Ann Surg Oncol (2019) 26:3652–3662
https://doi.org/10.1245/s10434-019-07644-w

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Standard Operating Procedures for Anesthesia Management in Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improve Patient Outcomes: A Patient Cohort Analysis

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ABSTRACT

Background. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) offer survival benefits in well-selected patients with peritoneal tumors. The complexity of CRS/HIPEC requires surgical specialization. In contrast, limited data are available regarding the impact of anesthesia management. We assessed the role of standard operating procedures (SOPs) for anesthesia on perioperative patient outcomes after CRS/HIPEC.

Methods. Between 2009 and 2015, 112 CRS/HIPEC were performed at the University Hospital of Zurich. Procedures were grouped in an "early or late" group before (n = 57) and after (n = 55) the introduction of SOPs, which defined management of fluids, serum albumin, hemostasis, and body temperature.

Results. Introduction of SOPs significantly changed patient management. Patients received in total less colloids (p = 0.03) and less diuretics (p = 0.007). We noticed an increased substitution of albumin (p = 0.001) and coagulation factors (p = 0.008). Body temperatures were higher at the end of the operation (p = 0.005), and more patients were extubated in the operating room (66% vs. 42%, p = 0.02). The rate of major complications (p = 0.003) and reoperations (p = 0.01) was reduced after the introduction of SOPs. On multivariate analysis, two independent prognostic factors were identified. The use of > 2000 mL of colloids [odds ratio (OR) 5.31 (1.06–26.56), p = 0.042] was associated with major morbidity. In contrast, substitution of albumin [OR 0.12 (0.01–0.96), p = 0.046] was associated with better outcomes.

Conclusions. SOPs for perioperative anesthesia management have a major impact on outcomes of patients after CRS/HIPEC. Management of colloid administration was an independent prognostic factor for perioperative outcomes. This highlights the role of the anesthesiologist and the need for specialization beyond the surgical team.

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has become a standard in the multimodal treatment options for peritoneal metastasis.[1,2] Together with modern systemic chemotherapy, CRS/HIPEC changed the perspective from palliation only to a chance to cure for many patients. For example, cure or long-term survival is possible for patients with peritoneal metastasis from appendix tumors, and at least a better tumor control can be achieved in many patients with colorectal peritoneal metastasis.[3,4] A median survival above 40 months after CRS/HIPEC could be documented in many series.[4–8] Despite the lack of a randomized trial with modern systemic chemotherapy in the control group, the Dutch randomized, controlled trial (RCT) and several cohort studies convinced a growing number of medical and surgical oncologist to add CRS/HIPEC to the multimodal treatment of peritoneal metastasis.[8–14]

First Received: 20 March 2019;
Published Online: 29 July 2019

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The main argument against CRS/HIPEC is the potential morbidity and mortality of the procedure, in the specific setting of a highly advanced disease.[15] Due to the long learning curve and complexity of the treatment, there is a broad consensus regarding the need for centralization and high surgical expertise.[16,17] In addition, CRS/HIPEC induces a complex pathophysiology before, during, and after surgery. Recently, the group from Lyon published data highlighting that standardization of processes improves patient outcomes.[18] Their clinical pathway focused on patient selection, nutrition, renal protection, pain management, prevention, and early detection of complications. The group showed a reduction in the failure-to-rescue rate and a better quality of care after introduction of their clinical pathway. However, despite the important role of the anesthesiologist during CRS/HIPEC, anesthesia management is clearly underreported in the current literature and therefore may be underestimated for the quality of CRS/HIPEC.[19,20] The purpose of our study was (1) to assess the effect of standard operating procedures (SOPs) for anesthesia management after its implementation, and (2) to define clinically relevant factors that influence patient outcomes after CRS/HIPEC.

PATIENTS AND METHODS

Between January 2009 and December 2015, 112 complete CRS/HIPEC procedures were performed at the University Hospital of Zurich. Patients with explorative laparotomy or incomplete CRS, and therefore no HIPEC, were excluded. In 2012, the SOP was introduced for anesthesia management to create a uniform standard. Procedures were grouped in an early group before introduction of the SOP from 2009 to 2012 and a late group from 2012 to 2015. Patient data were extracted from anesthesia protocols and patient records. The study protocol was approved by the local institutional review board (cantonal ethics commission, Zurich, Switzerland; KEK 2015-0331) and reporting was based on the STROBE checklist for reporting clinical studies.[21]

Patient Selection

Patients were selected for CRS/HIPEC based on the type of primary tumor, the absence of extraperitoneal disease, and a good performance status. Age was not a selection criterion. All patients were presented in an interdisciplinary tumor board, where systemic treatment was recommended before CRS/HIPEC in patients with aggressive carcinomas. Patients with noninvasive disease (pseudomyxoma) were directly operated. Informed consent was obtained from every patient.

