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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Implementation of an Enhanced Recovery After Surgery (ERAS) Program is Associated with Improved Outcomes in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Christopher Webb, MD[1], Ryan Day, MD[1], Cristine S. Velazco, MD[1], Barbara A. Pockaj, MD[1], Richard J. Gray, MD[1], Chee-Chee Stucky, MD[1], Tonia Young-Fadok, MD[2], and Nabil Wasif, MD, MPH[1]

[1]Department of Surgery, Division of Surgical Oncology, Mayo Clinic Arizona, Phoenix, AZ; [2]Department of Surgery, Division of Colorectal Surgery, Mayo Clinic Arizona, Phoenix, AZ

ABSTRACT

Background. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been associated with increased postoperative complications and a prolonged length of stay (LOS). We report on our experience following implementation of an Enhanced Recovery After Surgery (ERAS) program for CRS and HIPEC.

Methods. Patients were divided into pre- and post-ERAS groups. Modifications in the ERAS group included routine use of transversus abdominis plane blocks, intra- and postoperative fluid restriction, and minimizing the use of narcotics, drains, and nasogastric tubes.

Results. Of a total of 130 procedures, 49 (38%) were in the pre-ERAS group and 81 (62%) were in the ERAS group. Mean LOS was reduced from 10.3 ± 8.9 days to 6.9 ± 5.0 days ($p = 0.007$) and the rate of grade III/IV complications was reduced from 24 to 15% ($p = 0.243$) following ERAS implementation. The ERAS group received less intravenous fluid during hospitalization (19.2 ± 18.7 L vs. 32.8 ± 32.5 L, $p = 0.003$) and used less opioids than the pre-ERAS group (median of 159.7 mg of oral morphine equivalents vs. 272.6 mg). There were no significant changes in the rates of 30-day readmission or acute kidney injury between the two groups (p = non-significant). On multivariable analyses, ERAS was significantly associated with a reduction in LOS (− 2.89 days, 95% CI − 4.84 to − 0.94) and complication rates (odds ratio 0.22, 95% CI 0.08–0.57).

Conclusions. Implementation of an ERAS program for CRS and HIPEC is associated with a reduction in overall intravenous fluids, postoperative narcotic use, complication rates, and LOS.

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as an acceptable treatment modality for patients with peritoneal surface malignancies. This combined treatment can be considered standard of care for pseudomyxoma peritonei (PMP) and peritoneal mesothelioma, as well as for select patients with peritoneal metastasis from colorectal and advanced epithelial ovarian cancers.[1,2] Since the latter part of the late 1990s, CRS/HIPEC has grown significantly in practice throughout the US.[3]

In addition to the normal physiologic responses after CRS, administration of intra-abdominal chemotherapy and patient hyperthermia lead to a myriad of biologic responses. These include exaggerated fluid and electrolyte shifts, hemodynamic derangements, bone marrow suppression, and inhibition of wound healing.[4,5] Consequently, HIPEC

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N. Wasif, MD, MPH
e-mail: wasif.nabil@mayo.edu

TABLE 1 Implemented ERAS principles versus traditional perioperative management

	Traditional approach	Implemented ERAS principle
Nutrition	No routine preoperative protein and carbohydrate supplementation	Routine protein and carbohydrate supplementation
Intravenous fluid	Liberal fluid use	Goal directed/balanced fluids
Pain control	Reliance on opioids	Multimodal pain therapy, including TAP block
GI function and oral intake	Nil by mouth until return of bowel function, feeding tubes	Clear liquid diet POD 0, advance as tolerated, no feeding tube
Drains and tubes	Routine use of nasogastric tubes Routine use of abdominal drains	Use of drains and tubes only when indicated
Postoperative level of care	ICU	Intermediate/step-down

ERAS Enhanced Recovery After Surgery, *GI* gastrointestinal, *ICU* intensive care unit, *TAP* transversus abdominis plane, *POD* postoperative day

procedures have traditionally seen high rates of postoperative complications.[6–8] Traditional approaches to perioperative care have been liberal use of intravenous fluids to mitigate chemotherapy-induced nephrotoxicity, routine use of feeding/nasogastric tubes for anticipated ileus, delayed feeding, transabdominal drains, and use of intensive care units (ICUs).[9–12]

Guidelines for Enhanced Recovery After Surgery (ERAS) have been formalized by the ERAS Society for a variety of surgical procedures.[13] ERAS protocols encompass a holistic, systematic approach to optimizing postoperative recovery, beginning in the preoperative period, and have been shown to improve surgical outcomes and hasten recovery of patients.[13–19] Due to the relative rarity and breadth of CRS and HIPEC procedures, there are no established ERAS protocols. The goal of this study was to implement ERAS principles for patients undergoing CRS and HIPEC at our institution with the aim of reducing postoperative morbidity and mortality.

