Clinical characteristics of patients divided by group.

Characteristics	Group A (n=23)	Group B (n=47)	P value
Female, N (%)	13 (56.5)	31 (66.0)	0.443
Age in years, mean±SD	59±15	58±10	0.946
Primary tumour site N (%)			
Appendix	11 (47.8)	11 (23.4)	0.039
Colorectal	5 (21.7)	17 (36.2)	0.222
Ovarian	2 (8.7)	13 (27.7)	0.069
Mesothelioma	3 (13.0)	2 (4.3)	0.322
Gastric	0 (0)	3 (6.4)	0.546
Gallbladder	1 (4.3)	0 (0)	
Pancreatic	0 (0)	1 (2.1)	
Adenocarcinoma unknown origin	1 (4.3)	0 (0)	
Preoperative blood results			
CEA (ng/ml), median (IQR)	6 (44)	4 (10)	0.35
CA 19.9 (kU/l), median (IQR)	20 (135)	18 (35)	0.412
CA 125 (kU/l), median (IQR)	35 (91)	21 (70)	0.158
Creatinine (mmol/mol), median (IQR)	69 (22)	67 (24)	0.95
Albumin (g/l), mean±SD	34±19	38±4	0.231
Haemoglobin (g/l), mean±SD	110±16	126±7	<0.001
Platelets (x10^9/l), median (IQR)	377 (157)	240 (112)	<0.001
INR, mean±SD	1.1±0.1	1.0±0.1	0.007
Operative factors			
First CRS, N (%)	15 (65.2)	35 (74.5)	0.421
Operative PCI, median (IQR)	33 (31)	10 (22)	0.003
HIPEC regimen N (%)			
Mitomycin	11 (50)	26 (55.3)	
Cisplatin	0 (0)	11 (23.4)	
Carboplatin	1 (4.5)	3 (6.4)	
Oxaliplatin	2 (9.1)	3 (6.4)	
Mitomycin and cisplatin	3 (13.6)	3 (6.3)	
No HIPEC	5 (22.7)	1 (2.1)	
Operating time in hours, mean±SD	9.4±2.8	9.6±2.2	0.748
Estimated blood loss (ml), median (IQR)	1000 (1875)	1250 (1180)	0.391
Units of packed red blood cells, mean±SD	6.8±6.5	3.7±3.7	0.014
Units of plasma, mean±SD	1.7±2.3	1.8±2.7	0.915
Units of platelets, mean±SD	0.4±0.8	0.3±0.7	0.602
Units of cryoprecipitate, mean±SD	7.9±8.3	7.6±5	0.842
Post operative parameters			
Length of stay in days, median (IQR)	37 (46)	20 (9)	0.01
Post operative DVT or PE, N (%)	7 (30.4)	11 (23.4)	0.53

DISCUSSION

This is an innovative study that evaluated the use of ROTEM to identify patients with pre-existing or baseline hypercoagulability, which exists in one third of our patients with peritoneal carcinomatosis. Hypercoagulability was associated with increased tumour burden (i.e. PCI) and appendiceal primary tumours, which subsequently conferred higher incidence of VTE events. Hypercoagulability was also associated with lower baseline haemoglobin and consequent higher transfusion requirements of packed red blood cells. These findings highlight the increased sensitivity of ROTEM in identifying baseline changes in coagulation, supporting the increased use of ROTEM as a useful tool in goal-directed perioperative management of complex peritoneal carcinomatosis patients.

Baseline hypercoagulability identified with thromboelastometry (TEM) has also been reported in colorectal cancer, breast cancer, renal cell carcinoma and lung cancer.[14-16] In one study, hypercoagulability on thromboelastography (TEG) was shown to be significantly higher in patients with lung cancer with cryptogenic ischaemic stroke compared to those with lung cancer without ischaemic stroke and healthy controls, concluding that baseline hypercoagulability is a predictor of thromboembolic events.[15] This supports the idea that cancer patients with baseline hypercoagulability are at increased risk of developing thromboembolic

complications, and therefore require close monitoring and could benefit from early detection or additional prevention strategies. This has also been supported in other studies evaluating the use of ROTEM in non-cardiac surgery.[17]

On the other hand, there is ongoing debate about the utility of baseline use of ROTEM in predicting VTE events, as some studies did not demonstrate an association between hypercoagulability and VTE events.[14,18] One possible reason for these discrepancies may include the variability in standardising a definition of hypercoagulability between TEG and ROTEM. In the present study, baseline hypercoagulability was associated with overall higher rates of VTE but this did not reach statistical significance, likely due to the small sample size. Other factors which may have contributed in our cohort include the practice of standardised VTE prophylaxis, and emphasis on early mobilisation in keeping with guidelines for optimal perioperative care for CRS patients.[19] This includes preoperative and post operative chemical VTE prophylaxis, and mechanical prophylaxis with compressive stockings.