Surgical Management

Cytoreductive surgery was performed according to standardized protocols and by a constant team. In the pilot phase, the team was supported and supervised by an expert surgeon (P.G.) as recommended by others.[17] After midline incision, the abdomen was explored, the peritoneal cancer index (PCI) calculated, and resectability was assessed. Cytoreductive surgery included resection of the major and minor omentum and resection of diseased organs or peritoneum in patients with secondary carcinomatosis. In mesothelioma patients, total peritonectomy was performed. HIPEC was performed with the open coliseum technique for 90 min at 42 °C with mitomycin (15–30 mg/m^{2}xBSA), or cisplatin (50–75 mg/m^{2}xBSA), and doxorubicin (15 mg/m^{2}xBSA). Protective ileostomies were placed if more than one colonic or a low rectal anastomosis were performed.

Anesthesia Management

Before 2012, the choice of anesthesia management during CRS/HIPEC was an individual decision of every single anesthesiologist. In 2012, a standard operating procedure (SOP) was introduced based on the data from Kajdi et al.[19] This SOP focused mainly on less invasive monitoring (no pulse contour cardiac output, PiCCO, measurement), fluid or volume management with less colloids, avoidance of hypalbuminemia as a surrogate for the oncotic pressure, and management of hemostasis and hypothermia (Fig. 1). The surgical procedure was separated into defined periods, such as the preoperative phase, anesthesia induction, CRS, HIPEC, restitution, and the postoperative phase. In the preoperative phase, patients were admitted electively to the hospital the day prior surgery for bowel preparation and hydration. Due to the expected enteral fluid loss and volume shift by osmotic bowel preparation with Macrogol and for nephroprotection prior to HIPEC, 2000 mL of crystalloids were admitted intravenously overnight.[22] During anesthesia induction, intraoperative monitoring was standardized to electrocardiogram (ECG), pulse oximetry, arterial and central venous line, a nasopharyngeal temperature probe, and a urinary catheter. A nasogastric tube was inserted to decompress the stomach. If no contradictions were evident, thoracic epidural anesthesia was installed before surgery and used up to the third postoperative day. Induction of general anesthesia was performed with propofol, maintenance by volatile anesthetics, such as sevoflurane or desflurane, or by a continuous infusion of propofol. During CRS, fluid management was kept restrictive toward a physiologic diuresis. Crystalloids were substituted with a rate of 6–12 ml/kg/h and colloids with a rate of 2–4 ml/kg/h. In this context, albumin was not used for volume replacement.

