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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Restrictive Intraoperative Fluid Therapy is Associated with Decreased Morbidity and Length of Stay Following Hyperthermic Intraperitoneal Chemoperfusion

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ABSTRACT

Background. Recent data have demonstrated multiple benefits of intra- and postoperative fluid restriction in major abdominal surgery; however, data regarding the outcomes of fluid restriction in cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion (CRS/HIPEC) are limited. This study evaluates the safety and short-term clinical outcomes of restricted intraoperative fluid therapy in CRS/HIPEC.

Methods. This was a single-institution, retrospective review of all CRS/HIPEC procedures performed at the University of Massachusetts Medical School between January 2009 and July 2017. Recorded variables included demographics, intraoperative factors, 60-day postoperative complications, and length of stay (LOS). Outcomes based on the use of intraoperative permissive fluid therapy (PFT) versus restrictive fluid therapy (RFT) were compared.

Results. Overall, 169 CRS/HIPEC cases were performed during the study period; 84 were managed with PFT and 85 were managed with RFT. No significant differences were identified in patient demographics. There was a decrease in intraoperative administration of crystalloid (8.0 vs. 4.4 L, $p < 0.01$), colloid (900 vs. 300 mL, $p < 0.01$), and blood transfusion (0.26 vs. 0.04 units, $p < 0.01$) in the RFT cohort. LOS was reduced from 11.5 to 9.7 days ($p < 0.01$) and the incidence of any 60-day complication decreased from 45 to 28% ($p = 0.02$) in the RFT group. The overall 90-day mortality rate was 0.6% ($n = 1$). Adjusted logistic regression demonstrated the odds of having a Clavien–Dindo grade III or higher complication was 0.31 (95% confidence interval 0.10–0.95) with RFT.

Conclusion. Intraoperative RFT with standard anesthesia monitoring devices can be safely used in CRS/HIPEC and is associated with a decreased LOS and decreased rate of postoperative complications.

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The efficacy of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion (CRS/HIPEC) has been demonstrated in the management of peritoneal carcinomatosis.[1–7] However, because this treatment often requires a lengthy operation involving multivisceral resection, intestinal anastomoses, and exposure to hyperthermic chemotherapy, the incidence of major complications remains high (27–34%), often with an extended length of stay (LOS) even at high-volume centers.[8–10] Postoperative complications requiring intervention have been identified as significant risk factors for early disease recurrence and decreased overall survival.[11] Restrictive fluid regimens have demonstrated decreased perioperative mortality in other major surgical procedures.[12,13] Furthermore, goal-directed fluid therapy (GDFT) is gaining popularity as a viable means to reduce systemic complications and improve outcomes in high-risk and major abdominal surgical operations.[14–17] As the optimal fluid resuscitation strategy in patients undergoing CRS/HIPEC is undefined, we sought to investigate the impact of a restrictive intraoperative fluid therapy approach on short-term outcomes after CRS/HIPEC.

METHODS

Data Sources

All CRS/HIPEC procedures performed at the University of Massachusetts Medical School from 1 January 2009 to 1 July 2017 were identified and reviewed. The study was approved by the Institutional Review Board (IRB) of the University of Massachusetts Medical School and a Health Insurance Portability and Accountability Act (HIPAA) waiver of consent was granted given the retrospective and de-identified nature of the review. Demographics, socioeconomic factors, chronic conditions, operative characteristics, 60-day morbidity, and 90-day mortality were obtained.

Fluid Therapy Cohorts

All CRS/HIPEC procedures performed prior to 30 September 2014 were managed with a permissive intraoperative fluid therapy (PFT) approach ($n = 84$); however, starting in October 2014, all CRS/HIPEC cases were managed with a restrictive intraoperative fluid therapy (RFT) approach ($n = 85$).

Standard intraoperative monitoring devices were employed throughout the 8-year study period, including pulse oximeter, end tidal CO_2 monitor, continuous electrocardiography, arterial line, non-invasive blood pressure monitor, temperature sensing Foley catheter, and an esophageal temperature probe.[18] Intraoperative management of hemodynamics and fluid resuscitation was largely at the discretion of the attending anesthesiologist. From January 2009 through September 2014, the PFT approach was applied in which patients received an average 1000 mL/h of crystalloid plus or minus additional colloid. Beginning in October 2014, after multidisciplinary discussions regarding intraoperative resuscitation, a concerted effort was made to reduce fluid delivery to 500 mL/h with more liberal utilization of peripheral vasopressors. All decisions were made on a case-by-case basis with no specified endpoint. No special GDFT invasive monitoring devices were employed for the purposes of fluid resuscitation.

