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Impact of Intraoperative Anesthetic and Fluid Management on 30-day Postoperative Outcomes in a Newly Established Surgical Peritoneal Surface Malignancy Program

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Abstract

Background: Anesthetic and fluid management during cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) may influence 30-day postoperative outcomes. We investigated intraoperative management differences and their relation to outcomes in all consecutive patients undergoing HIPEC and CRS following the first 2 years after initiation of this surgical oncology program in a single center.

Methods: Following IRB approval we retrospectively recorded demographics, intraoperative anesthetic and fluid management and 30-day postoperative cardiopulmonary, renal, infectious, neurologic, and surgical complications, mortality and length-of-stay in patients undergoing CRS and HIPEC. The Chi-square, Fisher's exact and Wilcoxon two-sample tests were used for statistics. A $p < 0.05$ was significant.

Results: We identified 34 patients with a mean age of 53.9 ± 11.5 years. Postoperative complications occurred in 14 patients (41%), twelve of whom (35%) had pulmonary adverse events. Patients with complications were significantly older (p=0.04) and were significantly longer hospitalized (p=0.00). Neither primary malignancy type nor intraoperative fluid replacement differed between groups. Patients with complications had mild preoperative anemia (p=0.052).

Conclusions: In this initial single center experience with CRS and HIPEC, patients experienced liberal intraoperative fluid replacement, a high postoperative complication rate, but no 30-day mortality. Patients with postoperative complications were significantly older, while intraoperative anesthetic and fluid management were not different between groups. Preoperative anemia in patients developing postoperative complications deserves prospective study. A steep learning curve in patient selecion and intraoperative management was observed.

Keywords: Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Complications; Pulmonary

Abbreviations: CRS: Cyto Reductive Surgery; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; FFP: Fresh Frozen Plasma; Cryo: Cryoprecipitate; Plts: Platelets

Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) employ intra-abdominal cavity perfusion with chemotherapeutic agents immediately following intestinal and peritoneal tumor reduction. The physiologic demands on patients undergoing these often prolonged procedures, and subsequently the intra- and postoperative management challenges to the perioperative care team have been well described [1-3]. Appropriate and liberal fluid management to maintain adequate organ perfusion has been advocated for CRS and HIPEC, but poorly defined [2,4,5]. However, intraoperative fluid replacement up to 12 ml/kg/hr or more has been reported [1]. Although known for a high overall complication rate with relatively low perioperative mortality, data on short-term morbidity for this oncologic surgery are inconsistent. Two years following the start of this program at this single center, we changed our surgical approach to patient preparation, and subsequently our anesthetic and intraoperative fluid management. To report on our outcomes during the early phase of establishing CRS and HIPC at or institution we conducted this retrospective analysis to determine intraoperative fluid management differences and other factors between patients with and without 30-day adverse events.

Materials and Methods

Following IRB approval we conducted a retrospective chart review of all patients undergoing CRS and HIPEC in the first two years after inauguration of a peritoneal surface malignancy program.

Patient selection for this new program included ASA physical status classification I and II patients with a variety of malignancies but without any other major additional physiologic co- morbidities.

Anesthetic management consisted of a balanced anesthetic technique using isoflurane or sevoflurane in oxygen and air combined with an intravenous opioid. All patients were offered a thoracic epidural catheter placement for postoperative pain management. Invasive intra-arterial and central venous blood pressure monitoring was standard, and all patients received planned postoperative mechanical ventilation

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in an intensive care unit. Intraoperative crystalloid, colloid and blood product administration was at the discretion of the anesthesiology team based on clinical and laboratory assessment. The colloids used were either a hetastarch saline solution, Albumin 5% or both. Temperature management consisted of maintenance of normothermia with convective warming blankets and cooling with icepacks as needed during HIPEC.