METHODS

Data Source and Patient Selection

This was a retrospective analysis of a prospectively maintained database of patients who received HIPEC at the Mayo Clinic in Arizona from 2010 to 2018. Inclusion criteria were all consecutive cases in which heated chemotherapy was delivered into the abdomen for peritoneal disease, and included both laparotomy and laparoscopic procedures. Cases that were performed without delivery of HIPEC were excluded from the analysis. Patient selection was performed by multidisciplinary discussion and was based on performance status, primary tumor histology, and feasibility of adequate cytoreduction.

In the early part of 2016, ERAS principles were implemented for all HIPEC procedures, as detailed in Table 1. The changes included a goal-directed approach to intravenous fluid administration, early postoperative feeding and ambulation, multimodal pain modalities including transversus abdominis plane (TAP) blocks, and preoperative nutritional supplementation. Intraoperative fluid administration was goal-directed, with a target of 0.5 mL/kg/h of urine output. Pulse pressure variation (PPV) was used to assess fluid responsiveness and guide therapy. If a hypotensive patient was felt to be euvolemic, then judicious use of vasopressor therapy was permitted. Discharge criteria were identical pre- and post-ERAS: pain control with oral medicines, ability to tolerate a diet, and ambulation without assistance. Relevant demographic, clinical, intraoperative and postoperative data were extracted from the electronic medical record. Approval was obtained from the Institutional Review Board for this low-risk study.

The primary outcomes were 30-day morbidity and mortality, while secondary outcomes were length of hospital stay, 30-day rates of unplanned readmission and reoperation, and rates of acute kidney injury. Length of stay (LOS) was defined as the time from the operation to the time of discharge as recorded in the electronic medical record. Postoperative morbidity was graded according to the National Cancer Institute Common Toxicity Criteria for complication resolution: Grade I, no intervention; Grade II, medical treatment; Grade III, invasive intervention, such as placement of a percutaneous drain; and Grade IV, urgent definitive intervention, such as returning to the operating room or ICU. Acute kidney injury was defined as a rise in serum creatinine $\geq$ 1.5 times the known baseline value, or a rise in serum creatinine $\geq$ 0.3 mg/dL in the days following surgery.

Statistical Analysis

Patients were divided into two groups—pre- and post-ERAS implementation—to study the primary and

secondary outcomes. Planned subgroup analyses were also performed for open and laparoscopic cases. Categorical variables were compared using Pearson's Chi-square test, and continuous variables were compared using Student's *t* test. For non-parametric analyses, the Kruskal–Wallis test was used. Multivariable linear regression analysis was used to study the association of ERAS implementation with LOS, and logistic regression analysis was used to study the association of ERAS implementation with postoperative complications. A p value < 0.05 was set as our threshold for statistical significance, and 95% confidence intervals (CIs) were used unless otherwise indicated. All analyses were performed using STATA 12.0 (StataCorp LLC, College Station, TX, USA).

RESULTS

Patient Demographics and Operative Details

A total of 130 HIPEC procedures were identified in 119 patients with a mean age of 55 ± 12.5 years. The most common cancer histology was appendiceal (56%), followed by colon (25%). Comparing the pre-ERAS group with the ERAS group, there was no difference in median age, sex, mean peritoneal cancer index (PCI) score (11.5 vs. 12.0), or median time of surgery (Table 2).

The mean number of visceral resections and anastomoses, peritonectomies, and omentectomies was also similar between groups. A visceral resection was considered as removal of a segment of the gastrointestinal tract, including cholecystectomy, but not hepatectomy. A peritonectomy was defined as removal of the peritoneum in the right upper/lower, left upper/lower, right/left paracolic gutter, or the pelvis. Omentectomies were considered as total, partial, or none.