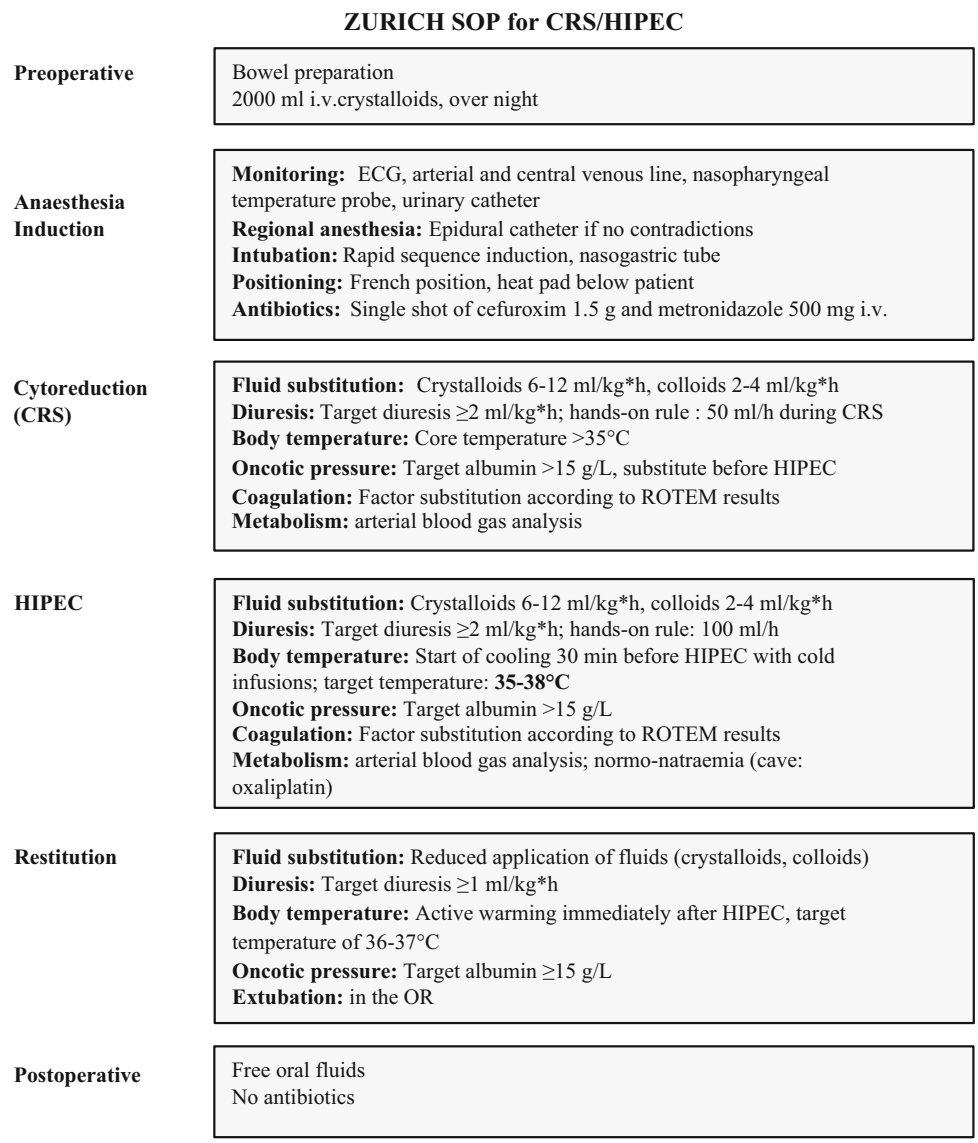

FIG. 1 Zurich SOP for CRS/HIPEC. The SOPs were introduced in 2012 to improve and standardize the perioperative management in patients undergoing CRS/HIPEC. *ECG* Electrocardiogram. ROTEM® (Rotational Thromboelastometry)

The goal was to achieve a target diuresis of ≥ 2 ml/kg/h. During CRS, the minimal urine output was set to 50 ml/h. During HIPEC, an uine output at 100 ml/h was targeted to avoid nephrotoxic effects of HIPEC. Coagulation was analyzed by ROTEM® (Rotational Thromboelastometry) during prolonged CRS and substituted by single factors. Hematocrit and ionized serum calcium was monitored by repeated blood gas analyses. Normothermia was achieved by aggressive warming and cooling of patients by warmed/cooled infusion and external heating and cooling. The target temperature range of patients was 35–38 °C; normothermia was aimed at the end of the procedure (36–37 °C). Usually during extensive CRS or toward the end of CRS, albumin was substituted with 20% human albumin to reach a target level of > 15 g/L in serum (normal value: 35–52 g/L). Albumin was not substituted for volume replacement but to substitute a sufficient blood level to maintain the oncotic pressure. After albumin substitution, serum levels were checked in the following hours and repeated only if not within the targeted range. During restitution, physiological conditions were reestablished, and patients were prepared for extubation. Postoperatively, patients were transferred to the intensive care unit (ICU).

Assessment of Postoperative Outcomes

Postoperative complications were discussed during a weekly morbidity and mortality conference and graded by the Clavien/Dindo score.[23] Complications grade ≥ 3b, requiring an intervention under general anesthesia, reoperation or readmission to the ICU, were defined as "major" morbidity.

Statistical Analysis

Continuous variables were compared with the Student *t*, Mann–Whitney *U*, one-way ANOVA, and Kruskal–Wallis tests, where appropriate. Differences among proportions derived from categorical data were compared using the Fischer's exact or the Pearson χ^2 tests, where appropriate. All *p* values were two-sided and considered statistically significant if $p \leq 0.05$. All *p* values in the univariate analysis were two-sided and considered statistically significant if $p \leq 0.05$. The backward stepwise logistic regression model was used to identify independent predictors of outcomes. Data are presented as mean (SD), median (IQR), and proportions (%) with odds ratios [OR] (95% confidence intervals [CI]), where appropriate. Statistical analysis was performed using SPSS for Mac v23.

RESULTS

Patient Characteristics

During the study period from 2009 to 2015, 112 consecutive and complete CRS/HIPEC procedures in 106 patients were performed and included in the analysis. Patients after incomplete CRS and without HIPEC were excluded. Fifty-seven (51%) procedures were performed before (early group), and 55 (49%) after the introduction of standardized anesthesia SOPs (late group). There was no difference between the two groups for age, gender, body mass index (BMI), comorbidity, and medication (Table 1), indicating that there was no shift toward healthier or younger patients over the two periods. In addition, no difference was found for tumor types, except for a higher incidence of patients with disseminated peritoneal adenomucinosis (DPAM) ($p = 0.050$) in the late group.