The surgical preoperative patient preparation included a bowel regimen consisting of Magnesium Citrate. The strategy during the procedure was directed at cytoreduction of all visible disease, followed by a HIPEC period using the closed technique [6]. After placement of two upper in flow and two lower outflow catheters a continuous closed loop circuit of plasmalyte heated to 42 degrees Celsius was established perfusate temperature monitoring was performed via right and left anterior abdominal wall temperature probes. Following confirmation of adequate closed loop flow at approximately one L per minute, 40 mg of Mitomycin C or 100 mg/m2 BSA of Cisplatin was added to the perfusate. Mechanical agitation of the abdomen was carried out for 90 minutes once adequate temperature was reached.

Data collection included the following: patient demographics; intraoperative fluid management; operative time – defined as time of operating room entry to exit; pulmonary complications - defined as pneumonia, pulmonary edema/ARDS, pneumothorax, pleural effusion, pulmonary embolus confirmed by imaging; cardiac complications – defined as myocardial infarction by cardiac catheterization or troponin elevation and new-onset atrial fibrillation; renal complications – defined as a postoperative two-fold creatinine increase from baseline within five days or need for renal replacement therapy; systemic infectious complications – defined as bacteremia or sepsis with a positive blood culture; neurologic complications – defined as delirium or stroke; and surgical complications, 30-day mortality, time to extubation (days) and hospital length of stay (days).

The Chi-square and Fisher's exact tests were used for categorical variables and the Wilcoxon two sample tests for continuous variables to compare patients with postoperative complications to those without. All tests were performed with SAS 9.2. (SAS Institute Inc. Cary, NC). Data are presented as means ± SD; a $p < 0.05$ was significant. A sub-analysis was performed to compare the fluid management of patients with pulmonary complications to those without. Because of the small sample size we did not perform a multivariate logistic regression analysis.

Results

Thirty-four patients (12 M, 22 F) were identified with a mean age of 53.9 ± 11.5 years ranging from 32 to 77 years.

A total of 24 defined postoperative complications were recorded in 14 patients (41%), 12 (35%) of whom experienced one or more pulmonary adverse events. Pulmonary complications included pulmonary edema/ARDS (n=4), pneumonia (n=7), pleural effusion (n=4) and pneumothorax (n=4) and represented 79% of all complications found in the study. Cardiac morbidity consisted of one myocardial infarction and one new-onset atrial fibrillation event. Two patients experienced bacteremia and one patient had a serious postoperative hemorrhage. No 30-day mortality occurred. There were also no pulmonary emboli, renal or neurologic complications.

Epidural catheters for postoperative analgesia were placed in 29 patients prior to surgery (27 thoracic and two lumbar). Ten of the 14 patients with complications, and 19 of the 20 patients without complications received an epidural catheter respectively.

Patients with complications were significantly older compared to uncomplicated patients (p=0.04). No difference was found for gender and primary malignancy distribution between groups (Table 1). The primary malignancies included pseudomyxoma peritonei (n=5), appendiceal cancer (n=16), colonic adenocarcinoma (n=7), ovarian cancer (n=3), and miscellaneous cancers (n=3).

The cumulative as well as hourly crystalloid administration, and the proportion of patients receiving colloids, was not different between groups. Although blood product administration was not significantly different statistically between groups, a large proportion of patients with complications received fresh frozen plasma (FFP), cryoprecipitate (Cryo) and platelets (Plts, Table 2).

Table 3 shows a summary of investigated intraoperative variables including operative time, estimated blood loss, hematocrit, glucose, central venous pressure, pH and temperature in aggregate and by group comparison. A trend toward a lower starting hematocrit and longer procedure duration in patients with postoperative complications was not significant.

Days ventilated and the hospital lengths of stay are shown in Table 4. Patients with complications had a significantly longer hospital stay, but their prolonged mechanical ventilation did not reach statistical significance.