Statistical Analysis

For all demographic, socioeconomic, and clinicopathologic data, categorical variables were compared using Chi square tests. For continuous variables, means and standard deviations (SDs) were reported from Student's t tests. The primary study endpoint was the presence of 60-day postoperative complications as defined by the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).[19] Secondary endpoints were LOS, 60-day complication severity as defined by the Clavien–Dindo classification system,[20] and 90-day mortality. Logistic regression was used to model the odds ratio (OR) of any complication or mortality. The models were adjusted for age, sex, prior chemotherapy, length of surgery, intraoperative blood loss, and specific intraoperative chemotherapeutic agent. Results were reported as OR with 95% confidence interval (CI). All analyses were performed using STATA software version 15.1 (StataCorp LLC, College Station, TX, USA).

RESULTS

Baseline Characteristics

A total of 169 consecutive CRS/HIPEC cases were included in the study, of which 84 (50%) were managed with an intraoperative PFT approach and 85 (50%) were managed with an RFT approach. Mean age for the entire cohort was 55 years, and males represented 34% of the study population. Patients in both groups had extensive previously diagnosed medical comorbidities. The baseline characteristics of all patients undergoing CRS/HIPEC are presented in Table 1. History of neoadjuvant chemotherapy, prior cytoreduction or HIPEC, and preoperative creatinine were similar between groups. Appendiceal (69%) and colorectal (18%) adenocarcinomas were the two most common indications for CRS/HIPEC, and primary tumor type did not differ between groups ($p = 0.20$). The mean pre-cytoreduction Peritoneal Cancer Index (PCI) was 17.6 (range 0–39).

Intraoperative Variables

Detailed operative characteristics are presented in Table 2. The extent of cytoreduction was similar in the two groups, as evidenced by the number of organ resections, anastomoses, peritonectomies, and operative time. Compared with PFT, patients managed with the RFT approach received less intraoperative crystalloid (4.4 vs. 8.0 L, $p < 0.01$), intraoperative colloid (0.3 vs. 0.9 L, $p < 0.01$), and fewer intraoperative transfusions (0.04 vs. 0.26 units, $p < 0.01$). There was no difference in length of surgery (7.8 vs. 9.3 h, $p = 0.1$) between RFT and PFT, suggesting a similar mix of case complexity. The chemotherapeutic agent of choice for intraperitoneal infusion did not significantly vary by fluid resuscitation approach ($p = 0.40$).

TABLE 1 Baseline characteristics of the study population

Characteristics	CRS/HIPEC (n = 169)	PFT (n = 84)	RFT (n = 85)	p value
Age, years [mean (SD)]	55 (10)	54 (11)	57 (9)	0.10
Male sex	58 (34)	27 (32)	31 (36)	0.39
BMI, kg/m^2 [mean (SD)]	27.9 (5.6)	26.8 (4.3)	28.8 (6.4)	0.17
Primary tumor type				0.20
Appendix	115 (69)	64 (76)	51 (61)	
Colorectal	30 (18)	10 (12)	20 (24)	
Primary peritoneal	17 (10)	8 (9)	9 (11)	
Uterine leiomyosarcoma	1 (1)	1 (1)	0 (0)	
Carcinoid	1 (1)	0 (0)	1 (1)	
Urachal	1 (1)	0 (0)	1 (1)	
Ovarian	2 (1)	1 (1)	1 (1)	
Unknown primary	2 (1)	0 (0)	2 (2)	
Neoadjuvant chemotherapy	59 (35)	29 (34)	29 (36)	0.78
Prior CRS	16 (10)	7 (8)	9 (11)	0.55
Prior HIPEC	9 (5.3)	2 (2)	3 (4)	0.61
Pre-cytoreduction PCI [mean (SD)]	17.6 (10.4)	19.8 (10.9)	15.5 (9.7)	0.01
ASA class [mean (SD)]	2.6 (0.8)	2.5 (0.5)	2.7 (0.9)	0.15
Hypertension	63 (37)	24 (29)	39 (48)	0.12
Diabetes	13 (8)	6 (7)	7 (9)	0.71
Coronary artery disease	11 (7)	2 (2)	9 (11)	0.03
Chronic kidney disease	0 (0)	0 (0)	0 (0)	–
Peak preoperative creatinine [mean (SD)]	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.41
Chronic obstructive pulmonary disease	4 (2)	1 (1)	3 (4)	0.30
Ascites	42 (25)	29 (34)	13 (16)	0.01
Myocardial infarction	4 (2)	1 (1)	3 (4)	0.30
Peripheral vascular disease	3 (2)	1 (1)	2 (2)	0.54
Congestive heart failure	3 (2)	0 (0)	3 (4)	0.08
Cerebrovascular accident	1 (1)	0 (0)	1 (1)	0.32

