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ORIGINAL ARTICLE – PEDIATRIC ONCOLOGY

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 anesthetic management and postoperative pain control strategies after CRS/HIPEC for DSRCT from 2013 to 2017 was performed.

Results. The review analyzed 10 CRS/HIPEC procedures performed for nine DSRCT patients with a median age of 19 years (range 10–24 years). Six of these patients were Caucasian, and seven were men. The median operative duration was 551 min (range 510–725 min), and the median anesthesia duration was 621 min (range 480–820 min). Postoperative mechanical ventilation was necessary in 5 patients for a median duration of 1 day (range 0–2 days). The median intraoperative intravenous fluid administration was 13 ml/kg/h (range 6.3–24.4 ml/kg/h), and the colloid administration was 12 ml/kg (range 0.0–53.0 ml/kg). The median blood loss was 15 ml/kg (range 6.3–77.2 ml/kg). Nine patients received intraoperative transfusion with a median red blood cell transfusion volume of 14 ml/kg (range 10.1–58.5 ml/kg). The median intraoperative urine output was 2 ml/kg/h (range 0.09–8.40 ml/kg/h), and half of the patients received intraoperative diuretics. Cisplatin was used during HIPEC for eight surgeries. Acute kidney injury was observed in two patients, one of whom required short-term dialysis. Epidural infusions were used in eight cases for a median of 4 days (range 3–5 days). Postoperative intravenous opioid use (morphine equivalent) was 0.67 mg/kg/day (range 0.1–9.2 mg/kg/day) administered for a median of 11 days (range 2–35 days).

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.

Desmoplastic small round cell tumor (DSRCT) is a mesenchymal soft tissue sarcoma that spreads on peritoneal surfaces, affecting primarily children, adolescents, and

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young adults. The most common primary tumor sites are the right diaphragm, the omentum, and the pelvis, and the most common sites of metastasis are the liver, lungs, mediastinum, and pleura.[1] First characterized in 1989 by Gerald and Rosai,[3] DSRCT is a rare and highly aggressive sarcoma, and 60–70% of the patients survive less than 3 years despite multi-modality treatment protocols.[2]

The current treatment for 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] After CRS is used to remove all visible tumor within the abdominal cavity, 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, producing a cytotoxic environment and eliciting an immune response against tumor cells.[8]

The use of HIPEC for children has been proved to be safe, and when used for DSRCT is associated with a disease-free survival benefit.[6] The use of CRS and HIPEC also has 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, this study aimed retrospectively to 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. The patients had received neoadjuvant and adjuvant therapy at St. Jude Children's Research Hospital (SJCRH) and had undergone CRS/HIPEC at Methodist University Hospital ($n = 5$) or SJCRH ($n = 5$). Institutional review board approval was obtained from each institution.

Description of the CRS/HIPEC Technique

After induction of anesthesia, the patients were placed in lithotomy position for placement of urinary catheters and esophageal temperature probes. These placements were followed by a midline laparotomy, 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 comprised attempted resection of all visible disease with a goal of achieving complete cytoreduction (CCR 0/1).[11]

At completion of CRS, inflow and outflow catheters were placed within the pelvis and upper abdomen, respectively, and connected to a Belmont Perfusion Pump (Belmont Instrument Corporation, Billerica, MA, USA). The abdomen was filled with saline and temporarily closed with a running nylon suture. The saline solution was circulated and heated to a target temperature of 42 °C. Once the target temperature was achieved, the chemotherapeutic agent was added to the perfusate and circulated at a flow rate of 1 l/min. 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 the 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 (Ringer's 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 the following four time points: T1 (beginning of cytoreduction), T2 (end of cytoreduction), T3 (start of HIPEC), and T4 (end of CRS/HIPEC). The fluids

administered are described as total volume (ml), volume per kilogram (ml/kg), and volume per kilogram per hour (ml/kg/h).

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/h. A patient-controlled analgesia (PCA) pump was used 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 or 2 morbidity, whereas major complications included Clavien-Dindo 3–5 morbidity. Renal toxicity was defined per standard criteria as acute kidney injury, an increase in creatinine above baseline, or a need for hemodialysis, and by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[13,14] The KDIGO criteria for acute kidney injury in the pediatric population are described as stage 1 (serum creatinine increase of 0.3 mg/dl in 48 h or increase of 150–200% during 7 days), stage 2 (increase of $\geq$ 200–300%), stage 3 (serum creatinine increase of $\geq$ 4 mg/dl, increase of $\geq$ 300%, or need for dialysis). Categorical variables were summarized using percentages, whereas continuous variables were summarized using the median with the range. All statistical analyses were performed using SPSS software, version 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient Characteristics

Nine patients (7 males and 2 females) underwent 10 CRS/HIPEC procedures between 20 January 2013 and December 2017. All the patients had an American Society of Anesthesiology (ASA) physical status score of 3, and the median body mass index was 21 kg/m^2 (range 16.7–29.2 kg/m^2). At the time of the initial diagnosis and CRS/HIPEC, two patients were younger than 12 years, and seven patients were 13–24 years old.