Surgical Parameters

Overall, the extent of peritoneal disease was higher, reflected by a higher PCI ($p = 0.02$) in the late group. Nevertheless, operating times remained constant, without differences between the two groups, and complete (CC-0) cytoreduction could be achieved in > 85% of the patients. Higher PCI values and a trend toward more complete CRS in the late group resulted in more complex resections. In detail, a higher rate of splenectomies ($p = 0.01$), liver capsule resections ($p = 0.01$), and colectomies ($p = 0.02$) was performed. In addition, radical peritonectomy more often included peritoneal and mesenterial quadrants in the late group (Table 2). An ileostomy, usually placed if more than one colorectal anastomosis was performed, was more frequent in the late group ($p = 0.001$). HIPEC was performed with a combination of mitomycin/doxorubicin for appendix and colorectal tumors and cisplatin/doxorubicin for mesothelioma, gastric and ovarian tumors, and remained constant over time. In contrast, the dose of mitomycin increased from 15 mg/m^{2}xBSA to 30 mg/m^{2}xBSA over the two periods; therefore, dosage of HIPEC was higher in the late group ($p = 0.02$). Overall, the second period includes patients with more complex CRS and a higher dosage of HIPEC.

Anesthesia Management

Introduction of SOPs for the anesthesia management significantly changed patient management. Standard intraoperative monitoring was limited to an arterial and central venous line as well as a urinary catheter, without the need for further invasive modalities such as extended hemodynamic monitoring with pulse contour cardiac output (PiCCO) unless indicated (Table 3). Thoracic epidural anesthesia was used in two third of patients if no contraindication was present. For anesthesia maintenance, volatile anesthetics were used significantly more often in the late group. Fluid management remained unchanged for a liberal use of crystalloids to maintain diuresis, but patients received less colloids ($p = 0.03$) and less diuretics ($p = 0.007$). Albumin levels were measured intraoperatively and kept > 15 mg/l to maintain the oncotic pressure, resulting in a higher use of albumin ($p < 0.001$). Active surveillance of coagulation by thromboelastography resulted in a higher proportion of patients who received substitution of coagulation factors (e.g., fibrinogen, factor XIII, etc.; $p = 0.008$). More details are given in Table 3.

Intraoperative Cardiovascular Parameters

The mean arterial pressure (MAP) showed no difference between the groups (Fig. 2). In contrast, a trend toward a lower central venous pressure (CVP) in the late group was observed, with a significant difference before the beginning of HIPEC (Fig. 2). This may reflect the stricter volume management observed in the late group above. Patient core temperatures were actively corrected by heating and cooling and remained at higher physiologic levels at the end of the operation ($p = 0.005$; Fig. 2). In addition, very low temperatures were avoided ($p = 0.02$) in the late group. Although significant between the two groups and observed at different time points, these temperature differences were small (0.3 °C). Finally, two thirds of patients were extubated directly in the operating room in the late group compared with 42% in the early group ($p = 0.02$; Table 3).

TABLE 1 Patient characteristics

Parameter	Early group (n = 57)	Late group (n = 55)	p value
Gender			
Male	23 (40.4%)	26 (47.3%)	
Female	34 (59.6%)	29 (52.7%)	0.57
Age	52 (43–58)	50 (42–59)	0.55
BMI	24.5 (21.5–27.7)	23.2 (21.5–26.8)	0.27
Charlson-Index	6 (6–8)	6 (6–9)	0.87
ASA			
ASA ≤ II	54 (94.7%)	49 (89.1%)	
ASA ≥ III	3 (5.3%)	6 (10.9%)	0.31
Comorbidity			
Cardiovascular	13 (22.8%)	22 (40.0%)	0.18
Pulmonary	4 (7.0%)	6 (10.9%)	0.71
Renal	2 (3.5%)	3 (4.4%)	0.73
Obesity (BMI > 35)	8 (14.0%)	4 (7.3%)	0.25
Medication			
None	24 (42.1%)	25 (45.5%)	0.85
Betablocker	2 (3.5%)	2 (3.6%)	1.0
Anti-hypertensive medication	4 (7.0%)	1 (1.8%)	0.36
Combination of two or more	5 (8.8%)	7 (12.7%)	0.55
Other	22 (38.6%)	20 (36.4%)	0.85
Tumor type			
Appendix	33 (57.9%)	29 (52.7%)	0.70
DPAM	13 (22.8%)	19 (34.5%)	0.05
PMCA	8 (14.0%)	2 (3.6%)	0.09
Adenocarcinoma	7 (12.3%)	4 (7.3%)	0.53
Signet ring cell	4 (7.0%)	2 (3.6%)	0.68
Carcinoid	1 (1.8%)	1 (1.8%)	1.0
Colorectal	13 (22.7%)	18 (32.7%)	0.29
Synchronous	5 (38.5%)	8 (44.4%)	0.39
Metachronus	8 (61.5%)	10 (55.6%)	0.61
Mesothelioma	5 (8.8%)	3 (5.5%)	0.72
Other	6 (10.6)	5 (9.1%)	1.0

