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Epidural analgesia? A prospective analysis of perioperative coagulation in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background: Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) is beneficial in peritoneal carcinomatosis. Epidurals provide excellent pain relief for laparotomies. Coagulopathy (platelet count $<100 \times 10^9$/L, INR>1.5 or PTT >45) occurs with CRS and HIPEC, increasing risk for bleeding complications with epidurals. This prospective study characterizes clot kinetics with thromboelastography (TEG) to determine suitability for epidural analgesia.

Methods: After Research Ethics approval, thirty consented patients had blood collected. Primary data collected included TEG and conventional coagulation measures (platelets, PTT and INR). Secondary data collected included demographics, disease, surgical, intraoperative factors and complications from epidural placement.

Results: Of 30 patients analyzed, two had incomplete data. Four developed abnormal coagulation between the second and fifth post-operative day. For all patients, TEG values remained normal. Post-operative INR was elevated until day 3 (all INR < 1.5). 17 patients received epidural analgesia, 3 demonstrated abnormal conventional coagulopathic criteria despite normal TEG.

Conclusions: In this study CRS and HIPEC do not contribute to the conventional definition of clinical coagulopathy. Clot kinetics indicate that epidural catheters may be recommended for post-operative analgesia.

Introduction

Treatment of peritoneal carcinomatosis has evolved to include cytoreductive surgery (CRS) in combination with heated intraperitoneal chemotherapy (HIPEC) which has demonstrated improved outcomes in subgroups of patients.[1] The indications for this aggressive management modality have increased.[2] This complex treatment strategy requires awareness of associated physiologic derangements, such as temperature swings as well as consequences of a large, raw peritoneal surface including hemodynamic lability, third spacing of fluids, electrolyte and coagulation abnormalities.

Epidural catheters improve post-operative analgesia and ventilation in large laparotomies.[3,4] Previous publications indicate that epidural analgesia for HIPEC procedures reduce postoperative ventilation requirements,[5] however its benefit requires balance with the potential concern of abnormal coagulation.[5–11] Coagulation derangements associated with HIPEC using conventional markers of coagulation have been previously investigated, however clot kinetics measured by thromboelastography (TEG™) remain unknown. TEG™ provides a dynamic assessment of clot formation and stability by integrating multiple coagulation components. In addition to conventional markers of coagulation, this study seeks to ascertain clot kinetics during surgical stages, and to determine suitability of patients for epidural analgesia. The study was

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designed to test the hypothesis that CRS and HIPEC will cause significant changes in coagulation with TEG™ exposing coagulation derangements earlier than commonly utilized conventional markers such as the international normalized ratio (INR) and partial thromboplastin time (PTT).

Methods

This prospective, observational cohort study received institutional approval by the Conjoint Health Research Ethics Board (CHREB: REB13-0439) at the University of Calgary and required written patient consent. Patients 18 years of age or older with any form of peritoneal carcinomatosis were considered. Patients with pre-existing coagulation disorders, or on therapeutic anticoagulation were excluded. All patients received general anesthesia. The anesthetic technique and placement of an epidural catheter was left to the discretion of the attending anesthesiologist. The surgical technique has been well described in the literature[12–14] and choice of intraperitoneal chemotherapy agent was based on pathology type and institutional protocol. Chemical venous thrombosis prophylaxis in the form of Dalteparin 5000 U administered subcutaneously, once daily for 28 days, was utilized postoperatively. Preoperative venous thromboprophylaxis is not routinely provided at our institution for this surgery unless otherwise specified by the surgeon. Post-operatively, the Acute Pain Service followed patients for all needs related to analgesia and nausea.