Differences in Management

In the pre-ERAS group, no TAP blocks were used, while in the ERAS group, 91% of procedures included TAP blocks, performed either preoperatively by the anesthesiologist or intraoperatively by the surgeon. The duration of HIPEC was between 60 and 90 min at a temperature of 41–43 °C, with 30 mg/m^2 of mitomycin used most commonly. A CC-0 or CC-1 resection was completed in 79% of the pre-ERAS group and 82% of the ERAS group.

Patients in the ERAS group received significantly less intravenous fluid on average, both intraoperatively (5.68 ± 3.05 L vs. 8.10 ± 4.15 L; $p < 0.001$) and postoperatively (13.55 ± 17.65 L vs. 24.71 ± 29.90 L; $p = 0.008$). Total intravenous fluids included crystalloid and colloid fluids. On average, the total amount of administered intravenous fluids during hospitalization decreased from 32.8 ± 32.5 L in the pre-ERAS group to 19.2 ± 18.7 L ($p = 0.003$) in the ERAS group. Intraoperative transfusion of packed red blood cells (pRBC) was administered to 11 patients (22.4%) in the pre-ERAS group and 4 patients (4.9%) in the ERAS group ($p = 0.011$). All transfused patients received ≤ 2 units, with the exception of one patient in the pre-ERAS group who received 10 units of pRBC. There was no change in transfusion parameters during the course of the study.

Outcomes

In the entire cohort, there was one mortality (0.8%) in the ERAS group secondary to respiratory failure. Overall, 24 patients (19%) experienced a grade III/IV complication, including 12 patients (24%) in the pre-ERAS group. After implementation of ERAS, the rate of III/IV complications decreased to 15% ($p = 0.243$). The rate of all grade I–IV complications fell from 63% pre-ERAS to 37% post-ERAS ($p = 0.004$) (Fig. 1). Details of the grade III/IV complications are outlined in electronic supplementary Table 1.

Of our secondary outcomes, only length of hospital stay decreased significantly, from 10.3 ± 8.9 days in the pre-ERAS group to 6.9 ± 5.0 days in the ERAS group ($p = 0.007$). The rate of unplanned surgical intervention decreased by half in the ERAS group (12% to 6%; $p = 0.188$). The rates of both 30-day readmission and acute kidney injury did not change significantly in the ERAS group.

Multimodal pain control implemented in the ERAS group resulted in less opioid use. Total opioid use measured in OMEs decreased from a median of 272.6 mg to 159.7 mg after implementation of TAP blocks and ERAS ($p = 0.137$) and a mean of 524.8 ± 1482.6 to 415.1 ± 474 mg ($p = 0.617$). Several outliers and wide variation in narcotic use resulted in wide standard deviations, thus a non-parametric comparison of medians was also performed. This showed that total narcotic use was significantly different in the open group ($p = 0.041$), but not the laparoscopic group ($p = 0.171$).

Open and Laparoscopic Hyperthermic Intraperitoneal Chemotherapy

Laparoscopic HIPEC was used for 39 (30%) procedures. The differences in patient outcomes pre- and post-ERAS stratified by laparoscopic or open HIPEC are presented in Table 3. When compared within their respective operations (open vs. laparoscopic), patients had similar PCI scores and similar surgical procedures performed. Use of intravenous fluids showed a significant reduction in both ERAS groups compared with the pre-ERAS groups. Within the open