Interestingly, we found that a significantly higher proportion of patients with appendix tumours were hypercoagulable and had a demonstratable association with a higher rate of VTE. Previous studies have revealed primary tumour and cancer stage to significantly affect VTE risk, with the highest rates of VTE in patients with pancreatic, stomach, ovarian, mesothelioma and lung cancers, and higher rates in advanced or metastatic cancer.[20,21] Given the rarity of appendix cancers, little data exists as to the risk of VTE in this population. Larger studies have demonstrated variations in their observations of VTE risk in those undergoing CRS with appendiceal primaries.[5,9] Therefore, this likely represents a novel finding.

In keeping with our results, previous literature suggests that a greater burden of disease, as measured by PCI, has been associated with abnormal postoperative coagulation.[10] Our study, however, has demonstrated that higher PCI is in fact significantly related to a preoperative or baseline hypercoagulable state that exists in these patients, rather than the effect of a systemic response to anaesthesia or surgery. This is another novel finding which has not been reported in the literature previously. Higher PCI is also a known predictor of more extensive surgery, longer operative times, length of stay as well as increased morbidity including risk of VTE events.[22,23] Early identification of those with higher PCI as high risk populations can therefore allow for individualised approaches to risk reduction of perioperative morbidity and mortality predicted from hypercoagulability.

ROTEM offers an alternative to conventional coagulation tests which have shown inadequacies in identifying hypercoagulability and in being poor predictors for post operative bleeding after major surgery.[12] Our results show that while preoperative platelets and INR were significantly higher in the hypercoagulable cohort, both groups had medians within a normal range. This adds to the existing literature around insufficiencies of conventional coagulation studies in patients undergoing CRS.[8,24,25] Conventional coagulation tests examine the plasma, whereas ROTEM samples the whole blood, from which it can more thoroughly assess the interaction of all blood components involved in coagulation.[13,26] Intraoperative stressors such as blood loss, consumption lysis, massive fluid and electrolyte shifts and HIPEC coagulopathy considerably affect coagulation in CRS patients.[8,9,12,25] Given baseline hypercoagulability, the established post operative coagulation changes in this patient population and consequent high VTE risk in this population, there is a need to explore more sensitive tests, such as ROTEM and TEG, to optimise perioperative care in CRS.

Another interesting observation from our study is the lower baseline haemoglobin in the hypercoagulable group. Not surprisingly, this group required a larger number of red blood cell transfusions, likely a consequence of preoperative anaemia. One-third of preoperative surgical oncology patients present with anaemia.[27] In the context of malignancy this is usually multifactorial and can be due to direct effects of the tumour such as intraluminal bleeding or tumour haemorrhage, indirect effects of the tumour such as anaemia of chronic disease, poor nutrition and haemolysis, and indirect effects of cancer treatment including bone marrow suppression from chemotherapy and radiotherapy and nutritional deficiencies.[28] It is known that preoperative anaemia predicts for poorer survival in colorectal cancer.[28,29] Compounding this, red blood cell transfusion is associated with poorer outcomes including reduced survivability due to their immunosuppressive and procoagulant effects.[22,29] In the context of CRS, use of blood products has been associated with abnormal post operative coagulation and thus restrictive blood transfusion policy is recommended in the care of CRS patients.[10,12,29] The practice of ROTEM guided intraoperative transfusion in the context of orthotopic liver transplant has demonstrated benefits including reduced operative blood loss, fresh frozen plasma transfusion and cost savings compared to conventional coagulation guided haemostatic resuscitation.[30] It remains to be elucidated the benefits of ROTEM-guided transfusion in CRS, however, identifying preoperative anaemia as a risk factor for patients requiring increased transfusion may help to direct perioperative anaesthetic management.[31]

This study is strengthened by the fact that it was performed in a high volume peritoneal malignancy unit. All data was retrieved from a prospectively maintained database. The authors acknowledge the primary weakness which is the modest sized cohort, largely due to the rarity of peritoneal carcinomatosis.[32] Additionally, the variation

in definition of hypercoagulability based on ROTEM may reduce the generalisability of these results. A future large, multicentre study to understand the longitudinal relationship between a preoperative hypercoagulable state and thromboembolic complications is needed.

CONCLUSION

The prevalence of preoperative hypercoagulability exists in one third of patients with peritoneal carcinomatosis undergoing CRS. Hypercoagulability was associated with increased PCI and appendix tumours. This translated to a significant increase in VTE events in those with an appendiceal primary, but not in the overall cohort. Lower preoperative haemoglobin was also a predictor of hypercoagulability with consequent increased transfusion of red blood cells. ROTEM was useful in detecting subtle changes in coagulation not detected by conventional pathology tests. This supports its use as a valuable goal-directed tool for perioperative management of complex peritoneal malignancy patients.

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