Primary outcomes included changes in TEG™ (R-time, K-time, alpha angle, maximum amplitude, lysis at 30 min (Ly30)), platelet count, INR and PTT, measured pre, intra and post-operatively. Intraoperative samples were collected in citrated tubes for metabolic variables and TEG™ analysis immediately after induction of anesthesia, at onset of HIPEC, midway through HIPEC and 30 min after conclusion of HIPEC. Samples for INR, PTT and platelet count were collected at initiation of HIPEC and repeated 30 min after its conclusion. Postoperative TEG™ samples were collected for the first three days as this time period is associated with the greatest likelihood of coagulopathy based on previous studies at our institution.[9] INR, PTT and platelet count were collected for the first five days postoperatively. Abnormal coagulation was defined by any one of: platelet count $<100 \times 10^9$/L, INR $\geq$1.5, PTT $\geq$45.[8] TEG™ samples were analyzed according to manufacturer's recommendation using TEG 5000 Hemostatis Analyzer System (Haemonetics Corporation, Braintree MA, USA) with kaolin reagent and heparinase cups which eliminated interference of potential heparin contamination including low molecular weight heparin used in venous thromboprophylaxis. Manufacturer reference values were used as control values for TEG™ parameters.

Statistical analysis

For a small effect size in determining a meaningful effect in coagulation using conventional markers, and 10% attrition, 94 patients were required. Given the relatively infrequent occurrence of this surgery at our institution, a pilot study aimed at recruiting 30 patients was undertaken. Intraoperative metabolic variables, coagulation metrics (platelet count, INR, PTT) and TEG™ parameters were assessed using the Shapiro-Wilk test ($P < 0.05$). Data is presented as mean ± standard deviation (SD) or median [interquartile range]. Multiple imputation was used to calculate missing data for coagulation metrics using an iterative Markov chain Monte Carlo approach. Friedman tests were completed to assess significant changes ($P < 0.05$) in intraoperative metabolic variables, coagulation metrics and TEG™ parameters over time. Significant Friedman test findings guided post-hoc pairwise Wilcoxon ranked sign tests with Bonferroni correction for multiple comparisons to assess significant differences among metabolic variables, TEG™ and coagulation variables. Incidence of epidural hematoma was accessed using the exact binomial test. Statistical analysis was completed using SPSS 19.0 software (IBM, Armonk NY, USA) and R Studio 1.0.153 (RStudio Inc, Boston, MA, USA).

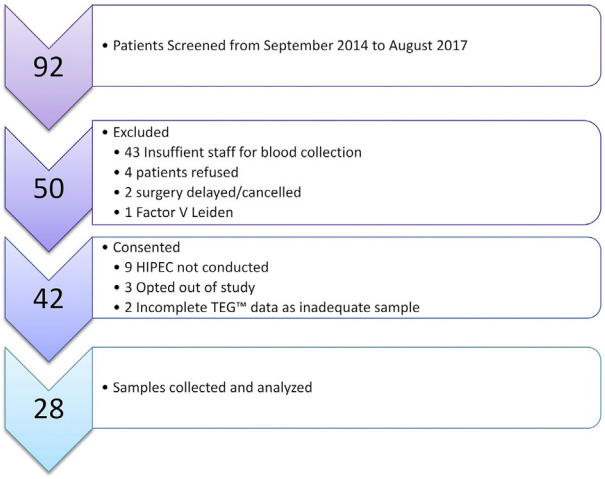

Fig. 1. Patient recruitment schematic diagram.

Results

Thirty patients completed the study; however, two patients were excluded on account of insufficient blood extraction volume for TEG™ analysis (Fig. 1). Patient demographics are presented in Table 1. Intraoperative variables are presented in Table 2. The median time for surgery was 360 min [304–416 min], with a median fluid balance of +5008 mL [3659–6357 mL] (Table 2). Hypothermia was consistently recorded post-induction with a mean of

Table 1
Demographic characteristics of 28 patients undergoing cytoreductive surgery and HIPEC.