TABLE 2 Patient characteristics and treatment descriptions

	Pre-ERAS	ERAS	Total	*p* value
Patient characteristics				
N	49	81	130	
Age, years	56.0 ± 10.9	54.4 ± 13.4	55 ± 12.5	0.517
PCI				0.781
Mean	11.5 ± 9.4	12.0 ± 8.4	11.8 ± 8.8	
Median	10 (0–32)	11 (0–36)	11 (0–36)	
Sex [*n* (%)]				0.894
Female	23 (47)	39 (48)	62 (48)	
Male	26 (53)	42 (52)	68 (52)	
Site of origin [*n* (%)]				
Appendix	26 (53)	47 (58)	73 (56)	
Colon	14 (29)	18 (22)	32 (25)	
Mesothelioma	4 (8)	7 (9)	11 (8)	
Ovarian	3 (6)	2 (2)	5 (4)	
Gastric	0 (0)	5 (6)	5 (4)	
Small bowel	1 (2)	1 (1)	2 (1)	
Other	1 (2)	1 (1)	2 (1)	
Treatment differences				
CC-0 or CC-1 completed (%)[a]	38/48 (79)	60/73 (82)	98/121 (81)	
Time of surgery, h	6.5 ± 2.2	6.5 ± 2.7	6.5 ± 2.5	0.983
TAP administered				
Yes	0 (0%)	74 (91%)	74 (57%)	
No	49 (100%)	7 (9%)	56 (43%)	
Visceral resections [*n* (%)]				0.154
0	25 (51)	32 (40)	57 (44)	
1	13 (27)	20 (25)	33 (25)	
2	9 (18)	15 (19)	24 (18)	
3	1 (2)	12 (15)	13 (10)	
4	1 (2)	2 (2)	3 (2)	
Anastomoses [*n* (%)]				0.639
0	27 (55)	48 (59)	75 (58)	
1	16 (33)	23 (28)	39 (30)	
2	5 (10)	10 (12)	15 (12)	
3	1 (2)	0 (0)	1 (1)	
Stoma [*n* (%)]				0.025
Yes	5 (10)	22 (27%)	27 (21%)	
No	44 (90)	59 (73%)	103 (79%)	
Peritonectomies [*n* (%)]				0.849
0	24 (49)	41 (51)	65 (50)	
1	13 (27)	14 (17)	27 (21)	
2	5 (10)	10 (12)	15 (12)	
3	3 (6)	8 (10)	11 (8)	
4	3 (6)	5 (6)	8 (6)	
5	1 (2)	3 (4)	4 (3)	
Omentectomies [*n* (%)]				0.350
Total	17 (35)	28 (35)	45 (35)	
Partial	29 (59)	41 (51)	70 (54)	
None	3 (6)	12 (15)	15 (11)	

TABLE 2 continued

	Pre-ERAS	ERAS	Total	*p* value
Diaphragm repair [*n* (%)]				0.318
Yes	2 (4)	8 (10)	10 (8)	
No	47 (96)	73 (90)	120 (92)	
Chemotherapy [*n* (%)]				
MMC	44 (90)	69 (85)	113 (87)	
Cisplatin	5 (10)	7 (9)	12 (9)	
Cisplatin + MMC	0 (0)	5 (6)	5 (4)	
Intravenous fluids, L				
Intraoperative – total	8.1 ± 4.1	5.7 ± 3.0	6.6 ± 3.7	< 0.001
Crystalloid	7.0 ± 3.3	4.8 ± 2.6	5.6 ± 3.1	< 0.001
Colloid	1.1 ± 1.1	0.8 ± 0.7	0.96 ± 0.9	0.122
Postoperative	24.7 ± 29.9	13.5 ± 17.6	17.7 ± 23.6	0.008
Total hospitalization	32.8 ± 32.5	19.2 ± 18.6	24.3 ± 25.6	0.003
Net hospital fluid balance	6.07 ± 16.8	3.00 ± 6.3	4.1 ± 11.5	0.142
OMEs, mg				
Oral + IV push	248.5 ± 1186.1	115.7 ± 148.1	198.4 ± 940.6	0.438
PCA	276.3 ± 519.8	299.4 ± 371.5	285.0 ± 468.0	0.786
Total OMEs	524.8 ± 1482.7	415.1 ± 474.0	483.4 ± 1204.0	0.617

ERAS Enhanced Recovery After Surgery, *PCI* peritoneal cancer index, *MMC* mitomycin C, *CC* completeness of cytoreduction, *OMEs* oral morphine equivalents, *PCA* patient-controlled analgesia, *TAP* transversus abdominis plane, *IV* intravenous, *HIPEC* hyperthermic intraperitoneal chemotherapy

