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REPORTS OF ORIGINAL INVESTIGATIONS

Coagulation after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a retrospective cohort analysis

Coagulation après cytoréduction chirurgicale et chimiothérapie hyperthermique intrapéritonéale : analyse de cohorte rétrospective

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Abstract

Purpose *Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) benefit patients with peritoneal carcinomatosis. Nevertheless, this therapy is associated with considerable postoperative pain due to the extensive abdominal incision. While epidural analgesia offers efficacious pain control, CRS and HIPEC therapy is associated with perioperative coagulopathy that may impact its use. The purpose of this retrospective study is to characterize the postoperative coagulopathy in this patient subset and to develop a model that will help predict those at risk.*

Methods *Our database of patients treated with CRS and HIPEC (n = 171) was reviewed to assess perioperative changes in platelet count, international normalized ratio (INR), and partial thromboplastin time (PTT). Abnormal coagulation was defined by platelet count* $< 100 \times 10^{-9} \cdot L^{-1}$, *INR* ≥ 1.5, *or PTT* ≥ 45 *sec. Severe abnormality in coagulation was defined by platelet count* $< 50 \times 10^{-9} \cdot L^{-1}$, *INR* > 2.0, *and/or PTT* > 60 *sec. A logistic regression model was developed to determine if patient, disease, and/or surgical factor(s) were associated with the development of postoperative coagulopathy. Epidural catheter management in this patient population was also reviewed.*

Results *Significant differences (adjusted* $P < 0.007$*) were noted between median preoperative and postoperative platelet and INR values on postoperative days (POD) 0 through 6 and days 0 through 3, respectively. Highest observed median differences between preoperative and postoperative values showed a decrease in platelet count of* $94 \times 10^{-9} \cdot L^{-1}$ *(POD 2 and P'OD 3), an increase in INR of 0.2 (POD 0 to POD 2), and a decrease in PTT of 3.1 sec (POD 5). Coagulopathy and severe coagulopathy occurred in 38% and 4.7% of patients, respectively. Predictors of coagulopathy included intraoperative transfusion of packed red blood cells (PRBCs) and perhaps the peritoneal carcinomatosis index (PCI). Epidural catheters were inserted in 26 patients for a median [IQR] duration of 7.0 [5.0-7.0] days without complication. At the time of their removal, no blood products were required to correct abnormal coagulation values.*

Conclusions *Altered coagulation may appear during the postoperative period in approximately 40% of our patients treated with CRS and HIPEC. Intraoperative transfusion of RBCs and possibly increased PCI are associated with abnormal postoperative coagulation. Close monitoring of coagulation parameters is required to help ensure safe removal of an epidural catheter.*

Résumé

Objectif *La cytoréduction chirurgicale (CRC) et la chimiothérapie hyperthermique intrapéritonéale (CHIP)*

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sont des thérapies offertes aux patients atteints de carcinomatose péritonéale. Néanmoins, ce traitement est associé à une douleur postopératoire considérable en raison de l'incision abdominale étendue. L'analgésie péridurale offre un contrôle efficace de la douleur, mais le traitement par CRC et CHIP est associé à une coagulopathie périopératoire qui pourrait en limiter l'utilisation. L'objectif de cette étude rétrospective est de caractériser la coagulopathie postopératoire dans ce groupe de patients et d'élaborer un modèle qui contribuera à prédire quels sont les patients à risque.

Méthodes *Notre base de données de patients traités par CRC et CHIP (n = 171) a été examinée pour évaluer l'évolution périopératoire du nombre de plaquettes, le rapport international normalisé (INR) et le temps de thromboplastine partiel activé (aPTT). Une coagulation anormale était définie par un nombre de plaquettes $< 100 \times 10^{-9}{\cdot}L^{-1}$, un INR $\geq$ 1,5, ou un aPTT $\geq$ 45 s. Une anomalie grave de la coagulation était définie par un nombre de plaquettes $< 50 \times 10^{-9}{\cdot}L^{-1}$, un INR $>$ 2,0 et/ou un aPTT $>$ 60 s. Un modèle de régression logistique a été élaboré pour déterminer si le patient, la pathologie et/ou des facteurs chirurgicaux étaient associés à la survenue de la coagulopathie postopératoire. La gestion des cathéters périduraux a également été analysée dans cette population de patients.*