Characteristics	mean ± standard deviation, median [interquartile range], or n (%)
Age (y)	58 [46–70]
Sex (female)	17 (60.7%)
Weight (kg)	79.0 ± 21.8
Height (cm)	167.9 ± 11.6
ASA status[a]	
1	2 (7.4%)
2	14 (51.9%)
3	10 (37.0%)
4	1 (3.7%)
Body mass index ($kg \bullet m^{-2}$)	27.8 ± 6.8
Primary cancer diagnosis	
Appendiceal	11 (39.3%)
Mesothelioma	5 (17.8%)
Colorectal	6 (21.4%)
Ovarian	4 (14.3%)
Bowel	1 (3.6%)
Gastric	1 (3.6%)
Peritoneal carcinomatosis index (PCI)	9.0 (0–20)
Completeness of cytoreduction score (CCS)[b]	
0 (no disease)	22 (91.7%)
1 (present < 0.25)	2 (8.3%)

HIPEC, hyperthermic intraperitoneal chemotherapy. ASA, American Society of Anesthesiologists.
[a] ASA status unavailable for one patient.
[b] CCS score unavailable for four patients.

Table 2
Intraoperative variables of 28 patients undergoing cytoreductive surgery and HIPEC.

Variable	mean ± standard deviation, median [interquartile range], or n (%)
Duration of case (min)	360 [304–416]
Fluid turnover (mL)	+5008 [3659–6357]
Input (mL)	+6309 [4615–8003]
Crystalloid (mL)	5700 [4223–7177]
Colloid (n = 7, mL)	1000 [500–1000]
Albumin (n = 4, mL)	500 [200–800]
Output (mL)	−935 [258–1612]
Estimated blood loss (mL)	500 [250–750]
Urine (mL)	500 [250–750]
Blood products in OR [N (%), mL]	
Red blood cells (RBC)	8 (28.6%), 713 ± 374
Fresh frozen plasma (FFP)	3 (10.7%), 1003 ± 1065
Platelets[a]	1 (3.6%), 244
Intraoperative heparin	4 (14.3%)
Intraoperative tranexamic acid	17 (60.7%)
Body temperature (°C)	
Post induction	35.9 ± 0.7
Start of HIPEC	36.3 ± 0.7
30 min after HIPEC start	37.3 ± 0.6
30 min after HIPEC end	37.1 ± 0.5

HIPEC, heated intraperitoneal chemotherapy. OR, operating room.
[a] Standard deviation is not available for platelets as n = 1.

35.9 °C ± 0.7 °C (Table 2).

Intraoperative metabolic parameters are presented in Fig. 2. Blood glucose levels were significantly elevated ($P < 0.017$) and blood pH significantly lower ($P < 0.017$) in relation to post-induction values. Significant increases ($P < 0.017$) in lactate levels occurred midway through HIPEC and persisted to 30 min post termination. Hemoglobin was significantly reduced (P < 0.017) at 30 min post HIPEC termination.

INR values from 30 min post termination of HIPEC to post-operative day (POD) 3 inclusive were significantly higher ($P < 0.013$) than preoperative INR (Fig. 3). PTT was significantly reduced ($P < 0.013$) from preoperative levels at 30 min post termination of HIPEC and on POD 1 (Fig. 3). Platelet counts were significantly reduced ($P < 0.013$) from POD 1 to POD 3 (Fig. 3). Four patients developed abnormal coagulation markers between POD 2 and POD 5.

TEG™ parameters, intraoperative R-time and maximum amplitude, showed significant decreases ($P < 0.017$) from initial values (Table 3). K-time was significantly elevated ($P < 0.017$) 30 min post termination of HIPEC. Alpha angle ($P = 0.158$) and Ly30 ($P = 0.137$) showed no significant changes from post-induction through the intraoperative period.