[a]Includes first-time HIPEC cases of curative intent

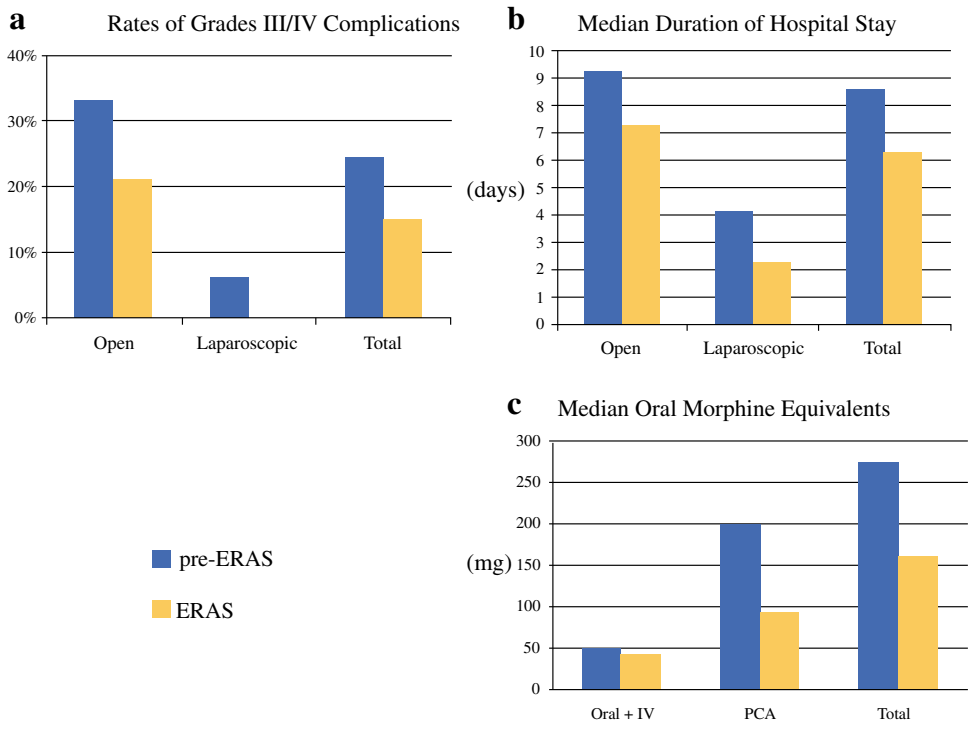

FIG. 1 Rates of serious complications, length of stay and use of narcotics pre-ERAS vs. ERAS

TABLE 3 Pre- and post-ERAS differences by open and laparoscopic HIPEC*

	Open HIPEC			Laparoscopic HIPEC		
	Pre-ERAS	ERAS	*p* value	Pre-ERAS	ERAS	*p* value
Patient details						
N	33	58		16	23	
Age, years	58 ± 9.6	52 ± 13.0	0.038	52.0 ± 12.6	59.7 ± 13.2	0.075
PCI	14.5 ± 9.3	14.3 ± 8.3	0.934	5.4 ± 6.4	6.0 ± 5.1	0.746
CC-0/CC-1 completed (%)[a]	24/33 (73)	45/56 (80)		14/15 (93)	15/17 (88)	
Site of origin [*n* (%)]						
Appendix	17 (52)	35 (60)		9 (56)	12 (52)	
Colon	11 (33)	13 (22)		3 (19)	5 (22)	
Mesothelioma	2 (6)	6 (10)		2 (13)	1 (4)	
Ovarian	1 (3)	2 (4)		2 (13)	0 (0)	
Gastric	0 (0)	0 (0)		0 (0)	5 (22)	
Small bowel	1 (3)	1 (2)		0 (0)	0 (0)	
Other	1 (3)	1 (2)		0 (0)	0 (0)	
Surgical details						
Time of surgery, h	7.2 ± 2.1	7.5 ± 2.4	0.520	5.1 ± 1.8	4.0 ± 1.6	0.054
TAP administered [*n* (%)]						
Yes	0 (0)	53 (91)		0 (0)	21 (91)	
No	33 (100)	5 (9)		16 (100)	2 (9)	
Visceral resections [*n* (%)]			0.167			1.000
0	11 (33)	13 (22)		14 (88)	19 (83)	
1	11 (33)	17 (29)		2 (12)	3 (13)	
2	9 (27)	14 (24)		0 (0)	1 (4)	
3	1 (3)	12 (21)		0 (0)	0 (0)	
4	1 (3)	2 (4)		0 (0)	0 (0)	
				0 (0)	0 (0)	
Anastomoses [*n* (%)]			0.477			1.000
0	13 (39)	29 (50)		14 (88)	19 (83)	
1	14 (42)	20 (34)		2 (12)	3 (13)	
2	5 (15)	9 (16)		0 (0)	1 (4)	
3	1 (3)	0 (0)		0 (0)	0 (0)	
Stoma [*n* (%)]			0.031			0.590
Yes	5 (15)	22 (38)		0 (0)	1 (4)	
No	28 (85)	36 (62)		16 (100)	22 (96)	
Peritonectomies [*n* (%)]			0.580			0.637
0	12 (36)	24 (41)		12 (75)	17 (74)	
1	11 (33)	9 (16)		2 (12)	5 (22)	
2	4 (12)	9 (16)		1 (6)	1 (4)	
3	3 (9)	8 (14)		1 (6)	0 (0)	
4	2 (6)	5 (9)		0 (0)	0 (0)	
	1 (3)	3 (5)		0 (0)	0 (0)	
Omentectomies [*n* (%)]			0.220			1.000
Total	2 (6)	11 (19)		6 (38)	9 (39)	
Partial	20 (61)	28 (48)		9 (56)	13 (57)	
None	11 (33)	19 (33)		1 (6)	1 (4)	

