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Anesthesia and Pain Management for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Desmoplastic Small Round Cell Tumors in Children, Adolescents, and Young Adults

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Abstract

Background—Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive sarcoma. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) may improve survival.

Methods—A retrospective review of the anesthetic management and postoperative pain control strategies after CRS/HIPEC for DSRCT from 2013 to 2017 was performed.

Results—Ten CRS/HIPEC procedures were performed on 9 patients with DSRCT with a median age 19 years (10–24), 6 Caucasian, 7 male. Median operative and anesthesia duration were 551 minutes (510–725) and 621 minutes (480–820), respectively. Postoperative mechanical ventilation was necessary in 5 patients for a median duration of 1 days (0–2). Median intraoperative intravenous fluid administration was 13 ml/kg/hr (6.3–24.4) and colloid administration was 12 ml/kg (0.0–53.0). Median blood loss was 15 ml/kg (6.3–77.2). Nine patients received intraoperative transfusion with a median red blood cell transfusion volume of 14 ml/kg (10.1–58.5). Median intraoperative urine output was 2.0 ml/kg/hr (0.09–8.40) and half of the patients received intraoperative diuretics. Cisplatin was utilized during HIPEC for 8 surgeries. Acute kidney injury was observed in 2 patients; 1 required short-term dialysis. Epidural infusions were utilized in 8 cases for a median of 4 days (3–5). Postoperative intravenous opioid use (morphine equivalent) was 0.67 mg/kg/day (0.1–9.2) and administered for a median of 11 days (2–35).

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Conclusion—Cytoreduction and HIPEC for DSRCT are associated with significant perioperative fluid requirements and potentially challenging pain management. Renal protective strategies should be considered for reduction of cisplatin-associated nephrotoxicity. Further investigation for a more effective, less systemically toxic HIPEC agent is warranted.

Keywords

Cytoreduction; HIPEC; Desmoplastic Small Round Cell Tumor; Anesthesia; Pain Management

BACKGROUND

Desmoplastic small round cell tumor (DSRCT) is a mesenchymal soft tissue sarcoma that spreads on peritoneal surfaces, affecting primarily children, adolescents, and young adults. The most common primary tumor sites include the right diaphragm, omentum and pelvis, with the liver, lungs, mediastinum, and pleura being the most common sites of metastasis.[1] First characterized in 1989 by Gerald and Rosai, DSRCT is a rare and highly aggressive sarcoma, and 60–70% of patients survive less than 3 years despite multi-modality treatment protocols.[2, 3]

Current treatment of DSRCT consists of multi-agent systemic chemotherapy, including cyclophosphamide, doxorubicin, and vincristine, followed by alternating ifosfamide and etoposide, with subsequent debulking surgery followed by adjuvant chemotherapy and whole abdomen radiation therapy.[4] The prognosis remains poor, however, despite such an aggressive, complex multimodality treatment approach. Recurrence after resection and disease progression contribute to early treatment failure and the overall survival rate remains 15–30% at 5 years.[5]

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have emerged as treatment options for the management of DSRCT.[6] CRS removes all visible tumor within the abdominal cavity and HIPEC is administered to eradicate any residual microscopic disease. Heated chemotherapy is administered as a peritoneal lavage which allows for increased regional delivery of chemotherapy with minimal systemic absorption or toxicity.[7] Hyperthermia denatures proteins, inhibits DNA repair processes, and activates heat shock proteins which produces a cytotoxic environment and elicits an immune response against tumor cells.[8]

The use of HIPEC in children has been proven to be safe and for DSRCT is associated with a disease free survival benefit.[6] CRS/HIPEC has also been investigated for other malignancies including rhabdomyosarcoma, Sertoli-Leydig tumor, Wilms tumor, colon adenocarcinoma, liposarcoma, and mesothelioma.[9] Despite this growing experience, the perioperative management of adolescents and young adults who undergo CRS/HIPEC has not been extensively described. Therefore, the aims of this study were to retrospectively review the anesthetic, fluid and pain management characteristics in children and young adult patients who undergo CRS/HIPEC for DSRCT.