	All (n = 34)	**Any complication (n = 14)**	**No complication (n = 20)**	**p-value**
Age (years, mean ± SD) (range)	53.9 ± 11.5 (32-77)	58.6 ± 10.3 (44-77)	50.6 ± 11.4 (32-76)	0.04
Gender Male Female	 35.3% (12) 64.7% (22)	 21.4% (3) 78.6% (11)	 45.0% 9) 55.0% (11)	 0.27
Diagnosis Appendiceal CA Ovarian CA Pseudomyxoma Colon CA Other	 47.1% (16) 8.8% (3) 14.7% (5) 20.65 (7) 8.8% (3)	 35.7% (5) 7.1% (1) 21.4% (3) 28.6% (4) 7.1% (1)	 55.0% (11) 10.0% (2) 10.0% (2) 15.0% (3) 10.0% (2)	 0.75

Table 1: Patients age, gender and primary cancer diagnosis. SD – standard deviation, CA – cancer.

	All (n=34)	**Any complication (n=14)**	**No complication (n=20)**	**p-value**
Crystalloids (ml)	12866 ± 6110 (4350-25200)	14064.3 ± 5994.7 (6700-23000)	12027.5 ± 6201.8 (4350-25200)	0.27
Crystalloid/hour (ml)	1305.8 ± 511.5 (624-2976)	1363.7 ± 505.4 (728.6-2183.5)	1265.3 ± 524.8 (624.4-2976.4)	0.47
Colloids Yes No	 61.8% (21) 38.2% (13)	 64.3% (9) 35.7% (5)	 60.0% (12) 40.0% (8)	 0.80
RBC Yes No	 70.6% (24) 29.4% (10)	 50.0% (7) 50.0% (7)	 85.0% (17) 15.0% (3)	 0.05
FFP Yes No	 91.2% (31) 8.8% (3)	 78.6% (11) 21.4% (3)	 100.0% (20)	 0.06
Cryoprecipitate Yes No	 94.1% (32) 5.9% (2)	 85.7% (12) 14.3% (2)	 100.0% (20)	 0.16
Platelets Yes No	 97.1% (33) 2.9% (1)	 92.9% (13) 7.1% (1)	 100.0% (20)	 0.44

Table 2: Intraoperative fluid and blood product administration. Continuous variables are reported in means + standard deviation, numbers in parenthesis are ranges. Categorical variables are reported in percentages and values in parenthesis reflect the corresponding number of patients.

	All	Any complication	No complication	p-value
Operative time (min)	586 ± 167 (391-1125) n=34	615.1 ± 121 (400-848) n=14	566.4 ± 194.4 (391-1125) n=20	0.17
EBL (ml)	591.8 ± 611.4 (100-2450) n=33	835.7 ± 810.8 (150-2450) n=14	412.1 ± 330.8 (100-1650) n=19	0.47
Initial HCT (%)	38.2 ± 5.5 (25.1-47.2) n=34	36 ± 5.4 (25.1-43.5) n=14	39.7 ± 5.2 (29-47.2) n=20	0.05
Maximum glucose (mg/dl) during HIPEC phase	140 ± 27.9 (72-187) n=24	146.7 ± 23 (98-187) n=11	134.3 ± 31.2 (72-185) n=13	0.35
Initial CVP (mmHg)	10.9 ± 4.3 (2-19) n=31	12.1 ± 4.5 (2-19) n=14	9.9 ± 4 (4-19) n=17	0.09
End of case CVP (mmHg)	9.9 ± 3.3 (5-18) n=29	10 ± 3.6 (6-18) n=12	9.9 ± 3.1 (5-16) n=17	0.89
Postoperative pH	7.39 ± 0.07 (7.25-7.54) n=31	7.40 ± 0.07 (7.30-7.54) n=13	7.38 ± 0.06 (7.25-7.54) n=18	0.66
Intraoperative highest temperature (oC)	38.1 ± 0.9 (35.9-40.1) n=27	38.2 ± 1 (36.4-40.1) n=12	38 ± 0.9 (35.9-39.7) n=15	0.59

Table 3: Analysis of intraoperative variables and their association with postoperative complications. All continuous variables are reported in means + standard deviation, followed by ranges in parenthesis. EBL – estimated blood loss, HCT – hematocrit, CVP – central venous pressure.