Résultats *Des différences significatives (P ajusté $<$ 0,007) ont été notées entre les valeurs pré- et postopératoires du nombre de plaquettes et de l'INR au cours, respectivement, des jours postopératoires 0 à 6 et 0 à 3. Les différences médianes les plus hautes observées entre les valeurs pré et post opératoires ont montré une diminution du nombre de plaquettes de $94 \times 10^{-9}{\cdot}L^{-1}$ (jours postopératoires 2 et 3) et une augmentation de l'INR de 0,2 (jours post op. 0 et 2) et une diminution de l'aPTT de 3,1 sec (jour post op. 5). Une coagulopathie et une coagulopathie sévère sont survenues chez, respectivement, 38 % et 4,7 % des patients. Les éléments prédictifs de la coagulopathie étaient, notamment, la transfusion peropératoire de culots de globules rouges et — peut-être — l'indice de carcinomatose péritonéale (ICP). Des cathéters épiduraux ont été insérés chez 26 patients pour une durée médiane (écart interquartile) de 7,0 (5,0-7,0) jours sans complication. Au moment de leur retrait, aucun produit sanguin n'a été nécessaire pour corriger les valeurs anormales des paramètres de coagulation.*

Conclusions *Un trouble de la coagulation peut apparaître au cours de la période postopératoire chez environ 40 % de nos patients traités par CRC et CHIP. La transfusion peropératoire de globules rouges et peut-être une augmentation de l'ICP sont associées à une coagulation postopératoire anormale. Une surveillance étroite des paramètres de coagulation est requise pour contribuer à assurer un retrait sécuritaire d'un cathéter épidural.*

Peritoneal carcinomatosis (PC) was previously considered a fatal stage of many gastrointestinal malignancies, and patients received palliative treatment with a median survival of three to nine months dependent on initial staging.[1] Presently, PC is viewed as a confined locoregional spread, analogous to isolated hepatic metastasis from colorectal cancer.[2] Peritoneal carcinomatosis patients frequently experience severe morbidity due to recurrent bowel obstruction, ascites, and tumour mass effect. Aggressive targeted treatments, including cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) are currently used to treat many forms of peritoneal carcinomatosis.[2,3] The surgery is undertaken to achieve macroscopic tumour resection, and the HIPEC is administered as a localized form of chemotherapy. The combination of CRS and HIPEC has shown mortality benefits in select patients with primary and secondary peritoneal carcinomatosis.[4-10] Due to the unfortunate incidence of PC[11] and encouraging long-term benefits of treatment, the number of patients undergoing CRS and HIPEC is expected to rise.

Patients treated with CRS and HIPEC[12] undergo an extensive surgical procedure that is associated with large fluid shifts, hyperthermic insult, and exposure to chemotherapeutic agents.[12-15] Managing postoperative pain can be challenging, owing to an extensive abdominal incision. While the benefits of epidural analgesia following major abdominal surgery are well described, the combination of CRS and HIPEC is associated with a postoperative coagulopathy[13-15] that can impact epidural management in this unique type of patient. While thoracic epidural analgesia has been described for patients undergoing CRS and HIPEC,[13,14,16,17] information is lacking regarding the identification of patients at risk of developing postoperative coagulopathy. Therefore, the objective of this study is to review the database of patients treated at our institution with CRS and HIPEC in order to characterize their postoperative coagulation profile and to assess whether patient or surgical factors are associated with the development of postoperative coagulopathy. Finally, we describe our experience with perioperative epidural management in this cohort.

Methods

Approval for this project was obtained from the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary (19 January 2012; E-24278). The records for

patients treated with CRS and HIPEC for carcinomatosis of gastrointestinal or mesothelial origin at the Foothills Medical Centre from January 2007 to October 2011were extracted from a database maintained by the Division of Surgical Oncology. Although this treatment has been performed at our institution since 2000, it has only been since January 2007 that records have been maintained in an electronic form that simplifies the extraction of relevant information. Patients were excluded from this analysis if they were found to have unresectable disease at the time of laparotomy and if they were not treated with HIPEC. A single senior anesthesia resident reviewed the database, patient charts, and laboratory values.