METHODS

Patients

A retrospective review of patients who underwent CRS/HIPEC for DSRCT from 2013 to 2017 was performed. Patients received neoadjuvant and adjuvant therapy at St. Jude Children's Research Hospital (SJCRH) and underwent CRS/HIPEC at Methodist University Hospital (N=5) or SJCRH (N=5). Institutional review board approval was obtained from each institution.

Description of CRS/HIPEC Technique

After induction of anesthesia, patients were placed in lithotomy position and urinary catheters and esophageal temperature probes were placed. A midline laparotomy was performed and the abdomen was inspected to determine the extent and distribution of disease and to calculate the peritoneal cancer index (PCI) score.[10] The operation consisted of attempted resection of all visible disease with a goal of performing complete cytoreduction (CCR 0/1).[11]

Upon completion of CRS, in-flow and out-flow catheters were placed within the pelvis and upper abdomen, respectively, and were connected to a Belmont Perfusion Pump (Billerica, MA). The abdomen was filled with saline and was temporarily closed with a running nylon suture. The saline solution was circulated and heated to a target temperature of 42°C. Once target temperature was achieved, the chemotherapeutic agent was added to the perfusate and circulated at a flow rate of one liter per minute. The abdomen was gently agitated during HIPEC to improve the distribution of chemotherapy throughout the abdominal cavity. Systemic hyperthermia was prevented with cold packs, cooling blankets, and forced cool ambient air, as needed. At the completion of HIPEC, the catheters were removed, gastrointestinal continuity was restored and drains were placed. All patients were admitted to the intensive care unit (ICU) for initial care after CRS/HIPEC.

Anesthesia and Pain Management Details

General anesthesia was induced with propofol, opioid and a non-depolarizing muscle relaxant and maintained with an inhalational agent and intermittent opioid doses. Standard monitoring included pulse oximetry, electrocardiogram, arterial blood pressure, temperature and urine output. Intravenous fluids were administered using crystalloids (ringers lactate and normal saline) and colloid (5% albumin). Blood transfusion and postoperative extubation were performed at the discretion of the anesthesiologist.

Anesthesia-related data collection included the duration of anesthesia, fluid management, blood loss, urine output, diuretic usage, and administration of blood products. Intraoperative hemodynamics and arterial blood gas data were collected at 4 time points: T1-beginning of cytoreduction, T2-end of cytoreduction, T3-start of HIPEC, T4-end of CRS/HIPEC. Fluids administered are described in total volume (milliliters-ml), volume per kilogram (ml/kg) and volume per kilogram per hour (ml/kg/hr).

Epidural analgesia was performed at the discretion of the anesthesiologist and consisted of either bupivacaine 0.1–0.2% or ropivacaine 0.125–0.2% titrated at 5–12 ml/hr. A patient-controlled analgesia (PCA) pump was utilized after epidural catheter removal for additional pain control, as needed. Intravenous opioid administration was analyzed and a conversion factor of 5:1 (5 mg morphine equals 1 mg of hydromorphone) was used to calculate the morphine equivalent dose (MED) when hydromorphone was used for pain relief. For consistency in opioid administration reporting, intravenous opioid dosages are reported as morphine equivalent doses (mg/kg/day).

Morbidity and Statistical Analysis

Complications were graded according to the Clavien-Dindo classification schema.[12] Minor complications included Clavien-Dindo 1–2 morbidity while major complications included Clavien-Dindo 3–5 morbidity. Renal toxicity was defined per standard criteria as acute kidney injury or increase in creatinine above baseline or when hemodialysis was indicated and by the KDIGO criteria.[13, 14] KDIGO criteria for acute kidney injury in the pediatric population are described as Stage I-increase in serum creatinine 0.3 mg/dL in 48 hours or increased150–200% over 7 days, Stage II-increase ≥ 200–300%, Stage III-increase of serum creatinine ≥ 4 mg/dL, increase ≥ 300% or needing dialysis. Categorical variables were summarized using percentages while continuous variables were summarized using the median with range. All statistical analysis was performed using SPSS software, version 24 (IBM Corporation, Armonk, NY).