TABLE 3 continued

	Open HIPEC			Laparoscopic HIPEC		
	Pre-ERAS	ERAS	*p* value	Pre-ERAS	ERAS	*p* value
Diaphragm repair [*n* (%)]			0.479			0.590
Yes	2 (6)	7 (12)		0 (0)	1 (4)	
No	31 (94)	51 (88)		16 (100)	22 (96)	
Chemotherapy [*n* (%)]						
Mitomycin	32 (97)	52 (90)		12 (75)	17 (74)	
Cisplatin	1 (3)	6 (10)		4 (25)	1 (4)	
Cisplatin + mitomycin	0 (0)	0 (0)		0 (0)	5 (22)	
Intraoperative pRBC transfusion [*n* (%)]	11 (33)	4 (6.9)	0.008	0	0	
Intravenous fluids						
Intraoperative – total	9.37 ± 4.33	6.41 ± 2.90	< 0.001	5.47 ± 2.07	3.83 ± 2.67	0.047
Crystalloid	7.98 ± 3.44	5.37 ± 2.49	< 0.001	4.94 ± 1.9	3.4 ± 2.6	0.053
Colloid	1.39 ± 1.18	1.04 ± 0.76	0.089	0.53 ± 0.46	0.41 ± 0.36	0.375
Postoperative	33.4 ± 32.9	17.4 ± 19.4	0.005	6.78 ± 5.95	3.77 ± 3.76	0.061
Total hospitalization	42.8 ± 35.4	23.8 ± 20.1	0.002	12.26 ± 6.71	7.61 ± 5.35	0.021
Net hospital fluid balance	8.1 ± 20.2	3.4 ± 7.0	0.105	1.82 ± 3.23	2.05 ± 4.50	0.864
OMES, mg						
Oral + IV push	158.7 ± 163.4	329.2 ± 1395.9	0.487	27.0 ± 28.2	44.9 ± 81.2	0.404
PCA	418.9 ± 399.8	378.3 ± 584.0	0.724	52.7 ± 65.3	19.2 ± 48.9	0.075
Total OMEs	577.6 ± 500.8	707.5 ± 226.0	0.674	79.7 ± 76.6	64.1 ± 96.6	0.593
Outcomes						
III/IV complications [*n* (%)]	11 (33)	12 (21)	0.218	1 (6)	0 (0)	0.410
Length of stay	13.1 ± 9.5	8.6 ± 4.9	0.004	4.5 ± 2.8	2.8 ± 2.4	0.044
30-day reoperation rate [*n* (%)]	6 (18)	5 (9)	0.197	0	0	
30-day readmission rate [*n* (%)]	7 (21)	12 (21)	1.000	0 (0)	1 (4)	0.590
Acute kidney injury rate [*n* (%)]	5 (15)	7 (12)	0.751	0	0	

*Includes first time HIPEC cases of curative intent

ERAS Enhanced Recovery After Surgery, *PCI* peritoneal cancer index, *CC* completeness of cytoreduction, *pRBC* packed red blood cell, *OMEs* oral morphine equivalents, *PCA* patient-controlled analgesia, *HIPEC* hyperthermic intraperitoneal chemotherapy, *TAP* transversus abdominis plane, *IV* intravenous

group, there was a decrease in the grade III/IV complication rate from 33% to 21% ($p = 0.218$), and a decrease in LOS from 13.1 ± 9.5 days to 8.6 ± 4.9 days ($p = 0.004$) after the ERAS principles were initiated. In the laparoscopic group, the grade III/IV complication rate decreased from 6.25% to 0%, and LOS went from 4.5 ± 2.8 days to 2.8 ± 2.4 days ($p = 0.044$).