Interval data are shown as median with 1.–3. interquartile range. Categorical data are shown as absolute values (n =) and percent of the respective total patient number. Mann–Whitney U test was used to test for differences between groups with interval data. Comparison in categorical data was performed using Pearson Chi square test

ASA American Society of Anesthesiologists, *BMI* body mass index, *DPAM* diffuse peritoneal adenomucinosis, *PMCA* peritoneal mucinous carcinomatosis

*Statistically significant results

Intra- and Postoperative Blood Parameters

There was no significant difference for hemoglobin. Lactate levels were significantly higher in the late group just before HIPEC, and serum creatinine levels were comparable (Fig. 3). The most striking difference was the higher serum albumin level in the late group, measured on arrival on the ICU, which remained significantly higher during the next 24 h (Fig. 3).

Outcomes and Multivariate Analysis of Prognostic Factors

Despite more complex surgery in the late group, reflected by a higher PCI and more complex surgical procedures, the rate of major complications (p = 0.003) and reoperations (p = 0.01) was lower compared with the early group. The better outcomes also translated to a shorter hospital stay for patients in the late group (Table 4).

TABLE 2 Surgical characteristics

Parameter	Early group (n = 57)	Late group (n = 55)	p value
PCI	8 (3–19)	10 (6–28)	0.02
CC-score			
CC-0	44 (77.2%)	47 (85.5%)	0.34
CC-1	4 (7.0%)	1 (1.8%)	0.36
CC-2/3	9 (15.8%)	7 (12.7%)	0.78
OR time (min)	510 (450–720)	625 (480–735)	0.26
Blood loss (mL)	500 (300–1500)	350 (200–800)	0.05
Peritonectomy procedures			
None	14 (24.6%)	8 (14.5%)	0.24
Selective	18 (31.6%)	17 (30.9%)	1.0
Subtotal parietal	21 (36.8%)	14 (25.5%)	0.22
Total parietal	3 (5.3%)	3 (5.5%)	1.0
Parietal and mesenterial	1 (1.8%)	13 (23.6%)	< 0.01
Surgical procedures			
Splenectomy	4 (7.0%)	14 (25.5%)	< 0.01
Colon/rectum resection	26 (45.6%)	37 (67.3%)	0.02
Small bowel resection	15 (26.3%)	16 (29.1%)	0.74
Liver capsule resection	19 (33.3%)	26 (47.3%)	0.01
Hysterectomy	17 (29.8%)	21 (38.2%)	0.35
Gastric resection	4 (7.0%)	2 (3.6%)	0.43
Loop ileostomy	7 (12.3%)	32 (58.2%)	< 0.01

Interval data are shown as median with 1.–3. interquartile range. Categorical data are shown as absolute values (n =) and percent of the respective total patient number

Mann–Whitney U test was used to test for differences between groups with interval data. Comparison in categorical data was performed using Pearson Chi square test

PCI peritoneal cancer index, *CC-score* completeness of cytoreduction score, *CC-0* no visible peritoneal carcinomatosis after CRS, *CC-1* nodules persisting < 2.5 mm after CRS, *CC-2* nodules persisting between 2.5 mm and 2.5 cm, *CC-3* nodules persisting > 2.5 cm, *OR* operating room

*Statistically significant results

On multivariate analysis, two independent prognostic factors were identified. The use of > 2000 mL of colloids [OR 5.31 (1.06–26.56), p = 0.042] was independently associated with major postoperative complications. In contrast, substitution of albumin for maintaining the oncotic pressure [OR 0.12 (0.01–0.96), p = 0.046] was highly associated with an improved outcome.

DISCUSSION

This study highlights the critical role of the anesthesiologist for patients undergoing CRS/HIPEC. Two novel and independent prognostic parameters regarding major postoperative morbidity after CRSHIPEC were identified. First, the extensive use of colloids should be avoided. Second, maintenance of the oncotic pressure by albumin substitution seems to be protective. Our findings highlight the role of the nonsurgical team during CRS/HIPEC, which is currently still underreported and underestimated.