RESULTS

Patient Characteristics

Nine patients underwent 10 CRS/HIPEC procedures between 1/2013 and 12/2017, including seven males and two females. All patients had an ASA physical status score of 3 and the median body mass index was 21 (range, 16.7–29.2). At the time of initial diagnosis and CRS/HIPEC, 2 patients were under the age of 12 years and 7 patients were 13–24 years.

Operative Characteristics

The length of anesthesia was 621 minutes (range, 480–820) and the operative length was 551 minutes (range 410–725) (Table 1). The median PCI score was 16 (range, 5–20) and complete cytoreduction was performed in 9 CRS/HIPEC procedures. Multivisceral resection of 4 or more organs was performed in 6 patients with the omentum, rectum, pelvic peritoneum and right diaphragm peritoneum being the most frequently resected organs. HIPEC was performed using cisplatin (100 mg/m^2 for 60 minutes, N=8), mitomcyin C (40 mg for 90 minutes, N=1) and melphalan (50 mg/m^2 for 90 minutes, N=1).

Hemodynamically, heart rate increased over each measured time point from the start of cytoreduction (T1) to the start of HIPEC (T3) while systolic blood pressure steadily decreased from T1-T3 (Figure 1A-B). Temperature started out low and reached the highest values during the HIPEC portion (T3) of the procedure (Figure 1C). Blood gas measurements were characterized by a steady decrease in the pH (Figure 1D) and a worsening of the base deficit (Figure 1E) with an increase in the serum lactate (Figure 1F)

over each measured time point. A detailed description of hemodynamic and blood gas measurements is presented in Supplemental Table 1. Five patients required postoperative mechanical ventilation but all were extubated the following day. The median ICU length of stay was 3 days (range, 1–25) and hospital length of stay was 9 days (range, 8–38). Details of the hemodynamic characteristics are presented in Table 2.

Intraoperative and Perioperative Fluid Management

Details of the intraoperative fluid management are presented in Table 2. The amount of intraoperative IV fluids administered was 122 ml/kg (range, 54.7–288.1) which equated to 13 ml/kg/hr (range, 6.3–24.4), intraoperative colloid was 12 ml/kg (range, 0–53.0) intraoperative red blood cells transfused was 14 ml/kg (range, 10.1–58.5) and intraoperative fresh frozen plasma transfused was 10 ml/kg (range, 9.2–11.3). The median intraoperative urine output (UOP) was 2 ml/kg/hr (range, 0.09–8.40) and blood loss was 15 ml/kg (range, 6.3–77.2).

Postoperative IV fluids were administered for a median of 8 days (range, 3–35) with a median of 33 ml/kg/day administered (range 23.4–65.6). Two patients received fluid therapy prior to CRS/HIPEC and 4 patients received a diuretic during the intraoperative or postoperative time periods.

Morbidity

Minor postoperative morbidities occurred in 6 patients, the most frequent being abdominal wound infection (N=3). Major morbidities occurred in 4 patients: one patient developed a pneumothorax requiring thoracostomy tube placement, two developed intraabdominal abscesses requiring percutaneous drainage and two developed acute kidney injury (AKI) from cisplatin-nephrotoxicity, one of whom required re-intubation and short-term hemodialysis. There were no operative or 30-day mortalities.

Alterations in renal function, as reflected by an increase in the creatinine level at >50% of preoperative baseline, were noted in 5 of 10 cases. All but one patient experienced a transient rise in serum creatinine. The impact on postoperative serum creatinine levels (mg/dL) was most pronounced in those who received cisplatin (N=8) as opposed to those who received melphalan (N=1) or mitomycin C (N=1) (Table 3).

Postoperative Pain Management

Postoperative pain management consisted of epidural analgesia, intravenous opioid agonists and non-opioid analgesics. Epidural analgesia was utilized in 8 surgeries for a median of 4 days (range, 3–5). No epidural analgesia related complications were observed. Intravenous opioids were administered to all patients for a median of 11 days (range, 2–35) with a median morphine equivalent dose of 0.67 mg/kg/day (range, 0.06–9.2). A detailed description of the postoperative pain management parameters are presented in Table 4.