The primary outcome of this study was the perioperative coagulation profile: that is, the platelet count, international normalized ratio (INR), and partial thromboplastin time (PTT) preoperatively through postoperative day (POD) 6. When more than one value was available for a given day, the most abnormal value was recorded unless it was clear in the progress notes or subsequent laboratory results that the data were spurious. Although there is lack of consensus regarding the precise definition of "coagulopathy", we considered abnormal coagulation to include a platelet count $<100 \times 10^{-9}\cdot L^{-1}$, INR $\geq$ 1.5, or PTT $\geq$ 45 sec. We considered severe abnormality to include a platelet count $< 50 \times 10^{-9}\cdot L^{-1}$, INR > 2.0, or PTT > 60 sec. These criteria are in keeping with other studies concerned with the potential harmful impact of abnormal coagulation values on placement or removal of an epidural catheter.[18]

Demographic information extracted from the patient records included age, sex, weight, and comorbidities. Information was also sought for tumour-related variables (type, histology); peritoneal carcinomatosis index (PCI), i.e., preoperative scoring of tumour burden over 13 segments of the abdomen[9]; completeness of cytoreduction score (CCR)[19]; procedure-related factors (blood loss, surgical duration, crystalloid infused, colloid infused, blood products transfused); chemotherapy protocol utilized; epidural use (duration, coagulation profile at removal, complications); procedural complications (mortality rates, reoperation rates, intensive care unit admission, perioperative complications); and duration of hospitalization.

The anesthetic technique was not standardized and the surgical procedure has been described elsewhere.[20] In 2008, the chemotherapy protocol changed (from mitomycin C 15 mg *ip* in the operating room [OR] followed by chemotherapy utilizing 5-fluorouracil 1,000 mg daily for five days) to a new regime (oxaliplatin 400 mg *ip* and 5-fluorouracil 800 mg *iv* administered in the OR). There were also slight variations in the chemotherapy protocol for patients with mesothelioma or gastric primary tumours. In all cases, the intraoperative intraperitoneal chemotherapy was given for 60 min at 40-42°C. Venous thromboembolism prophylaxis was used in all patients with adherence to American Society of Regional Anesthesia (ASRA) guidelines.

Statistical analysis

Patient demographic, intraoperative, and postoperative variables were assessed for normality using the Shapiro-Wilk test ($P < 0.05$). Data are presented as either mean (SD) or median [interquartile range (IQR)]. Count data are presented as number (n) and percentage (%). Normal distribution of coagulation metrics (daily platelet, INR, and PTT) was assessed using the Shapiro-Wilk test ($P < 0.05$). Values are reported as either mean (SD) or median [IQR] and minimum-maximum. All platelet values are reported as $10^{-9}\cdot L^{-1}$. Freidman tests were completed to assess significant changes ($P < 0.05$) in coagulation metrics over time (preoperative to POD 6). Significance was further evaluated using *post hoc* Wilcoxon signed-rank tests with separate Bonferroni correction for each coagulation metric (adjusted $P = 0.007$). Individual comparisons were restricted to preoperative *vs* postoperative values.

A model to predict the probability of coagulopathy was developed using logistic regression. The following variables were considered as possible covariates: preoperative platelet values, preoperative anticoagulation medication, prior surgical score (PSS - two levels: none/biopsy/limited and debulking/CRS + HIPEC), tumour type (six levels), CCR (three levels: CCR 0 = no macroscopic residual disease; CCR 1 = no residual nodule > 5 mm in diameter; and CCR 2 = diameter of residual nodules > 5 mm),[9] blood loss, PCI, presence of splenic and hepatic stripping (two levels), intraoperative fresh frozen plasma (FFP) transfusion, HIPEC drug (three levels), surgical duration, and intraoperative red blood cell (RBC) transfusion. Covariates with missing data (preoperative platelets = 19 [11.1%] missing) were subjected to ten imputations upon which missing data were calculated, and an average value was generated using an iterative Markov chain Monte Carlo approach. Preoperative INR and PTT values were not considered for multiple imputation and subsequent consideration for model inclusion due to missing values in a considerable percentage of patients (74.9% and 77.2%, respectively). Prior to univariate analysis of the candidate covariates, correlations of $P > 0.7$ were found via Spearman's rank coefficient between intraoperative RBC transfusion, intraoperative FFP transfusion, and blood loss. Univariate logistic regression was then used to assess the strength of these three variables in predicting the probability of coagulopathy. Wald statistics were 18.54, 12.93, and 10.46 for RBC transfusion, blood loss, and FFP transfusion, respectively,

supporting the inclusion of intraoperative RBC transfusion as a candidate covariate in our predictive model. Univariate logistic regression was also used to select a single surgical score (PSS, PCI, or CCR) to consider for model inclusion. Wald statistics of 0.88 (PSS), 20.04 (PCI), and 7.05 (CCR) supported the inclusion of PCI as a candidate covariate in predicting the probability of coagulopathy.