Epidural catheters were placed in 17 (60.7%) patients (14 pre-operatively) with no reports of hematoma ($P < 0.05$; 95% CI:

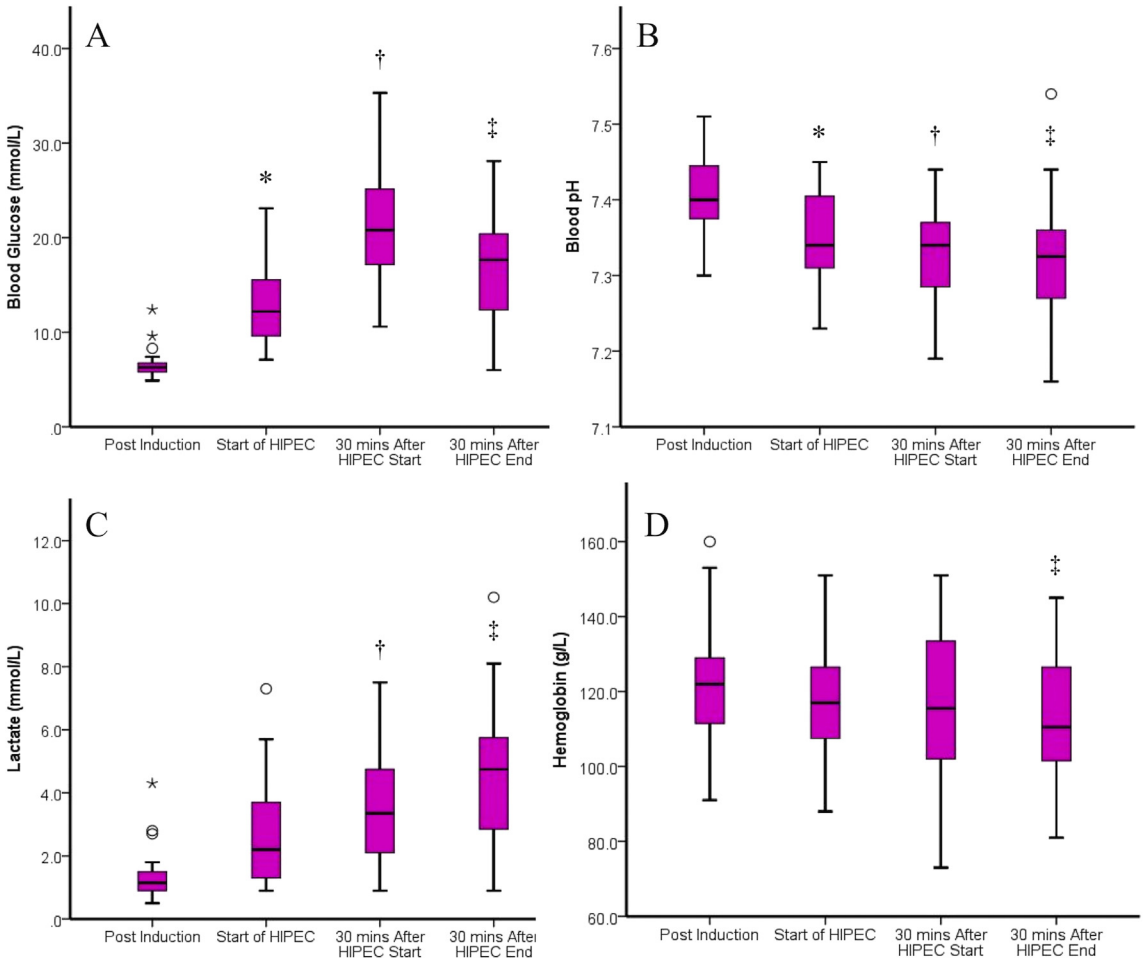

Fig. 2. Intraoperative metabolic variables: A. blood glucose (mmol/L); B. blood pH; C. Lactate (mmol/L); D. Hemoglobin (g/L).
*Significant difference between post-induction and start of HIPEC (adjusted P < 0.017); †Significant difference between post-induction and 30 min after HIPEC start (adjusted P < 0.017).
‡Significant difference between post-induction and 30 min after HIPEC end (adjusted P < 0.017).