DISCUSSION

The perioperative management of patients undergoing CRS/HIPEC remains a challenge for the anesthesiologists, surgeons and intensivists alike. While a significant body of literature exist for adults, only one study regarding the anesthetic management of pediatric patients undergoing CRS/HIPEC has been reported.[15] Owusu-Agyemang et al reported on 10 patients who underwent HIPEC in a phase 1 trial of escalating doses of cisplatin for sarcomatosis. The anesthetic management, intraoperative fluid and blood requirements and postoperative renal function were described. Aggressive intraoperative fluid administration was required to maintain satisfactory urine output and all experienced a transient rise in postoperative serum creatinine. In the current study, despite significant intraoperative and perioperative fluid administration, transient rise in creatinine occurred in all but one with significant acute kidney injury occurring in two patients. Moreover, despite epidural analgesia, a high consumption of opioid therapy was necessary for a prolonged period to maintain adequate pain control.

Perioperative fluid management and volume therapy are important aspects of anesthetic management in maintaining hemodynamic stability during CRS/HIPEC.[16] A restrictive fluid approach is detrimental to outcome and is associated with increased risk of complications, while liberal fluid administration risks fluid overload, tissue edema and pulmonary complications.[17– 19] In adults, fluid administration at an average rate of 9–12 ml/kg/h is recommended to maintain satisfactory urine output.[15, 16] In children and young adults, however, the most appropriate rate of fluid administration remains undetermined. Patients received approximately 133 ml/kg of crystalloids intraoperatively in this series, which equated to 13 ml/kg/hr. Blood loss was significant (15 ml/kg), however, and intraoperative urine output was adequate, approximately 2 ml/kg/hr. Despite being administered what appears to be adequate intraoperative volume replacement in adults, in a younger aged population, however, it is possible that more vigorous fluid resuscitation may be necessary to avoid oliguria and potentiate cisplatin-related nephrotoxicity. Owusu-Agyemang et al observed that intraoperative fluid administration at a rate of 6–15 ml/kg/hr was necessary to maintain urine output at 3 ml/kg/h.[15]

The incidence of grade 3–4 nephrotoxicity after CRS/HIPEC in adults is 6% and as high as 25% in pediatric and young adults.[20, 21] In a report of 50 patients who underwent CRS/HIPEC, Hayes-Jordan et al reported two patients experienced grade III AKI while three patients developed grade IV acute renal failure. [9] Thong et al, in an adult study of 111 patients undergoing 113 CRS/HIPEC procedures, noted that 6 patients experienced renal impairment with one experiencing AKI and 2 patients requiring hemodialysis.[22] Postoperative serum creatinine rose above baseline in all but one patient in the current series with two patients developing severe AKI. The two patients who developed severe AKI (patient 8 & 10) also were significantly under-resuscitated based on intraoperative urine output (Table 2). One required short-term hemodialysis and both eventually recovered renal function. While cisplatin is known to be nephrotoxic, inadequate fluid resuscitation with oliguria may potentiate the renal injury observed after HIPEC.

Cisplatin causes acute tubular necrosis within the proximal collecting system and a reduced glomerular filtration rate.[23] The nephrotoxic effects of cisplatin can be mitigated with preoperative hydration, osmotic diuresis and administration of renal protective agents such as theophylline.[24, 25] In a study of 54 patients who underwent 58 HIPEC procedures with cisplatin, Green et al. noted a reduction in the incidence of grade III/IV nephrotoxicity from 25% to 0% after implementation of a renal protective protocol.[21] In that protocol, patients received preoperative hydration at 150% of the standard maintenance fluid rate with simultaneous administration of sodium thiosulfate during HIPEC. Sodium thiosulfate was administered as a continuous infusion for 24 hours after HIPEC and continued for 48 hours after HIPEC. In the current series, adoption of a formalized renal protective strategy may have minimized the degree of nephrotoxicity observed after HIPEC. While these efforts are necessary and helpful to minimize cisplatin-associated nephrotoxicity, development of a more effective, less toxic HIPEC agent for DSRCT warrants further investigation.