The procedure for selecting a variable for inclusion in a multivariate model followed that of Hosmer *et al.*[21] Candidate variables were considered for inclusion in a multivariate model if $P < 0.25$.[21] Pooled P values are reported for imputed candidate variables. As such, seven variables met this criterion. Given that coagulopathy was limited to 65 events in our cohort, the six candidate covariates with the highest Wald statistics were considered for initial development of a multivariate model. Results of the initial predictive multivariate model guided generating a reduced covariate model incorporating only covariates presenting with $P < 0.01$. Estimated independent covariate coefficients in the reduced model were compared with their respective values in the initial multivariate model. If regression coefficients associated with significant covariate predictors ($P < 0.01$) presented with a change of $> 20\%$ between initial and reduced covariate models, covariates not initially included in the reduced predictive model were added separately to assess the resulting adjustment. If the added covariate generated a subsequent adjustment in parameter coefficient values of the significant predictors to $< 20\%$ of that in the initial multivariate model, the covariate—despite absence of statistical significance—was included in the final predictive model.[21] The final reduced covariate model was compared with the initial covariate model using the likelihood ratio Chi square (χ^2) test. The performance of the final predictive model was assessed using the concordance index (c-statistic). Additionally, on account of its utility as a preoperative clinical index, a range of PCI cut-off values for predicting coagulopathy was explored with respect to specificity and sensitivity from a receiver operator characteristic (ROC) curve. All statistical tests were completed using IBM SPSS® 19.0 statistics software (IBM, Armonk, NY, USA).

Results

Preoperative, intraoperative, and postoperative patient characteristics are presented in Tables 1 through 3. Significant differences (adjusted $P < 0.007$) were noted

Table 1 HIPEC & CRS patient demographics (n = 171)

Variable	n (%); Median [IQR]
Sex M/F	75 (44) / 96(56)
Age	53.0 [47.0-64.0]
Weight (kg)	80.0 [66.0-89.0]
ASA I/II/III	14 (8) / 83 (49) / 74 (43)
*Preoperative Anticoagulation	15 (9)
Preoperative Chemotherapy	60 (35)
Primary Tumour Location	
Appendix	99 (58)
Colon	57 (3)
Small Bowel	3 (2)
Gastric	6 (4)
Mesothelioma	4 (2)
Ovary	2 (1)
PSS	
None/Biopsy/Limited	153 (89)
Debulking /CRS + HIPEC	18 (11)

ASA = American Society of Anesthesiologists; CRS + HIPEC = cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; IQR = interquartile range; PSS = prior surgical score. *Anticoagulation was defined as administration of therapeutic dose heparin/low molecular weight heparin, or coumadin, not prophylactic dosing

Table 2 HIPEC & CRS patient intraoperative variables (n = 171)

Variable	n (%); Median [IQR]
Duration of case in minutes	415 [350-477]
PCI	21.0 [6.0-34.0]
HIPEC Drug	
Mitomycin C	35 (21)
Oxaliplatin	129 (75)
Cisplatin + Adriamycin	7 (4)
Hepatic stripping and/or Splenic stripping/resection	88 (49)
Fluids in OR Median [IQR]	
Crystalloid (mL)	5,000 [3,613-6,775]
Colloid (mL)	1,000 [500-1,500]
Blood Products in OR	
n patients given; median units/doses [IQR]	
RBC (units)	76; 3 [2-5]
Platelets (unit = 4 pooled donors)	17; 1 [1-2]
FFP (units)	27; 4 [2-8]
Cryoprecipitate (units)	4; 10 [10-10]
Tranexamic acid (n)	103 (60)
CCR	
0 (no disease)	154 (90)
1 (present < 0.25 cm)	17 (10)

CCR = completeness of cytoreduction score; IQR = interquartile range; FFP = fresh frozen plasma; HIPEC & CRS = hyperthermic intraperitoneal chemotherapy and cytoreductive surgery; OR = operating room; PCI = peritoneal carcinomatosis index; RBC = red blood cells

Table 3 HIPEC & CRS postoperative variables (n = 171)