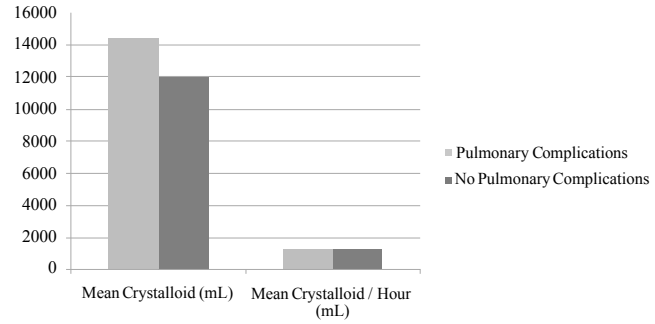

Figure 1:

Figure 1 shows the crystalloid administration between patients experiencing pulmonary adverse events exclusively compared to those who did not.

Discussion

Our study investigated intraoperative management and outcomes in all patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy over two years following introduction of this program in a single center. Although no 30-day mortality occurred, 41% of patients had a total of 24 complications, and 79% of these were pulmonary in nature. Pneumothoraces in our patients could be attributed to intraoperatively recognized breach of the diaphragm in the course of the extensive peritonectomy. However, in cases with a less clear causal relationship, additional etiologies including central line placement at the beginning of surgery, but also the chemotherapeutic agents used, need to be considered.

Mitomycin C given systemically has been shown to have some pulmonary toxicity [7,8]. A retrospective analysis comparing pulmonary toxicties in patients who underwent CRS alone versus CRS and HIPEC showed a statistically significant increase in pulmonary toxicities in the HIPEC group versus control ($p<0.05$). Pulmonary toxicities were present in 86% (n=36) of patients with the following distribution: 76% (n=32) atelectasis, 64% (n=27) pleural effusions, 24% (n=10) pulmonary edema, 5% (n=2) pneumonia and 5% (n=2) pneumothoraces [9].

Capone et al. [10] recently reported their outcomes in 30 patients with an emphasis on infectious complications. Similar to our findings, of the 29 non-infectious complications they encountered, the majority were also pulmonary in origin. The mean patient age in Capone's study was 57 years, which is closer to the age of our patients that had complications [10]. Remarkably, the mean age in our study closely resembled that found in larger investigations of patient population with peritoneal carcinomatosis, likely reflecting the preponderance for this disease in this age group [1,4,5,11].

Older age in our series was significantly associated with complications, and when these occurred, the hospital length of stay significantly increased. Although intuitive, age was not consistently identified as a risk factor in similar studies. While Feldman found better outcomes in 49 patients with mesothelioma that are less than 60 years old [11], age did not matter in a study by Elias including 106 patients with a variety of primary tumor diagnosis [12].

Our patients mean hospital length of stay was near identical or similar to that reported in larger series [4,12], and increased significantly in patients with complications. The operative time in this series was similar to reports in the literature [5]. Operative time and estimated blood loss were both increased in patients who developed complications, but this difference was not statistically different compared to uncomplicated patients. In larger series these parameters were significant risk factors [12], and the small sample size may have prevented significance in our investigation.

Fluid management during these physiologically stressful procedures is challenging. The complexity of intraoperative fluid management and their components for major surgeries has recently been described, and an individual demand oriented strategy has been suggested in the general surgical adult population [13,14]. However, most reports on intraoperative fluid management for peritoneal surface malignancy surgery emphasize the importance of liberal fluid administration to maintain adequate organ perfusion [1,2,4,5]. Some authors in this specific area of oncologic surgery have begun to explore a goal directed approach to intra- and perioperative fluid administration following flow derived perfusion parameters to facilitate perioperative patient management and improve outcomes [2]. In our cohort, fluid replacement was extensive with a mean cumulative amount of 12866 ml, very similar to that described by Miao et al. [5]. We also determined a large variability of fluid replacement between cases, ranging from 4,350 ml to 25,200 ml. The factors that determine this large disparity are not clear and include patient condition, surgical course and anesthesiologists' practice preferences. Interestingly there was no statistically significant difference in the amount of crystalloid and colloid administration between patients with or without complications, and the categorical use of colloids did not appear to affect outcomes.