Postoperative pain management in children and young adults who undergo CRS/HIPEC has not been previously described. Eight patients received epidural analgesia in this study and there were no epidural related complications necessitating early removal. Thoracic epidural analgesia is an excellent option for postoperative pain management and is commonly utilized in many HIPEC centers.[26, 27] Epidural analgesia use is associated with reduced opioid requirements, decreased need for postoperative mechanical ventilation, reduced ICU length of stay and can be safely performed with minimal morbidity.[28–31] However, despite epidural analgesia use in this series, intravenous opioid use after CRS/HIPEC was higher and for longer duration than anticipated. The median duration of intravenous opioid use was 11 days with a median morphine equivalent dose of 0.67 mg/kg/day. This opioid dose is greater than previously reported after pediatric abdominal surgery and contrasts with the data reported from adult studies in which epidural analgesia is associated with opioid use for a shorter duration.[27]

There are several limitations to this study. The results reflect a single institution experience for a rare pathology with a limited number of patients. Although the surgeons were the same, patients were treated at two locations by two separate anesthesia provider practice groups. Inconsistent pre-hydration, intermittent diuretic use and lack of a formalized renal protective protocol may have impacted cisplatin-associated nephrotoxicity. Lastly, lack of a standard perioperative pain management regimen may have contributed to significant opioid use.

CONCLUSION

CRS/HIPEC for DSRCT is associated with significant intravenous fluid requirements along with increased and prolonged opioid use. Adoption of a renal protective strategy may minimize cisplatin-associated nephrotoxicity. Further investigation for a more effective, less toxic HIPEC agent is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SYNOPSIS

Cytoreduction and hyperthermic intraperitoneal chemotherapy for desmoplastic small round cell tumor are associated with significant perioperative fluid requirements and potentially challenging pain management. Renal protective strategies should be considered for reduction of cisplatin- associated nephrotoxicity.