The majority of available studies are focused on the learning curve of the surgeon. Overall, they conclude that the experience of the surgical team depends on the case load, the individual experience of the surgeon, and recommend performing around 100 procedures before reaching an expert level.[16] One particular report from the Netherlands highlights that the learning curve can be abbreviated if unexperienced teams are supervised by experienced surgeons.[17] This confers to the situation of the present study, where the surgical team was trained by an experienced surgeon (P.G.), resulting into acceptable rates for perioperative morbidity, also among first patients. This should not undetermine the need or relevance of the surgical learning curve, which was certainly still present. We believe that the major role of a senior surgeon is to avoid futile surgery and to increase the rate of complete resections in borderline cases at the beginning of a center experience. Without any doubt, the surgical performance may have improved over time, reflected by constant operating times and a lower complication rate during the

TABLE 3 Anesthesia parameter

	Early group (n = 57, 50.9%)	Late group (n = 55, 49.1%)	p value
Monitoring			
Arterial line	56 (98.2%)	55 (100%)	0.32
Central venous catheter	57 (100%)	55 (100%)	1.0
PiCCO	51 (89.5%)	18 (31.6%)	< 0.01
Pulmonary artery catheterization	3 (5.3%)	2 (3.6%)	0.68
TEE	0 (0%)	1 (1.8%)	0.31
Anesthesia			
Intravenous (propofol)	37 (64.9%)	22 (40.0%)	0.01
Inhalation (volatile anesthetics)	20 (35.1%)	33 (60.0%)	0.01
thEDA	43 (75.4%)	42 (76.6%)	1.0
Removal of thEDA (days)	3 (1–3)	1 (0–3.5)	0.16
Fluids			
Crystalloids (mL)	5900 (4500–7600)	6500 (4700–8700)	0.17
Colloids (mL)	2500 (1500–4000)	1500 (1000–3000)	0.03
Diuretics	32 (59.3%)	18 (32.7%)	0.01
Furosemide	26 (45.6%)	9 (16.7%)	< 0.01
Mannitol	20 (35.1%)	9 (16.7%)	0.03
Albumin			
Human albumin (20%, mL)	0 (0)	100 (100–225)	< 0.01
Transfusion			
RBC concentrates	15 (21.3%)	9 (16.4%)	0.25
FFP	3 (5.3%)	5 (9.1%)	0.47
PC	4 (7.0%)	2 (3.6%)	0.68
Hemostasis			
Overall, factors given (n)	21 (36.8%)	35 (63.6%)	< 0.01
Fibrinogen	21 (36.8%)	30 (54.5%)	< 0.01
Factor XIII[1]	6 (10.5%)	27 (49.1%)	< 0.01
Factors (IX, II, VII, X)[2]	9 (15.8%)	6 (10.9%)	0.5
Tranexamic acid	0 (0%)	14 (25.5%)	< 0.01
Extubation			
Operating room	24 (42.1%)	36 (65.5%)	0.01
Intensive care unit	33 (57.9%)	19 (34.5%)	

Interval data are shown as median with 1.–3. interquartile range. Categorical data are shown as absolute values (n =) and percent of the respective total patient number

Mann–Whitney U test was used to test for differences between groups with interval data. Comparison in categorical data was performed using Pearson Chi square test

PiCCO pulse contour cardiac output, *TEE* transesophageal echocardiography, *thEDA* thoracic epidural anesthesia, *RBC* red blood cells, *FFP* fresh frozen plasma, *PC* platelet concentrates

[1]Fibrogammin®

[2]Beriplex®

*Statistically significant results

second period, despite more aggressive surgery. However, the surgeon's subjective impression that the patient went through the procedure more smoothly over time triggered the present study, with a focus and assessment of anesthesiology parameters, particularly after the introduction of our institutional SOPs after our initial experience.[19]

In the initial phase of the program, the minds were set, and CRS/HIPEC was considered an unpredictable high-risk procedure. Major physiologic changes and morbidity was expected by the anesthesiologists, and a major goal was to avoid complications of intraoperative chemotherapy: e.g., nephrotoxicity. As a result, volume management and maintenance of physiological diuresis was given highest