Operative Characteristics

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

TABLE 1 Operative and perioperative characteristics

Variable	All (n = 10) Median (range)
Anesthesia length: (min)	621 (480–820)
Operative length (min)	551 (410–725)
Intraoperative fluid management	
Intravenous fluid administered (ml)	6450 (4000–16,500)
Intravenous fluid administered (ml/kg)	122 (53.69–288.06)
Intravenous fluid administered (ml/kg/h)	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/h)	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: n (%)	5 (50)
Day of extubation	0.5 (0–2)
Re-intubation	1 (10)
Day of nasogastric tube removal	3.0 (1–6)
Nasogastric tube reinsertion: n (%)	3 (30)
Day of ambulation	2 (1–3)
Day of Foley catheter removal	5 (3–8)

(40 mg for 90 min, $n = 1$), and melphalan (50 mg/m^2 for 90 min, $n = 1$).

Hemodynamically, heart rate increased during each measured time point from the start of cytoreduction (T1) to the start of HIPEC (T3), whereas systolic blood pressure steadily decreased from T1 to T3 (Fig. 1A, B). Temperature started out low and reached the highest values during the HIPEC portion (T3) of the procedure (Fig. 1C). Blood gas measurements were characterized by a steady decrease in the pH (Fig. 1D) and a worsening of the base deficit (Fig. 1E), with an increase in the serum lactate (Fig. 1F), during each measured time point. A detailed description of the hemodynamic and blood gas measurements is presented in Table S1. Five patients required postoperative mechanical ventilation, but all were extubated the next day. The median intensive care unit (ICU) stay was 3 days (range 1–25 days), and the hospital stay was 9 days (range 8–38 days). Details of the hemodynamic characteristics are presented in Table 2.