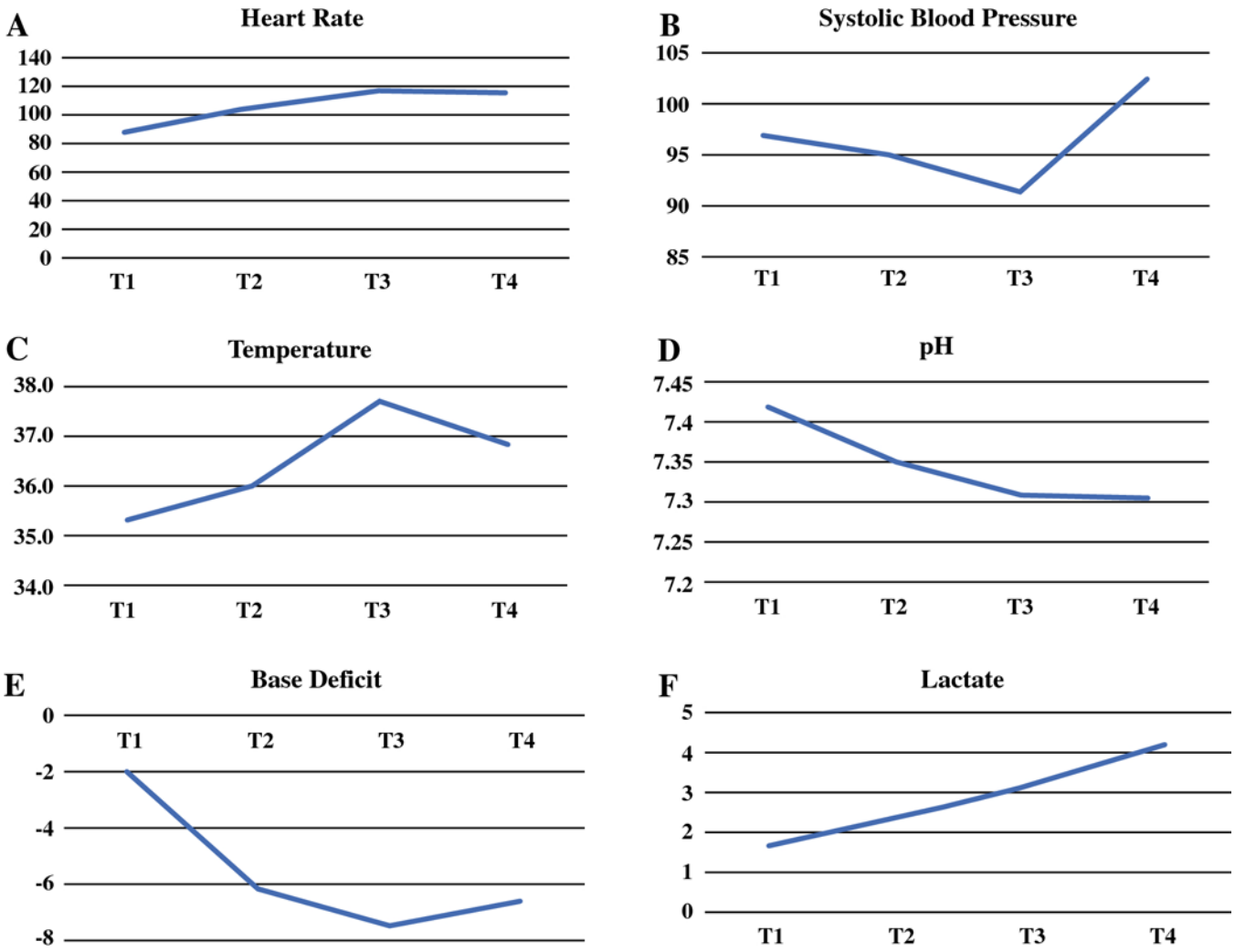

Figure 1A-F:

Hemodynamic and blood gas measurements during the beginning of cytoreduction (T1), end of cytoreduction (T2), start of HIPEC (T3), and the end of cytoreduction/HIPEC (T4). Results reported as median value for each time point.

Table 1.

Operative and Perioperative Characteristics

Variable	All N=10
Anesthesia Length (minutes)	621 (480–820)
Operative Length (minutes)	551 (410–725)
Intraoperative Fluid Management	
Intravenous Fluid Administered (ml)	6450 (4000–16500)
Intravenous Fluid Administered (ml/kg)	122 (53.69–288.06)
Intravenous Fluid Administered (ml/kg/hr)	13 (6.3–24.2)
Colloid Administered (g)	50 (25.0–150.0)
Colloid Administered (ml)	1000 (500–3000)
Colloid Administered (ml/kg)	12 (0.0–53.0)
Urine Output (ml)	1200 (360–4000)
Urine Output (ml/kg)	3 (0.84–73.53)
Urine Output (ml/kg/hr)	2 (0.09–8.40)
Red Blood Cell Transfusion (ml)	800 (580–3200)
Red Blood Cell Transfusion (ml/kg)	14 (10.13–58.52)
Fresh Frozen Plasma Transfusion (ml)	570 (500–630)
Fresh Frozen Plasma Transfusion (ml/kg)	10 (9.19–11.33)
Blood Loss (ml)	900 (300–4300)
Blood Loss (ml/kg)	15 (6.33–77.2)
Postoperative Fluid Management	
Median (ml/kg/day)	33 (6.62–384.60)
Duration of Fluid Management (days)	8 (3–35)
Baseline Weight (kg)	58.4 (40.0–89.8)
Day 1 (kg)	65.5 (45.4–89.8)
Final (kg)	57.8 (38.3–84.0)
Difference (kg)	−2.0 (−7.0-+5.0)
Postoperative Mechanical Ventilation	5 (50)
Day of Extubation	0.5 (0–2)
Re-intubation	1 (10)
Day of Nasogastric Tube Removal	3.0 (1–6)
Nasogastric Tube Re-Insertion	3 (30)
Day of Ambulation	2 (1–3)
Day of Foley Catheter Removal	5 (3–8)

Results presented as frequency (percent) or median (range).

Table 2.