As for blood product administration, analyzed separately from colloids, a majority of patients with complications were transfused FFP, Cryo and Plts, while none of the patients without complications received any of these products, which is of clinical significance.

In a sub-analysis of the intraoperative crystalloid amount for patients with pulmonary complications versus all others, a slightly higher amount administered was not statistically significant. Liberal crystalloid fluid replacement for CRS and HIPEC as administered in our series, may not be directly associated with postoperative complications, including pulmonary adverse events, while the same may not hold true for blood product administration.

Interestingly, we observed a trend towards a lower preoperative hematocrit in patients with complications compared to those without, that did not reach statistical significance (p=0.052). A recent systematic review underscores the potential implications for adverse outcomes of preoperative anemia in orthopedic surgical patients [15]. In another study of more than 23,000 patients undergoing colorectal surgery, Leichtle et al. reported an increased incidence of adverse events even in the presence of mild preoperative anemia (hematocrit of 30%–37%) [16]. Applying the latter studies ranges of anemia to our analysis, patients with a complication had a mean preoperative hematocrit within mild anemia (36%), and those without complications were well within the non-anemic category (39.7%). A larger sample size may have resulted in a significant difference in our cohort. However, it remains unclear what the clinical implications of such an association would represent, other than identifying risk. Furthermore it is uncertain what specific physiologic impairment any state of preoperative anemia comports that subsequently renders these surgical candidates more susceptible to postoperative complications, particularly in the setting malignancy. Clearly more outcome oriented studies are needed in this area.

None of the additional intraoperatively assessed parameters including peak glucose level, peak core temperature, end-of case CVP and pH, appeared to be relevant to the adverse postoperative events examined in this study.

The limitations of our study include the retrospective design and the small sample size of a newly established surgical oncology program. We were not able to report more specifically on exact amounts and type of colloids administered per patient per group, other than categorical tracking. The study design will inevitably lead to some missing data points and dependence on the completeness of clinical charting performed without study intention. However, our findings may serve the development of targets for prospective controlled studies investigating the effects of preoperative anemia, intraoperative blood product administration and refined fluid management on short term outcomes.

Establishing a new clinical program can be expected to be associated with a learning curve that may be reflected in the earlier clinical outcomes, which then subsequently change, indicating increased team expertise [4]. Interestingly, our management indices and outcomes were similar to larger, more established programs. Despite several studies reporting on perioperative outcomes, their definitions are inhomogeneous, limiting the ability to compare between investigations. As our program continues to evolve, several changes in our surgical and anesthetic management have occurred, preventing a larger consistent sample size. Specifically, patients no longer receive a bowel preparatory regimen before the procedure. The intraoperativ fluid management is now more restrictive. Planned postoperative mechanical ventilation has been abandoned in favor of an individualized approach and an anesthetic regimen targeting end-of-surgery extubation as a goal that is now frequently achieved. We have integrated intraoperative parameters such as pulse pressure, stroke volume variation and the extravascular lung water index to guide fluid therapy and assist clinical decision making at the end of surgery.

Conclusions

This study retrospectively examined 30-day outcomes of 34 consecutive patients undergoing CRS and HIPEC surgery within two years of a new surgical peritoneal surface malignancy program at a single institution. The intraoperative anesthetic management required liberal fluid replacement and a high postoperative complication rate was observed, mostly pulmonary in nature. Older age was associated with postoperative complications, and there was a trend for a lower preoperative hematocrit in patients who experienced these complications.

Case duration and fluid management strategies were variable, but there was no difference in overall fluid management for patients with and without postoperative complications. Blood product administration other than red blood cells occurred only in patients who developed postoperative complications. These initial results are similar to larger reported series. We describe a learning curve and a changed surgical and anesthetic approach beginning two years following program implementation and begun a prospective data collection. A larger prospective study, including goal directed fluid management, is needed to better determine intraoperative factors and modifiable risk factors contributing to postoperative morbidity in patients undergoing CRS and HIPEC.

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