Data are expressed as n (%) unless otherwise specified

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *PFT* permissive fluid therapy, *RFT* restrictive fluid therapy, *SD* standard deviation, *BMI* body mass index, *PCI* Peritoneal Cancer Index, *ASA* American Society of Anesthesiologists

Postoperative Outcomes

Primary and secondary postoperative outcome measures of the study cohort are presented in Table 3. Median LOS was significantly lower for RFT compared with PFT (9.7 vs. 11.5 days, $p < 0.01$). Patients who were resuscitated using the intraoperative RFT approach experienced fewer 60-day postoperative complications (28% vs. 45%, $p = 0.02$). Despite fluid restriction, there was no association with cardiac or renal complications, and peak postoperative serum creatinine levels did not significantly differ (0.82 vs. 0.89 mg/dl, $p = 0.42$). High-grade complications (Clavien–Dindo grade III or higher) occurred in 14.2% of the entire study population. While there was no statistically significant difference in these complications between the RFT and PFT groups (11% vs. 18%, $p = 0.20$), multivariate logistic regression demonstrated a reduced risk of Clavien–Dindo grade III or higher complications for the RFT group (OR 0.31, 95% CI 0.10–0.95). The operative mortality rate of the entire cohort was 0.6%, with one recorded mortality in the RFT group. Ninety-day mortality did not vary by fluid resuscitation approach (1.2% vs. 0%, $p = 0.3$).

Blood transfusion in the intraoperative or postoperative period was required in 17.8% of patients (12 in the RFT cohort and 18 in the PFT cohort, $p = 0.20$) (Fig. 1), while rates of intraoperative blood transfusion were significantly less in the RFT cohort (2 vs. 9 patients, $p = 0.02$). There was no difference in overall blood volume administration

TABLE 2 Intraoperative characteristics of the study population

Characteristics	PFT ($n = 84$)	RFT ($n = 85$)	p-Value
Operative time, hours [mean (SD)]	9.3 (2.9)	7.8 (2.4)	0.10
Large bowel resection/anastomosis	26 (30)	17 (20)	0.17
Small bowel resection/anastomosis	14 (16)	23 (27)	0.06
Gastrectomy	0 (0)	1 (1)	0.32
Splenectomy	28 (33)	23 (27)	0.56
Peritonectomy	39 (45)	38 (45)	0.84
Lesser omentectomy	21 (24)	16 (19)	0.47
Greater omentectomy	71 (83)	76 (89)	0.02
Cholecystectomy	16 (19)	24 (28)	0.10
Appendectomy	18 (21)	15 (18)	0.70
Hysterectomy	12 (14)	5 (6)	0.09
Salpingoophorectomy	23 (27)	13 (15)	0.09
Complete cytoreduction (CC0/1)	63 (76)	71 (85)	0.09
Intraoperative crystalloid, *L* [mean (SD)]	8.0 (3.2)	4.4 (1.8)	< 0.01
Intraoperative colloid, *L* [mean (SD)]	0.9 (1.1)	0.3 (0.5)	< 0.01
Intraoperative transfusion, units [mean (SD)]	0.26 (0.9)	0.04 (0.2)	< 0.01
Intraoperative blood loss, *L* [mean (SD)]	0.44 (0.3)	0.34 (0.3)	0.05
Epidural	76 (93)	82 (96)	0.30
Intraoperative chemotherapy			0.40
Mitomycin C	77 (92)	75 (88)	
Carboplatin	6 (7)	10 (12)	
Doxorubicin	1 (1)	0 (0)	

Data are expressed as *n* (%) unless otherwise specified

PFT permissive fluid therapy, *RFT* restrictive fluid therapy, *SD* standard deviation