Intraoperative Fluid Management

Patient	Wt (kg)	Anes (min)	Op (min)	IVF (mL/kg/hr)	COL (mL/kg)	RBC (mL/kg)	UOP (mL/kg/hr)	EBL (mL/kg)
1	54.4	551	525	14.9	27.6	58.8	8.40	27.6
2	89.8	665	608	13.2	11.1	17.8	1.31	10.0
3	56.5	680	582	7.7	53.1	14.2	6.11	9.7
4$^{\alpha}$	74.5	575	513	6.3	20.1	10.7	1.50	13.4
5	79.0	494	420	10.9	19.0	10.1	-	6.3
6$^{\beta}$	44.5	480	410	13.2	11.2	13.8	0.34	6.7
7	55.7	820	707	24.4	17.9	45.5	0.22	77.2
8	40.0	639	543	14.9	20.0	14.5	0.09	18.8
9*	76.0	697	559	12.6	13.2	11.2	0.16	11.8
10	60.3	603	536	15.1	12.4	10.25	0.19	16.6

$^{\alpha}$-Melphalan administered during HIPEC,

$^{\beta}$-Mitomycin C administered during HIPEC

*-Repeat HIPEC

Abbreviations: Wt-Weight (kg); Anes-Anesthesia Length (minutes); Op-Operative Length (minutes); IVF-Intravenous Fluid Infusion Rate (mL/kg/hr); COL-Colloid Infusion Rate (mL/kg); RBC-Red Blood Cell Infusion Rate (mL/kg); UOP-Urine Output (mL/kg/hr); EBL- Estimated Blood Loss (mL/kg)

Table 3.

Perioperative Fluid Management

Patient	Diuretics			Postoperative IVF (ml/kg/day)				Serum Creatinine (mg/dL)			
	Lasix	Mannitol	Preoperative Hydration	Min	Max	Median	Days	Pre-op	Post-op Max	% Increase	KDIGO
1	Y	Y	-	6.62	44.98	33.75	9	0.70	0.80	14.3	-
2	-	-	-	19.49	42.71	27.77	6	0.70	1.30	42	I
3	-	-	-	9.79	50.29	30.70	6	0.40	1.10	175	I
4$^{\alpha}$	-	-	-	13.13	47.76	32.79	5	0.40	0.70	75	I
5	-	-	-	12.97	33.59	23.41	3	1.10	1.10	-	-
6$^{\beta}$	-	-	-	17.96	157.53	28.61	8	0.33	0.38	15.2	-
7	-	-	-	34.78	384.6	65.64	14	0.54	1.02	88.9	I
8	Y	-	-	58.53	218.80	59.71	35	0.27	5.76	2033.3	III
9*	Y	Y	1.5 x MIVF	32.91	166.79	51.07	20	1.61	1.92	19.3	I
10	Y	Y	2 x MIVF	34.48	197.73	43.55	30	0.51	5.05	890.2	III

$^{\alpha}$-Melphalan administered during HIPEC,

$^{\beta}$-Mitomycin C administered during HIPEC,

*-Repeat HIPEC

Abbreviations: IVF-intravenous fluid; Min-minimum; Max-maximum; Pre-op-preoperative serum creatinine; Post-op Max-postoperative maximum serum creatinine; MIVF-maintenance intravenous fluid, KDIGO-acute kidney injury criteria in pediatric population

Table 4.

Postoperative Pain Management

Patient	Postoperative Epidural				Postoperative Opioids (MED; mg/kg/day)			
	Agent	Fentanyl	Rate	Days	Min	Max	Median	Days
1	Ropivicaine 0.2%	5	7	3	0.27	0.32	0.30	2
2	Ropivicaine 0.2%	5	5	3	0.01	0.75	0.30	6
3	-	-	-	-	0.04	1.03	0.13	12
4	-	-	-	-	0.07	1.40	0.73	9
5	Bupivicaine 0.2%	-	6	4	0.0	0.35	0.06	7
6	Ropivicaine 0.125%	2	8	4	0.45	1.18	0.73	8
7	Ropivicaine 0.125%	2	10	4	0.09	1.38	0.61	14
8	Ropivicaine 0.125%	2	8	3	0.56	6.38	2.46	35
9 *	Bupivicaine 0.1%	-	10	5	1.39	19.67	9.64	20
10	Ropivicaine 0.125%	2	12	4	0.04	6.22	1.47	33

*-Repeat HIPEC

Abbreviations: Fentanyl-mcg/hr; Postoperative Epidural Rate-mL/hr; MED-morphine equivalent dose (7 mg morphine equivalent to 1 mg hydromorphone); Min-minimum; Max-maximum