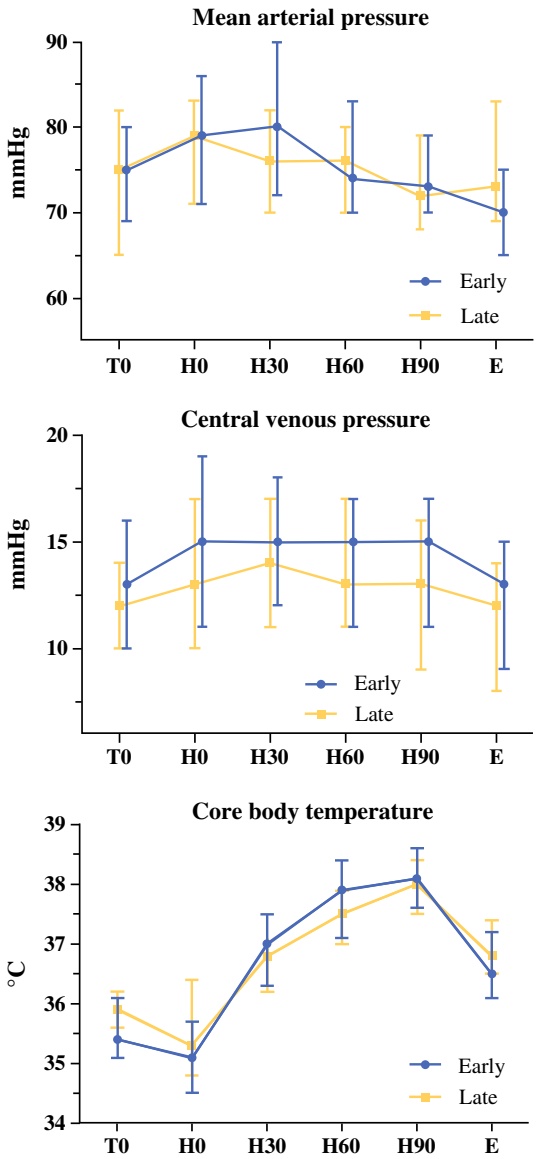

FIG. 2 Perioperative patient physiology. Serum parameters before surgery (T0), before (H0) and during (H30, H60, H90) HIPEC, and at the end (E) of the procedure. Minimal differences were observed for core temperature between early and late patients. No difference was observed for MAP, and a trend toward lower CVP in late patients

priority, and substitution was probably excessive, particularly during cytoreduction—the initial phase of the procedure. This is well reflected by a higher central venous pressure and lower lactate levels before HIPEC. Very interestingly, aggressive and more invasive monitoring, e.g., the PiCCO system, during the initial phase did not avoid overhydration, and monitoring and maintenance of diuresis at physiologic levels may be as good as sophisticated measurement of the volume status. This resulted in clinically relevant differences in outcomes, e.g., the reduced need for postoperative thoracic drains for pleural effusions, despite more extensive peritonectomy

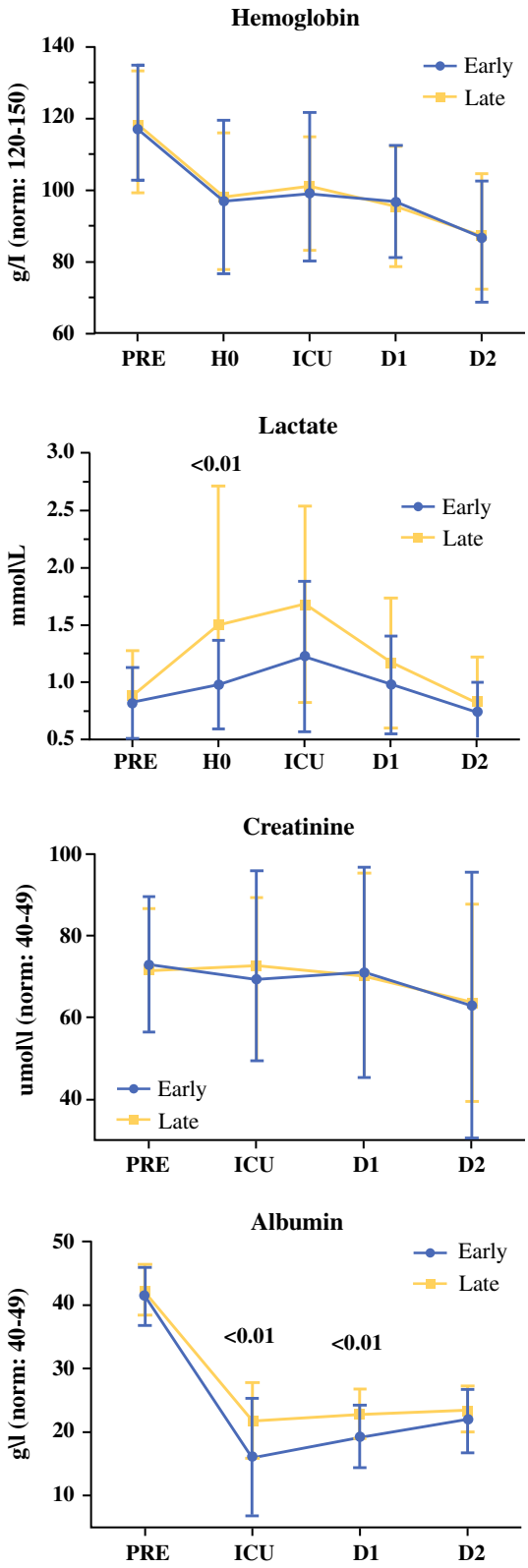

FIG. 3 Serum parameters. Analyses were performed before (PRE) surgery, before HIPEC (H0), and on arrival on the intensive care unit (ICU), and on day 1 (D1) and day 2 (D2)