Variable	n (%)
Immediate postoperative ICU admission	80 (46.8)
ICU length of stay (days) median [IQR]	0.0 [0.0-2.0]
Blood Products	
n patients given; median [IQR]	
RBC (units)	63; 2 [2-4]
Platelets (unit = 4 pooled donors)	5; 1 [1-1]
FFP (units)	23; 4 [2-6]
Cryoprecipitate (units)	3; 10 [10-10]
*Anticoagulated (≤ 6 days postoperatively)	8 (4.6)
VTE Prophylaxis	
None	1 (0)
Heparin 5,000 U *bid*	6 (4)
Heparin 5,000 U > *tid*	45 (26)
LMWH	119 (70)
EPIC used	43 (25)
EPIC duration (hours) median [IQR]	0 [0-1]
Return to OR	
Bleeding Complication	3 (2)
Non-Bleeding Complication	14 (8)

EPIC = early postoperative intraperitoneal chemotherapy; FFP = fresh frozen plasma; HIPEC & CRS = hyperthermic intraperitoneal chemotherapy and cytoreductive surgery; ICU = intensive care unit; IQR = interquartile range; LMWH = low-molecular-weight heparin; OR = operating room; RBC = red blood cells; VTE = venous thromboembolism

*Anticoagulation was defined as administration of therapeutic dose heparin; no patient receiving anticoagulation therapy was given an epidural

between median preoperative platelet values and values collected on POD 0 through POD 6, inclusive (Tables 4, 5). The greatest observed median [IQR] reduction in platelet count from preoperative values (255 [212-325] $\times 10^{-9}\cdot L^{-1}$) occurred on POD 3 (median difference, −94; 95% CI, −106 to −87), with median values falling to 151 [125-208] $\times 10^{-9}\cdot L^{-1}$ (Tables 4, 5). Platelet counts recovered to 223 [161-316] $\times 10^{-9}\cdot L^{-1}$ by POD 6 (Table 4). Preoperative median [IQR] INR values (1.0 [1.0-1.1]) were significantly lower than values collected on POD 0 through POD 3, inclusive (Tables 4, 5). The highest observed median values of 1.2 were reported on POD days 0 through 2 and POD 6 (Table 4). Preoperative and postoperative PTT values were not significantly different (Tables 4, 5).

Thirty-eight percent (n = 65) of patients presented with coagulopathy (platelet count $<100\times 10^{-9}\cdot L^{-1}$, INR ≥ 1.5, or PTT ≥ 45 sec). Severe coagulopathy (INR > 2.0, platelet counts < 50 $\times 10^{-9}\cdot L^{-1}$, and/or PTT > 60 sec) in the postoperative period occurred in 4.7% of patients. Fibrinogen < 1.5 $\mu Mol\cdot L^{-1}$ during the postoperative period occurred in 5.8% of patients (Table 6). The first iteration from initial multivariate to final reduced covariate model showed a change of 32% in the parameter estimate of intraoperative RBC transfusion (Table 7). Inclusion of PCI in the final model changed the parameter estimates of intraoperative RBC transfusion to within 1% of the initial multivariate model. As such, PCI—despite absence of statistical significance—was included in the final reduced multivariate predictive coagulopathy model, and we consider both intraoperative RBC transfusion and PCI to be predictive of postoperative coagulopathy (Table 8). Log odds (coagulopathy) = $-1.56 + (0.03 \cdot \text{PCI}) + (0.23 \cdot \text{units RBCs transfused in OR})$.

For PCI, the odds ratio was 1.03 (99% CI, 0.99 to 1.07) and for units of RBCs transfused in the OR, the odds ratio was 1.26 (99% CI, 1.01 to 1.58) (Table 7). Using an event (coagulopathy) probability cutoff of 0.5, sensitivity and specificity were 46.2% and 87.7%, respectively, with a c-statistic = 0.73 (95% CI, 0.65 to 0.81). Final multivariate Cox-Snell pseudo R^2 was within 8.9% of the initial multivariate model. The likelihood ratio Chi square test was not significant (χ^2 = 3.95; P = 0.41) (Table 7).