Multivariable Analyses

A multivariable linear regression analysis was performed to determine the association of implementation of an ERAS program with LOS, when controlling for other clinically significant variables (Table 4). As expected, grade III/IV complications, open procedures, and duration of surgery were all associated with an increase in LOS, whereas implementation of an ERAS program resulted in a reduction in LOS ($\beta = -2.89$ days, 95% CI −0.94 to −4.84). Similarly, the implementation of an ERAS program was associated with a reduction in complications (odds ratio 0.22, 95% CI 0.08–0.57) on logistic regression analysis, whereas increased length of surgery and increasing age were associated with an increase in complications.

DISCUSSION

Although ERAS programs have been associated with improved postoperative outcomes in several surgical procedures, this has not been demonstrated for CRS and HIPEC.[13–19] In this study, we showed for the first time that implementation of an ERAS program was associated with a lower 30-day grade III/IV complication rate and a shorter LOS without an increase in readmissions or the rate of acute kidney injury. Those in the ERAS pathway had similar PCI scores and duration of surgery, yet had significantly lower total fluid and narcotic requirement.

TABLE 4 Multivariable analyses for length of hospital stay and complications

Characteristic	Multivariable linear regression for LOS		Multivariable logistic regression for any complications	
	Coefficient (95% CI)	*p* value	OR (95% CI)	*p* value
Age	0.03 (− 0.04 to 0.11)	0.433	1.04 (0.99–1.07)	0.058
Length of procedure	0.69 (0.19–1.18)	0.006	1.6 (1.2–2.0)	0.000
Laparoscopic versus open	3.06 (0.49–5.62)	0.02	1.4 (0.41–4.88)	0.58
Any resection	− 0.21 (− 3.54 to 3.13)	0.903	0.93 (0.21–4.06)	0.925
Any anastomosis	1.45 (− 1.52 to 4.41)	0.336	1.37 (0.38–4.95)	0.632
ERAS	− 2.89 (− 4.84 to − 0.94)	0.004	0.22 (0.08–0.57)	0.002
Grade III/IV	5.59 (3.12–8.05)	0.000	NA	NA
PCI	NA	NA	1.04 (0.98–1.10)	0.197

PCI peritoneal cancer index, *LOS* length of stay, *CI* confidence interval, *OR* odds ratio, *ERAS* Enhanced Recovery After Surgery, *NA* not applicable

The use of CRS and HIPEC as a viable treatment modality for cancers with peritoneal involvement has traditionally been associated with high mortality and morbidity rates. One early study of CRS and HIPEC reported morbidity and mortality rates of 27–65% and 0–9%, respectively.[20] More recently, a 2016 systematic review of several large series showed that rates of grade III/IV complications ranged from 22 to 34% and mortality from 0.8 to 4.1%.[21] Our overall mortality rate of 0.8% and grade III/IV complication rate of 19% suggests that contemporary outcomes with CRS and HIPEC compare favorably with other major surgeries such as esophagectomies and pancreatectomies, as has been pointed out by others.[22] In the ERAS group, these outcomes are further improved by a decrease in grade III/IV complications from 24 to 15% and overall complication rate from 63 to 37%, both clinically significant reductions. This suggests that further improvements in morbidity and mortality for patients undergoing CRS and HIPEC may be possible with the implementation of ERAS principles.

Although we demonstrate improved outcomes following implementation of ERAS principles, a causal association can only be established with a randomized trial. Furthermore, a natural learning curve for CRS and HIPEC has been identified in which centers with greater than 100–140 cases show improved outcomes.[23,24] Less is known about what variables influence this improvement in outcomes, and it is likely a mix of technical proficiency, better postoperative management and improved patient selection. Our pre-ERAS group comprised the first 49 procedures and the post-ERAS group comprised the next 81 procedures, meaning we were able to show improved outcomes relatively early on our institutional learning curve. Since CRS and HIPEC remains a highly specialized procedure, moving beyond this learning curve may take up to a decade for many centers and surgeons. It should be noted that the procedures were performed by a single surgeon, and our progress on the learning curve may have biased the results away from the null hypothesis. Nevertheless, we believe that implementation of ERAS principles for CRS and HIPEC represents one way in which all centers may further improve outcomes while still on the learning curve. Furthermore, it is possible that early implementation of these principles may help shorten the overall learning curve.