TABLE 4 Postoperative outcomes

Parameter	Early group (n = 57)	Late group (n = 55)	p value
Complication grading (Clavien)			
None	27 (47.4%)	36 (65.4%)	0.06
I	1 (1.8%)	3 (5.5%)	0.36
II	16 (28.1%)	14 (25.4%)	0.13
IIIa	4 (7.0%)	0 (0%)	0.12
IIIb	5 (8.8%)	2 (3.6%)	0.44
IVa	2 (3.5%)	0 (0%)	0.50
IVb	0 (0%)	0 (0%)	1.0
V	2 (3.5%)	0 (0%)	0.5
Major morbidity (≥ IIIb)	11 (19.3%)	2 (3.6%)	0.01
Reoperation	9 (15.8%)	2 (3.6%)	0.01
ICU stay (days)	1 (1–2)	1 (1–2)	0.5
In-hospital stay (days)	17 (14–25)	15 (11–20)	0.03
Gastrointestinal function			
Flatulence (day)	4 (2–5)	3 (2–4)	0.15
Passage of stool (day)	6 (5–7)	4 (3–5)	< 0.01

HIPEC hyperthermic intraperitoneal chemotherapy; *PC* peritoneal carcinomatosis; *DPAM* diffuse peritoneal adenomucinosis; *PMCA* peritoneal mucinous carcinomatosis; *AC* adenocarcinoma; *PCI* peritoneal cancer index; *ICU* intensive care unit

Interval data are shown as median with 1.–3. interquartile range. Categorical data are shown as absolute values (n =) and percent of the respective total patient number. Mann–Whitney U test was used to test for differences between groups with interval data. Comparison in categorical data was performed using Pearson Chi square test

procedures, e.g., in the right upper quadrants. A study published in 2017 supports the presumption of a positive outcome through more restrictive volume management during CRS/HIPEC.[24] The authors concluded that a more restrictive fluid management with a maximum of 15.7 mL/kg/h is associated with a lower overall comprehensive complication index. In the late group, we managed to reach a perioperative fluid rate of 10.2 mL/kg/h, which fits well with the results of the mentioned study.

The impact of albumin substitution on postoperative outcomes was somehow a little surprise. Replacement of albumin is generally considered no longer indicated for volume replacement after large randomized trials, e.g., in patients with septic shock.[25] However, the setting of CRS/HIPEC may reflect a different situation due to the large fluid and protein loss after peritonectomy. Albumin substitution targeting serum levels above 15 mg/L maintains a physiologic oncotic pressure and may reduce massive third space leakage.[26]

Regarding temperature management, the observed significant differences were very small and therefore probably not clinically relevant. However, together with a more physiologic volume management, it may contribute to the growing majority of patients who can be extubated in the operating room. Early extubation is critical for patient recovery, as already known from many other surgical fields.[27]

We would like to account the limitations of the present study, which represents the retrospective experience of a single center. However, the entire cohort of included patients was recorded in a prospective database, and anesthesia records could be completely recovered. An important question is which component of the SOP contributes to better outcomes. It remains unclear which are the critical factors. For example, preoperative hydration did not translate into a benefit in an RCT, including patients who underwent general major surgery.[28] However, this may be different in preventing kidney injury before HIPEC, particularly if cisplatin is used, and is still performed in many centers. The need for preoperative hospitalization and costs will certainly trigger further prospective studies. Management of coagulation is another open dispute. The use of rotational thromboelastometry as performed in this study has shown some improvements in early detection of coagulopathy and also was cost-effective, e.g., in the setting of liver transplantation.[29,30] However, this expensive technology may not be necessary for all patients undergoing CRS/HIPEC and could be reserved for patients with extensive CRS.

CONCLUSIONS

Our data demonstrate a major impact of SOPs for perioperative anesthesia management on outcomes of patients after CRS/HIPEC. Independent factors associated with perioperative outcomes were albumin substitution and the use of > 2000 mL of colloids. These findings highlight the need for a specialized and interdisciplinary management of patients with CRS/HIPEC and warrant further studies.

DISCLOSURE All authors declare no conflict of interest referring to this work. No third-party financial funds or materials were accepted or necessary for execution of this research project.

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