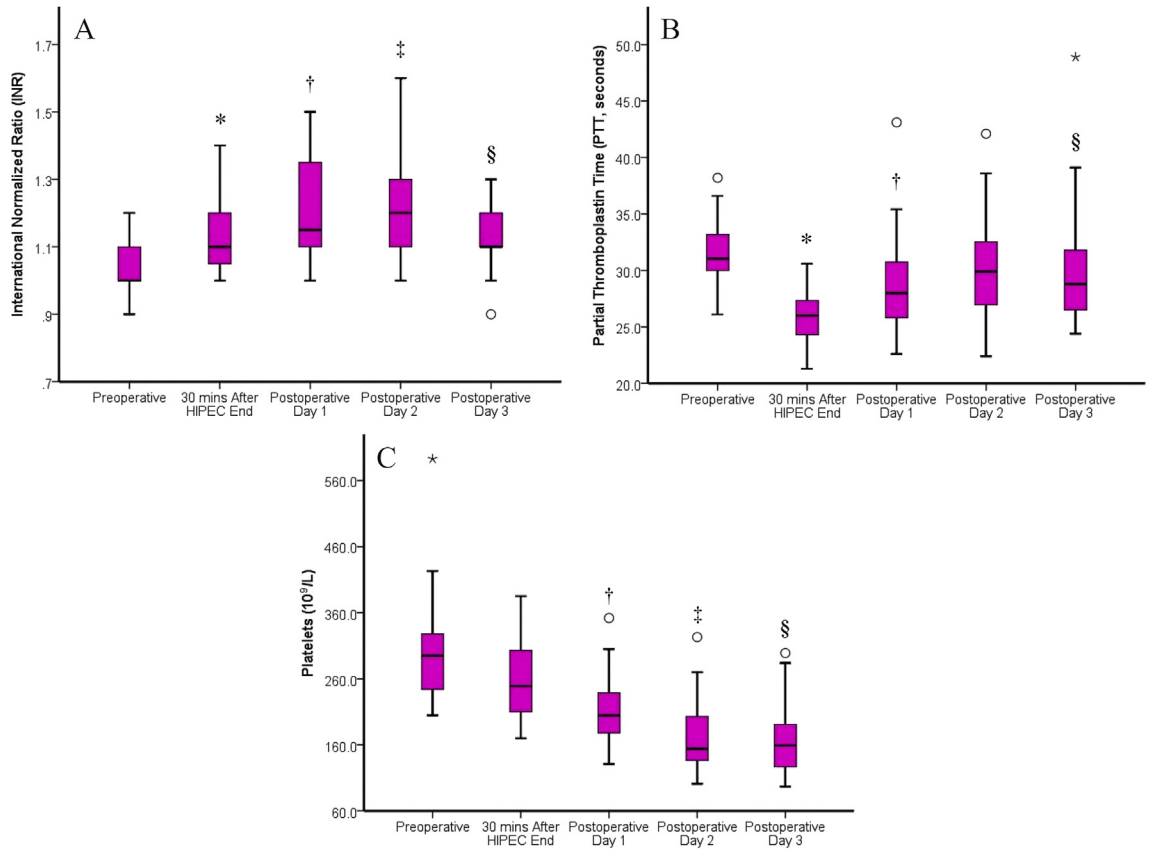

Fig. 3. Coagulation metrics: A. international normalized ratio (INR); B. partial thromboplastin time (PTT, seconds); C. platelets (10^9/L).
*Significant difference between post-induction and 30 min after HIPEC start (adjusted P < 0.013); †Significant difference between post-induction and postoperative day 1 (adjusted P < 0.013); ‡Significant difference between post-induction and postoperative day 2 (adjusted P < 0.013); §Significant differences between post-induction and postoperative day 3 (adjusted P < 0.013).

Table 3
Intra-operative (A) and postoperative (B) TEG™ values in HIPEC patients.