Table 4 Pre- and postoperative coagulation metrics median [interquartile range]

Measurement	Platelets ($10^{-9}\cdot L^{-1}$)			INR			PTT (sec)		
	n	Median [IQR]	Min-Max	n	Median [IQR]	Min-Max	n	Median [IQR]	Min-Max
Pre-Op	152	255 [212-325]	97-989	43	1.0 [1.0-1.1]	0.9-1.4	39	31.0 [28.9-33.2]	25.6-41.9
POD 0	103	195 [140-244]	63-509	105	1.2 [1.1-1.4]	1.0-1.9	98	28.3 [25.9-33.3]	20.5-101.7
POD 1	169	180 [151-230]	60-502	148	1.2 [1.1-1.3]	0.9-2.4	45	28.6 [26.4-31.4]	22.0-150.0
POD 2	167	156 [128-202]	56-433	134	1.2 [1.1-1.3]	0.9-2.0	123	29.8 [27.4-32.7]	22.6-50.0
POD 3	162	150 [125-208]	61-483	111	1.1 [1.0-1.2]	0.9-2.2	102	27.9 [26.1-31.0]	22.2-150.0
POD 4	128	167 [124-231]	60-576	40	1.1 [1.1-1.2]	1.0-1.7	27	29.1 [26.1-31.5]	23.5-80.6
POD 5	130	192 [149-272]	47-583	37	1.1 [1.1-1.2]	0.9-1.8	23	28.4 [26.1-30.4]	23.6-36.0
POD 6	131	223 [161-316]	55-792	29	1.2 [1.1-1.3]	1.0-2.1	16	27.7 [25.9-31.0]	21.8-40.2

IQR = interquartile range; INR = international normalized ratio; n = number of patients with measurements; POD = postoperative day; PTT = partial thromboplastin time

Table 5 Preoperative *vs* postoperative coagulation metrics

Comparison	Platelets (10^{-9}·L)			INR			PTT (sec)		
	n	Median Difference	95% CI Median Difference	*n*	Median Difference	95% CI Median Difference	*n*	Median Difference	95% CI Median Difference
Pre-Op - POD 0	94	−80*	−104 to −68	30	0.2†	0.2 to 0.3	25	−0.5 ($P = 0.85$)	−3.2 to 3.7
Pre-Op - POD 1	150	−72*	−87 to −50	39	0.2†	0.1 to 0.2	35	−2.6 ($P = 0.07$)	−4.4 to 1.0
Pre-Op - POD 2	148	−94*	−110 to −83	36	0.2†	0.1 to 0.2	28	0.2 ($P = 0.72$)	−2.9 to 1.0
Pre-Op - POD 3	144	−94*	−106 to −87	30	0.1†	0.1 to 0.2	25	−2.7 ($P = 0.06$)	−4.7 to 0.1
Pre-Op - POD 4	112	−78*	−94 to −57	15	0.1 ($P = 0.03$)	0.0 to 0.1	10	−1.3 ($P = 0.86$)	−5.6 to 4.8
Pre-Op - POD 5	116	−45*	−67 to −29	13	0.1 ($P = 0.04$)	0.0 to 0.2	8	−3.1 ($P = 0.07$)	−8.3 to 1.9
Pre-Op - POD 6	117	−17*	−39 to −2	8	0.2 ($P = 0.03$)	0.1 to 0.6	3	0.0 ($P = 0.32$)	−9.0 to 0.0

CI= confidence interval; INR = international normalized ratio; *n* = number of comparisons available for Wilcoxon signed-rank test analysis; POD = postoperative day; PTT = partial thromboplastin time. 95% CI for median difference: $[(n+1)/2] \pm 1.96 \cdot (n^{1/2})/2$; where *n* = number of values. *Significant difference (adjusted $P < 0.007$ for multiple comparisons) between preoperative and postoperative platelet values, as assessed via a Wilcoxon signed-rank test. †Significant difference (adjusted $P < 0.007$ for multiple comparisons) between preoperative and postoperative INR values, as assessed via a Wilcoxon signed-rank test

Table 6 Summary of abnormal postoperative coagulation tests

Measurement	*n* (%)
Platelets < 100	29 (17)
Platelets < 50	1 (0.6)
INR > 1.5	40 (23.4)
INR > 2.0	3 (1.8)
PTT > 45	16 (9.4)
PTT > 60	5 (2.9)
INR ≥ 1.5/platelets ≤ 100/PTT ≥ 45	65 (38.0)
INR ≥ 2.0/platelets ≤ 50/PTT ≥ 60	8 (4.7)
Fibrinogen < 1.5	10 (5.8)

INR = international normalized ratio; PTT = partial thromboplastin time

In evaluating the utility of the PCI score as a preoperative coagulopathy discriminant, values of 5.5 and 12.5 corresponded to sensitivities of 0.9 and 0.8, respectively, and to specificities of 0.3 and 0.46, respectively, in differentiating between coagulopathic and non-coagulopathic patients. The c-statistic of the ROC curve was 0.71 (95% CI, 0.63 to 0.79).