The outcomes at our center after implementing ERAS indicate that significant reduction in length of hospital stay could be accomplished without increasing 30-day readmission rates. Traditionally, CRS and HIPEC have prolonged hospital stays, largely related to the magnitude of surgery, HIPEC-induced ileus, and postoperative complications. A large review in 2009 by Chua et al. showed a median length of hospital stay of 19 days.[25] A large Dutch review showed a median of 16 days,[26] and a more recent National Surgical Quality Improvement Program (NSQIP) review reported an average LOS of 13 days.[27] We report a reduction in LOS from a mean of 10.3 days to 6.9 days following implementation of our ERAS program, without a reciprocal increase in 30-day readmission rates. Our readmission rate of 14% and 16% pre- and post-ERAS, respectively, compares with that of 11% reported by the same NSQIP review.[27] The 33% reduction in LOS, on average, seen in this study represents one of the highest reductions in LOS reported for any ERAS program.

We believe our results can be explained in part by the decreased use of fluids and narcotics seen post-ERAS. Several studies have shown that goal-directed or even a restrictive fluid strategy postoperatively is associated with improved outcomes in major abdominal and colorectal surgery compared with a liberal fluid strategy.[28,29] Concerns about chemotherapy-induced nephrotoxicity, replacement of large-volume ascites, and the dehydration from preoperative bowel preparations are all considerations that have led to a liberal fluid strategy. As part of our ERAS protocol promoting euvolemia, patients are

encouraged to drink clear liquids up to 2 h before the operation. Bowel preparations are used only if indicated preoperatively, and potentially nephrotoxic agents (e.g. ketorolac) are used judiciously. We were able to show that goal-directed therapy can be achieved without an increase in the rate of acute kidney injury or renal dysfunction. Although cisplatin has been associated with nephrotoxicity in HIPEC, no patients who received cisplatin had acute kidney injury in our cohort, thus no conclusions were made regarding renal toxicity of specific HIPEC agents. Another concern in this patient subset was the high rate of postoperative ileus secondary to the heated chemotherapy and possibly abdominal and visceral agitation for 60–90 min during the perfusion. The prolonged use of high-dose narcotics likely exacerbates this phenomenon. We mitigate this by using non-narcotic pain control, primarily TAP blocks with liposomal bupivacaine, which are effective at reducing narcotic use postoperatively,[30] and with intermittent rather than continuous visceral agitation.

In our study, there was no set date or formal process for implementing ERAS principles and it occurred over time in the order of months. This was a limitation of our study as there were a small number of patients who had partial ERAS pathways. For the purposes of this study, the main group assignment was largely based on receipt of a TAP block as this was the most binary ERAS variable. Analyses were completed using an intention-to-treat approach, so that the seven patients in the ERAS group without TAP blocks still retained the ERAS designation for the purposes of analyses. Another limitation was the issue of compliance, which was difficult to determine for the use of preoperative nutritional supplements, frequency of drains and nasogastric tubes, and amount of food intake postoperatively. For factors that we considered within our control, i.e. primarily fluid restriction and TAP blocks, compliance with ERAS principles was $> 90\%$. These factors should bias our results towards the null hypothesis, and it is possible that the actual differences between pre- and post-ERAS may be larger. The return of bowel function or lack thereof in the form of an ileus, described in part as the absence of flatus, was purposefully not collected due to the inherit difficulty and imprecision in assessing this from the electronic medical record. Although passage of the first stool is a more discrete outcome, clinically this may occur several days after passage of the first flatus.

CONCLUSIONS

We present the first study on the impact of implementation of an ERAS program for CRS and HIPEC. Compared with pre-ERAS, a reduction in intravenous fluid and narcotic use without an increase in readmission or acute kidney injury rates was seen in the ERAS group, in association with a reduction in LOS of 33% and a grade III/IV complication rate of 38%. We believe the results of this study show that implementation of ERAS for CRS and HIPEC reduces total fluid and narcotic use and may be associated with lower complication rates and a decreased LOS. In particular, these principles may help shorten the traditionally long surgeon and institutional learning curve needed for optimal outcomes, especially when implementing a new HIPEC program.

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