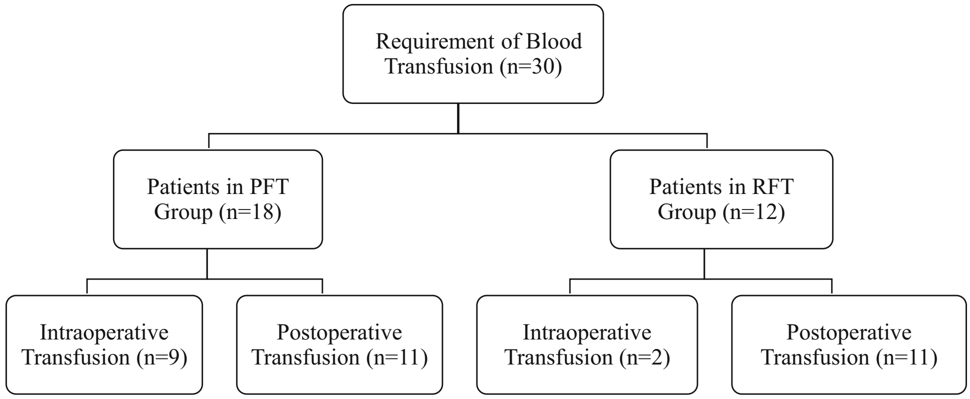
TABLE 3 Postoperative outcomes of the study population

Characteristics	PFT ($n = 84$)	RFT ($n = 85$)	p-Value
Length of stay [mean (SD)]	11.5 (5.9)	9.7 (3.7)	< 0.01
Superficial surgical site infection	2 (2)	3 (4)	0.61
Deep surgical site infection	1 (1)	1 (1)	0.97
Intra-abdominal abscess	4 (5)	4 (5)	0.93
Cardiac arrest	1 (1)	0 (0)	0.32
Myocardial infarction	1 (1)	0 (0)	0.32
Reintubation	2 (2)	3 (4)	0.61
Anastomotic leak	3 (4)	3 (4)	0.94
Acute renal failure	2 (2)	1 (1)	0.60
Peak postoperative creatinine [mean (SD)]	0.82 (0.3)	0.89 (0.7)	0.42
Any 60-day postoperative complication	38 (45)	24 (28)	0.02
Clavien–Dindo grade III or higher complication	15 (18)	9 (11)	0.20
90-day mortality	0 (0)	1 (1)	0.30

Data are expressed as *n* (%) unless otherwise specified

PFT permissive fluid therapy, *RFT* restrictive fluid therapy, *SD* standard deviation

FIG. 1 Blood transfusion requirements



*PFT – Permissive Fluid Therapy ; RFT – Restrictive Fluid Therapy
**3 Patients required both Intraoperative and Postoperative Blood Transfusion

($p = 0.44$) or rate of postoperative blood transfusion ($p = 0.97$).

DISCUSSION

CRS/HIPEC is a well-established therapeutic option in the management of selected patients with peritoneal carcinomatosis.[1–4] While adaptations to surgical technique and chemotherapy delivery have improved both oncologic and surgical outcomes, the physiologic perturbations inherent to the procedure still create a significant perioperative challenge. During cytoreduction, risks of hypothermia and hypovolemia arise from the large midline abdominal incision and the associated insensible losses from surface exposure. Evacuation of large volumes of ascitic fluid and mucin, combined with extensive cytoreduction and blood loss, can lead to hemodynamic instability. The HIPEC phase introduces risks secondary to hyperthermia, increased intra-abdominal pressure, and the chemical toxicity of the chemotherapy agent. As a result, CRS/HIPEC can result in alterations in cardiac output (CO), systemic vascular resistance, end-tidal CO_2, core body temperature, and metabolic abnormalities.[21–23]

Perioperative fluid management strategies have begun to shift in clinical practice, from traditionally liberal to more restrictive, as randomized trials have consistently demonstrated reductions in morbidity with a restrictive approach.[12,13] The optimal volume of fluid resuscitation to manage the physiologic variability during a CRS/HIPEC procedure remains unknown and likely fluctuates throughout the course of the operation as it progresses from cytoreduction to chemoperfusion. The combination of a long, extensive operation combined with chemical and hyperthermic trauma unavoidably results in fluid shifts and hemodynamic changes. The ultimate goal of perioperative resuscitation is to minimize these physiologic alterations without additional negative sequelae. While inadequate infusion volumes may result in hemodynamic instability, tissue hypoperfusion, end-organ damage, and nephrotoxicity, excessive volume administration may result in fluid overload, tissue edema, and an increased risk of major intra-abdominal complications.