Epidural catheters were inserted in 26 patients. Sixteen were placed in the preoperative period, eight in the recovery room, and two on the ward or in the intensive care unit. Epidural catheters were maintained for a median [IQR] duration of 7.0 [5.0-7.0] days without complication. At the time of their removal, no blood products were required to correct abnormal coagulation values. Median [IQR] platelet count at epidural removal was 199 [161-310] $\times 10^{-9}$·L^{-1} ($n = 21$); this information was not available for five patients. Values ranged from 88-492 $\times$ 10^{-9}·L^{-1}, with only one count < 100 $\times$ 10^{-9}·L^{-1}. At the time of catheter removal, the INR was known for eight subjects and all were < 1.3. Partial thromboplastin time was known for seven patients and all values were < 35 sec.

Discussion

We observed that patients treated with CRS and HIPEC may reveal abnormal coagulation tests during the postoperative period. The median platelet counts reached nadir on POD 3, while median INR values reached a maximum value on PODs 0-2 and 6. No significant changes in PTT values were observed. Statistically significant (adjusted $P < 0.007$) differences were found between the median preoperative platelet value and values collected on POD 0 through POD 6, inclusive, and between the median preoperative INR value and values collected on POD 0 through POD 3, inclusive. Thirty-eight percent of patients were identified as "coagulopathic", and 4.7% were classified as "severely coagulopathic". The results of our study with respect to postoperative changes in coagulation tests are similar to those described previously in the same type of patient where decreases in platelet count and increases in INR and PTT have been described.[13-15,22]

The underlying cause of coagulopathy in this patient population is likely multifactorial,[13] and the relative contributions of hyperthermia, chemotherapy, and surgical insult to deranged coagulation are not known. Importantly, regardless of the underlying causes, the postoperative coagulopathy that may develop is relevant to the management of epidural analgesia that would offer superior postoperative pain relief required by these patients. Currently, there is a lack of accepted guidelines for the management of epidural catheters in patients who

Table 7 Univariate and multivariate logistic regression models to predict postoperative coagulopathy

	Univariate		Initial Multivariate		*Final Reduced Multivariate	
	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value	Odds Ratio (99% CI)	*P* value
Variable						
Preoperative platelets (10^{-9}·L^{-1})	1.00 (1.00 to 1.00)	0.60				
Preoperative anticoagulation use ("No" ref.)						
Yes	1.99 (0.68 to 5.76)	0.21				
PCI	1.06 (1.03 to 1.09)	<0.01	1.03 (0.99 to 1.07)	0.18	1.03 (0.99 to 1.07)	0.03
Presence of splenic and hepatic stripping ("No" ref.)						
Yes	2.95 (1.54 to 5.64)	0.01	1.11 (0.45 to 2.75)	0.83		
HIPEC drug (mitomycin C ref.)		0.06		0.17		
Oxaliplatin	2.97 (1.21 to 7.30)	0.02	2.55 (0.95 to 6.88)	0.06		
Cisplatin or Adriamycin	3.00 (0.54 to 16.6)	0.21	1.58 (0.23 to 10.93)	0.64		
Surgical duration (min, anesthetic chart)	1.00 (1.00 to 1.01)	0.01	1.00 (1.00 to 1.00)	0.87		
Intraoperative RBC transfusion (units)	1.40 (1.20 to 1.64)	<0.01	1.26 (1.06 to 1.49)	<0.01	1.26 (1.01 to 1.58)	<0.01
Tumour type (appendiceal ref.)		0.94				
Colon	0.77 (0.39 to 1.50)	0.44				
Small bowel	0.00 (0.00 to N/A)	1.00				
Mesothelioma	1.42 (0.27 to 7.36)	0.68				
Gastric	0.47 (0.05 to 4.70)	0.52				
Primary peritoneal	0.00 (0.00 to N/A)	1.00				

CI = confidence interval; PCI = peritoneal carcinomatosis index; RBC = red blood cells

*Likelihood Ratio χ^2 Test = 3.95 (P = 0.41)

Table 8 Variables predicting coagulopathy (INR > 1.5, Platelets < 100, PTT > 45) using logistic regression

Predictor	Coagulopathy				
	B	SE	*P* value	OR	99% CI
Peritoneal Carcinomatosis Index (PCI)	0.03	0.02	0.03	1.03	0.99 to 1.07
Intraoperative RBC transfusion	0.23	0.09	<0.01	1.26	1.01 to 1.58
Constant	−1.58	0.33	<0.01	0.21	