A.	Post-induction	Start of HIPEC	30 min after HIPEC start	30 min after HIPEC end	*P* Value
R-time (min)	4.9 [4.4–5.4]	3.6* [2.9–4.3]	4.2†[3.6–4.8]	3.8‡[3.0–4.6]	<0.001
K-time (min)	1.2 [1.1–1.4]	1.4 [1.2–1.6]	1.4 [1.2–1.6]	1.5‡[1.1–1.9]	0.036
Alpha angle (°)	71.0 [68.6–73.4]	69.7 [66.7–72.7]	70.0 [65.0–75.0]	68.5 [64.7–72.3]	0.158
Maximum amplitude (mm)	68.6 [64.4–68.8]	63.9*[59.9–67.9]	66.7†[64.3–69.1]	65.5‡[62.2–68.8]	0.003
Ly30 (%)	0.15 [0.0–0.55]	0 [0–0.05]	0 [0–0.15]	0 [0–0.25]	0.137
B.	**Post-induction**	**Postoperative Day 1**	**Postoperative Day 2**	**Postoperative Day 3**	***P* Value**
R-time (min)	4.9 [4.4–5.4]	4.8 [3.9–5.7]	5.4 [4.5–6.3]	5.0 [4.2–5.8]	0.536
K-time (min)	1.2 [1.1–1.4]	1.3 [1.1–1.5]	1.3 [1.1–1.5]	1.2 [1.0–1.4]	0.202
Alpha angle (°)	71.0 [68.6–73.4]	68.7 [64.4–73.0]	71.0 [67.2–74.8]	71.0 [67.8–74.2]	0.239
Maximum amplitude (mm)	68.6 [64.4–68.8]	67.6 [64.6–70.6]	69.2 [66.0–72.4]	71.7‡[68.6–74.8]	<0.001
Ly30 (%)	0.15 [0–0.55]	0.35 [0–0.85]	0.80†[0.05–1.55]	0.10 [0–0.4]	0.015

Statistics are presented as median [interquartile range].
*Significant difference between post-induction and start of HIPEC (A.)/postoperative day 1 (B.) (adjusted $P < 0.017$); †Significant difference between post-induction and 30 min after HIPEC start (A.)/postoperative day 2 (B.) (adjusted $P < 0.017$); ‡Significant difference between post-induction and 30 min after HIPEC end (A.)/postoperative day 3 (B.) (adjusted $P < 0.017$).
HIPEC, hyperthermic intraperitoneal chemotherapy. R-time, reaction time. K-time, kinetics time. Ly30, lysis at 30 min.

0–19%). Inadequate analgesia (n = 12) and nausea and vomiting (n = 10) were the most common reported outcomes post-catheter placement.

Discussion

While epidural analgesia has advantages for pain management in CRS with HIPEC surgery, concerns exist for its safety as coagulation disturbances are common and epidural hematoma development is possible after catheter insertion or removal.[2,4–9,14–19] In this study, we used TEG™ to determine the effects of CRS and HIPEC on coagulation, with the intention of determining suitability for epidural placement and to allow for corrections in coagulation aberrations in the event that catheter manipulation or dislodgment occurs. Compared to baseline, significant decreases in intraoperative TEG™ values were determined in our study, but all values were within normal limits and recovered by POD1. Hence, our results of this small pilot study indicate that CRS and HIPEC do

not impact coagulation in a clinically significant manner.

Our findings using conventional markers of coagulation are similar to those previously published.[5–9,11] 17 patients received tranexamic acid, four received preoperative Heparin thromboprophylaxis and all patients received prophylactic doses of Dalteparin postoperatively. Of the patients attributed with abnormal conventional coagulation parameters, one had received preoperative Heparin, but its contribution to a single elevated INR (1.6) on POD 2 is doubtful. Consistent with the anticipated systemic inflammatory response with HIPEC, our intraoperative metabolic data reveals similar trends of increased lactate and decreased pH.[5] When preventing coagulopathy, correcting metabolic derangements and preventing hypothermia are essential and in our study is most pertinent immediately post induction.