A major challenge in the existing literature has been the lack of consensus definitions pertaining to RFT and GDFT. A recent meta-analysis of GDFT including 23 randomized trials from 1995 to 2014 in patients undergoing elective major abdominal surgery demonstrated more than five techniques used to monitor stroke volume (SV) and CO to guide GDFT.[24] Interestingly, GDFT was associated with reductions in morbidity, LOS, and time to passage of flatus with no differences in short-term mortality, regardless of the technique used.[24] In 2015, Colantonio et al. published the results of a randomized controlled trial investigating a GDFT strategy in CRS/HIPEC patients. This is the only published study of the impact of GDFT in CRS/HIPEC compared with PFT. In that study, the Vigileo monitoring device system, which augments arterial line measurements to record SV, CO, and oxygen delivery (DO_2) to guide resuscitation was utilized.[25] The authors reported that CRS/HIPEC patients receiving GDFT had reduced major abdominal complications (10.5% vs. 38.1%, $p = 0.005$), reduced length of hospital stay (19 vs. 29 days, $p < 0.0001$), and reduced mortality (0% vs. 9.5%, $p = 0.12$).[25] While this was the first study to define the potential role of restrictive fluid resuscitation in CRS/

HIPEC patients, major criticisms of the manuscript included the routine transfusion of plasma, and its possible effects on violating fluid protocols.[26]

Our study demonstrates a significant decrease in 60-day morbidity, length of hospital stay, and a risk reduction in Clavien–Dindo grade III or higher complications using a restricted intraoperative fluid regimen during CRS/HIPEC. The findings of our study further support the association between intraoperative fluid therapy and postoperative morbidity. Regarding transfusion protocols, patients in the PFT group were more likely to receive an intraoperative blood transfusion. Despite the increased rate of intraoperative transfusion and an equivalent overall estimated blood loss (EBL) between the PFT and RFT cohorts, the need for postoperative transfusion was equivalent, raising the possibility that the liberal intraoperative fluid resuscitation strategy induced a transient state of hemodilution during which patients met the transfusion criteria and received blood products unnecessarily.

Patients undergoing CRS/HIPEC represent a unique population at high-risk for the detrimental effects of fluid overload. Both RFT and GDFT regimens have been shown to reduce 30-day and 60-day complications, which are significant risk factors for early disease recurrence and decreased overall survival. Thus, it is possible that intraoperative fluid restriction may play a significant role in not only surgical outcomes but also oncologic outcomes.

Limitations

Our study has the limitations inherent to a retrospective review of data. As there was no randomization to a specific resuscitation strategy, direct cause and effect relationships cannot be made. Anesthesiologists received guidelines pertaining to the intraoperative RFT approach, however there was no defined protocol with titratable endpoints to follow. All intraoperative management decisions regarding crystalloid, colloid, and blood product transfusion were at the discretion of the attending anesthesiologist and were based on a given patient's hemodynamic status and overall clinical condition. Postoperatively, liberal use of vasopressors and epidural adjustment were encouraged in the event of hypotension, however there were no formal fluid resuscitation guidelines. Given the chronological division between the PFT (January 2009–September 2014) and RFT (October 2014–July 2017) groups, it is possible that surgeon experience, patient selection, and hospital practice changes could partially account for the reduced rate of complications within the RFT group. It is also important to note that our conclusions regarding an RFT approach are limited to short-term outcomes and cannot be extrapolated to long-term outcomes.

CONCLUSION

CRS/HIPEC can be performed safely with a restrictive intraoperative fluid management strategy. Minimizing the volume of intraoperative crystalloid and colloid to approximately 500 mL/h is associated with a decrease in 60-day complications and hospital LOS. As demonstrated in our study, standard American Society of Anesthesiologists monitoring devices are sufficient to guide a restricted fluid resuscitation approach and yield equivalent improvement in outcomes compared with GDFT approaches, while sparing the additional cost of special invasive monitoring devices. Further randomized controlled trials are needed to more thoroughly address these questions.

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