See Table 7 "Final Reduced Multivariate" model

B = regression coefficient; CI = confidence interval; INR = international normalized ratio; OR = odds ratio; PTT = partial thromboplastin time; RBC = red blood cells; SE = standard error

Linearity of PCI (P = 0.342) and intraoperative RBC transfusion (P = 0.612) assessed via the Box-Tidwell procedure

are at risk for developing postoperative coagulopathy. The abnormal parameters for coagulation tests that we used to define "coagulopathy" reflect those associated with catheter placement or removal which are recognized to increase a patient's risk for spinal cord hematoma.[23,24] Of relevance, these parameters have also been used to assess the risk of neuraxial technique in patients undergoing hepatic resection who may also show indications of postoperative coagulopathy.[18,25,26]

The median nadir platelet count we observed during the postoperative period was well above accepted limits that would preclude safe epidural catheter removal. The risk of epidural-related spinal hematoma in patients with thrombocytopenia may depend on how rapidly the platelet count declines, its underlying etiology, and any accompanying other type of coagulopathy.[23] There is a current lack of consensus in the literature as to a specific platelet count below which there is an increase in the risk of hematoma.[23] With regard to clotting factors, the 2010 ASRA consensus[24] suggests that the risk of spinal hematoma increases considerably if the level of any factor falls to < 40% of baseline (assuming normal range) or when the INR is > 1.5.[24] The elevation in INR that we observed (INR < 1.3) is likely below the level for cause of concern for an increased risk of bleeding at time of removal. In our study, at the time of planned epidural

catheter removal, platelet counts were > 80 x $10^{-9} \cdot L^{-1}$,[23] and the INR was < 1.5, so no blood products were administered to reduce the risk of spinal hematoma. Nevertheless, in a recent study of 215 HIPEC patients who received perioperative epidural analgesia, two patients required platelet infusion to correct a postoperative thrombocytopenia prior to epidural catheter removal.[22] Our observations, and others,[22,23,26] suggest that, while the potential for postoperative coagulopathy is not a contraindication to epidural analgesia in this patient population, appropriate coagulation tests are required during the postoperative period to ensure that the epidural catheters may be safely removed.

A secondary goal of our study was to identify factors associated with postoperative coagulopathy. Intraoperative transfusion of RBCs was the only factor we identified as being significantly ($P < 0.01$) associated with postoperative coagulopathy. The PCI was included in the model despite absence of statistical significance, as its addition generated a needed adjustment to the regression coefficient associated with intraoperative RBC transfusion. In point of fact, the confidence interval associated with PCI is sufficiently wide to suggest that it may be associated with postoperative coagulopathy, and future investigation on this point is required. The requirement for intraoperative RBC transfusion may aid in the management of perioperative analgesia, particularly if catheter insertion is to be considered during the postoperative period, as was the case with two patients in this study.

There are several limitations to our study. Its retrospective nature is a primary limitation that may impact on the accuracy and reliability of data collection. The lack of standardized anesthesia, surgical and postoperative care (including fluid and temperature management), and an altered chemotherapy protocol during the study period may have contributed to the confounding variables that influenced our findings. Another limitation is the lack of preoperative INR and PTT values on all patients, although we anticipate that the majority of patients would have shown normal test results. In addition, we acknowledge that INR and PTT data were available for fewer than 40 (24%) patients per day after POD 3, reaching a nadir of 29 and 16 available INR and PTT measurements, respectively, on POD 6. This greatly restricted the sample sizes available for statistical comparisons between preoperative values and POD 4 through POD 6 values (Table 5). As such, conclusions regarding a lack of significance in median differences between these values must be approached with caution given the low power associated with these comparisons. Moreover, the small number of patients treated with epidural analgesia precludes the ability to make accurate assessments of the rare adverse events and the risk associated with its use.

In conclusion, approximately 40% of our patients treated with CRS and HIPEC showed abnormal coagulation during the postoperative period. Intraoperative transfusion of RBCs and possibly increased PCI were found to be predictors of postoperative coagulopathy. In the majority of our patients, postoperative changes in coagulation are not of sufficient magnitude to affect the management of epidural analgesia. Nevertheless, close monitoring of coagulation tests are required to ensure safe removal of the epidural catheter.

Conflicts of interest None declared.

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