As a point of care test, TEG™ is valued for the rapid assessment of coagulation and despite the study's normal values, can validate resuscitation efforts. TEG™ has been tested in clinical scenarios such as in cardiac and hepatic surgery as well as transplantation to decrease the number of transfusions and as a screening tool for hypercoagulability and management of patients with bleeding disorders.[20] In this study with HIPEC, TEG™ assessed perioperative clot kinetics and may be used to guide management for the correction of aberrations in coagulation. Normal TEG™ values in this study is also reassuring given our concerns for the rare but devastating complication of epidural hematoma formation. Support for the minimal impact of CRS and HIPEC on clot kinetics can be found by studies that show no change in GpIIb/IIIa platelet receptors.[6] When reviewing current evidence affecting coagulation during HIPEC, there are few studies which demonstrate a medically significant coagulopathy (INR>1.5, PTT>45).[6,8,11] Although this study illustrated normal clot kinetics using TEG™ even in conventional medically defined “coagulopathic” patients, due to the low numbers of medically significant coagulopathy in this study and the even rarer rate of epidural hematoma formation, no definite conclusions regarding the safety of epidural analgesia with this treatment modality can be made.

This study confirms that despite multimodal analgesia use, postoperative pain control can be challenging[2,3,19] with more than half our patients with functional epidurals reporting poor analgesia. The incidence of pulmonary complications can be greater than 80%,[22,23] with diaphragmatic peritonectomy presenting the highest risk.[24] Schmidt et al.[14] reported that epidural analgesia reduced intraoperative needs for opioids and decreased the need for postoperative ventilation. Epidurals also confer the benefits of safe early extubation, is associated with improved patient satisfaction and the early mobilization of patients.[18,21] We believe the best time to place epidural catheters is pre-operatively as derangements in coagulation is least likely and usually self-limited.[5–9,18] At our institution epidural catheters are not routinely inserted preoperatively due to concerns with intraoperative coagulation perturbations. Consequently, early extubation is not always feasible. The use of TEG™ clarifies coagulation derangements and may help guide decisions related to epidural catheter insertions, manipulations and early removal. Despite our study showing normal clot kinetics, a trend of continued metabolic derangements including increased INR and decreased platelets post-operatively (nadir on POD 3) occurred and may impact early dislodgement or removal. While we advocate for preoperative placement of epidurals for postoperative analgesia, previous studies document a high likelihood of intractable hypotension with intraoperative use due to local anesthetic sympathectomy.[7,16,25]

Limitations of this study include significant heterogeneity in the study group, which could impact coagulation outcomes. Tumor type and burden impact operating time, bleeding risk, temperature changes and other metabolic derangements influencing the coagulation cascade. While the use of heparinase cups during TEG™ measurements negates the effect of heparin on our elastographic measure, the use of tranexamic acid will alter coagulation. TEG™ measurement is validated for resuscitation efforts, however its use in coagulation kinetics for epidural placement is controversial. Due to the infrequent occurrence of this procedure only a pilot study was feasible. Already insufficiently powered for rare events, such as epidural hematoma, this is further heightened through the inclusion of only 28 patients.[9] Reassuringly, a multicenter international survey in which HIPEC was studied, reported no epidural hematoma or abscess formation in their catchment patient size of 8000 + patients.[19]

In this pilot study with CRS and HIPEC, conventional or clinical medical definitions of coagulopathy can occur but are rare, and despite this derangement clot kinetics using TEG™ are within normal limits. Future studies using larger numbers of patients may suggest that the use of an epidural catheter for post-operative analgesia with CRS and HIPEC can be recommended.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.01.034.

References

1. Hamilton T, Lanuke K, Mack L, Temple W. Long-term follow-up in the treatment of peritoneal carcinomatosis. *Am J Surg*. 2011;201:650–654.
2. Bell J, Rylah B, Chambers R, et al. Perioperative management of patients undergoing cytoreductive surgery combined with heated intraperitoneal chemotherapy for peritoneal surface malignancy: a multi-institutional experience. *Ann Surg Oncol*. 2012;19:4244–4251.
3. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. *J Am Med Assoc*. 2003;290(18):2455–2463.
4. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev*. 2000;(4):CD001893.
5. Schmidt C, Creutzenberg M, Piso P, et al. Peri-operative anaesthetic management of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Anaesthesia*. 2008;63(4):389–395.
6. Korakianitis O, Daskalou T, Alevizos L, et al. Lack of significant intraoperative coagulopathy in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) indicates that epidural anaesthesia is a safe option. *Int J Hyperther*. 2015;31(8):857–862.
7. Owusu-Agyemang P, Soliz J, Hayes-Jordan A, et al. Safety of epidural analgesia in the perioperative care of patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2014;21(5):1487–1493.
8. Piccioni F, Casiraghi C, Fumagalli L, et al. Epidural analgesia for cytoreductive surgery with peritonectomy and heated intraperitoneal chemotherapy. *Int J Surg*. 2015;16(Pt A):99–106.
9. Hurdle H, Bishop G, Walker A, et al. Coagulation after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a retrospective cohort analysis. *Can J Anaesth*. 2017;64(11):1144–1152.
10. Elias D, Di Pietrantonio D, Boulet T, et al. “Natural history” of complete

cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol*. 2009;35:434–438.
11. Miao N, Pingpank JF, Alexander HR, et al. Cytoreductive surgery and continuous hyperthermic peritoneal perfusion in patients with mesothelioma and peritoneal carcinomatosis: hemodynamic, metabolic and anesthetic considerations. *Ann Surg Oncol*. 2009;16:334–344.
12. Sugarbaker PH. Laboratory and clinical basis for hyperthermia as a component of intracavitary chemotherapy. *Int J Hyperther*. 2007;23(5):431–442.
13. Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. *Cancer Treat Rev*. 2001;27(6):365–374.
14. Schmidt C, Steinke T, Mortiz S, Bucher M. Thoracic epidural anesthesia in patients with cytoreductive surgery and HIPEC. *J Surg Oncol*. 2010;102:545–546.
15. Cook TM, Counsell D, Wildsmith JA. Royal college of anaesthetists third national audit project. Major complications of central neuraxial block: report on the third national audit project of the royal college of anaesthetists. *Br J Anaesth*. 2009;102:179–190.
16. Liang Y, Wang S. The best anesthesia regimen for patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Int J Surg*. 2015;19:103.
17. Desgranges FP, Steghens A, Mithieux F, et al. Potential risks of thoracic epidural analgesia in hyperthermic intraperitoneal chemotherapy. *J Surg Oncol*. 2010;101(5):442.
18. Cooksley TJ, Haji-Michael P. Postoperative critical care management of patient underdoing cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC). *World J Surg Oncol*. 2011;9:169–173.
19. Maciver AH, Al-Sukhni E, Esquivel J, et al. Current delivery of hyperthermic intraperitoneal chemotherapy with cytoreductive surgery (CS/HIPEC) and perioperative practices: an international survey of high-volume surgeons. *Ann Surg Oncol*. 2017;24:923–930.
20. Chitlur M, Sorensen B, Rivard GE, et al. Standardization of thromboelastography: a report fromteh TEG-ROTEM working group. *Haemophilia*. 2011;17:532–537.
21. Ali M, Winter DC, Hanly AM, et al. Prospective randomized, controlled trial of thoracic epidural or patient controlled opiate analgesia on perioperative quality of life. *Br J Anaesth*. 2010;104:292–297.
22. Chen MYM, Chiles C, Loggie BW. Thoracic complications in patients undergoing intraperitoneal heated chemotherapy with mitomycin following cytoreductive surgery. *J Surg Oncol*. 1997;66(1):19–23.
23. Preti V, Chang D, Sugarbaker PH. Pulmonary complications following cytoreductive surgery and perioperative chemotherapy in 147 consecutive patients. *Gastroenterol. Res. Pract.*. 2012:635314.
24. Malfroy S, Wallet F, Maucort-Boulch D, et al. Complications after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis: risk factors for ICU admission and morbidity prognostic score. *Surgical Oncology*. 2016;25:6–15.
25. de la Chapelle A, Perus O, Soubielle J, et al. High potential for epidural analgesia neuraxial block-associated hypotension in conjunction with heated intraoperative intraperitoneal chemotherapy. *Reg Anesth Pain Med*. 2005;30(3):313–314.