Intra- and Perioperative Fluid Management

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

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

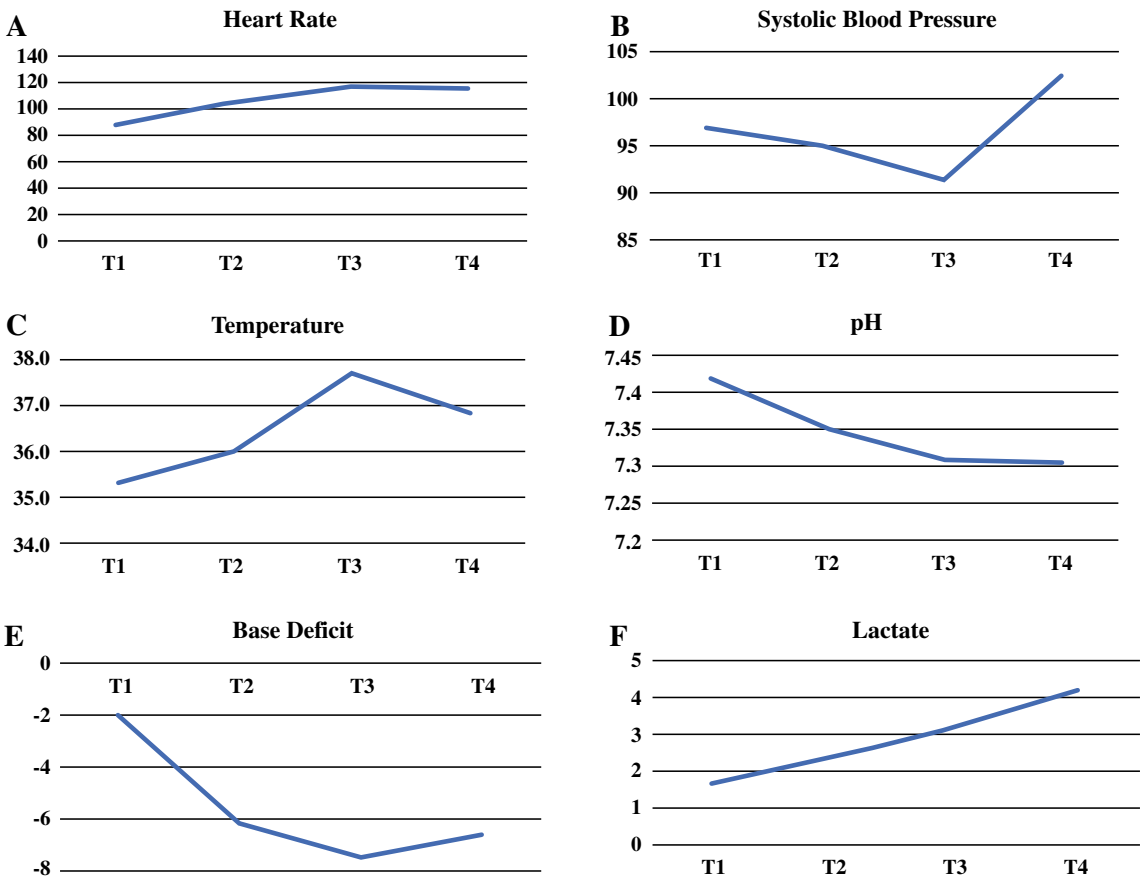

FIG. 1 A–F Hemodynamic and blood gas measurements at the beginning of cytoreduction (T1), the end of cytoreduction (T2), the start of hyperthermic intraperitoneal chemotherapy (HIPEC) (T3), and the end of cytoreduction/HIPEC (T4). Results are reported as the median value for each time point

TABLE 2 Intraoperative fluid management

Patient	Wt (kg)	Anes (min)	Op (min)	IVF (mL/kg/h)	COL (mL/kg)	RBC (mL/kg)	UOP (mL/kg/h)	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[a]	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[b]	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[c]	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

Wt weight (kg), *Anes* anesthesia length (min), *Op* operative length (min), *IVF* intravenous fluid infusion rate (mL/kg/h), *COL* colloid infusion rate (mL/kg), *RBC* red blood cell infusion rate (mL/kg), *UOP* urine output (mL/kg/h), *EBL* estimated blood loss (mL/kg)

[a]Melphalan administered during hyperthermic intraperitoneal chemotherapy (HIPEC)

[b]Mitomycin C administered during HIPEC

[c]Repeat HIPEC

Morbidity

Minor postoperative morbidities occurred for six patients, with abdominal wound infection occurring the most frequently ($n = 3$). Major morbidities occurred for four patients. A pneumothorax developed in one of the patients, requiring thoracostomy tube placement. Intraabdominal abscesses developed in two patients, requiring percutaneous drainage. Two patients experienced acute kidney injury (AKI) from cisplatin-nephrotoxicity, one of whom required re-intubation and short-term hemodialysis. No operative or 30-day mortalities occurred.

Alterations in renal function, as reflected by an increase in the creatinine level by more than 50% of the 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 ($n = 8$) compared with 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 used in eight surgeries for a median of 4 days (range 3–5 days). No epidural analgesia-related complications were observed. Intravenous opioids were administered to all patients for a median of 11 days (range 2–35 days), with a median morphine equivalent dose of 0.67 mg/kg/day (range 0.06–9.2 mg/kg/day). A detailed description of the postoperative pain management parameters is presented in Table 4.

DISCUSSION

The perioperative management of patients undergoing CRS/HIPEC remains a challenge for anesthesiologists, surgeons, and intensivists alike. Whereas a significant body of literature exists for adults, only one study regarding the anesthetic management of pediatric patients undergoing CRS/HIPEC has been reported.[15] Owusu-Agyemang et al.[15] reported on 10 patients who underwent HIPEC in a phase 1 trial of escalating cisplatin doses 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 the patients experienced a transient rise in postoperative serum creatinine.

In the current study, despite significant intra- and perioperative fluid administration, a transient rise in creatinine occurred for all but one patient, with two patients experiencing significant acute kidney injury. 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 associated with increased risk of complications, whereas liberal fluid administration risks fluid overload, tissue edema, and

TABLE 3 Perioperative fluid management

Patient	Diuretics		Preoperative hydration	Postoperative IVF (ml/kg/day)				Serum creatinine (mg/dL)			KDIGO
	Lasix	Mannitol		Min	Max	Median	Days	Preop	Postop Max	% Increase	
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	1
3	–	–	–	9.79	50.29	30.70	6	0.40	1.10	175	1
4[a]	–	–	–	13.13	47.76	32.79	5	0.40	0.70	75	1
5	–	–	–	12.97	33.59	23.41	3	1.10	1.10	–	–
6[b]	–	–	–	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	1
8	Y	–	–	58.53	218.80	59.71	35	0.27	5.76	2033.3	3
9[c]	Y	Y	1.5 × MIVF	32.91	166.79	51.07	20	1.61	1.92	19.3	1
10	Y	Y	2 × MIVF	34.48	197.73	43.55	30	0.51	5.05	890.2	3

IVF intravenous fluid, *Min* minimum, *Max* maximum, *Preop* preoperative serum creatinine, *Postop max* postoperative maximum serum creatinine, *KDIGO* Acute Kidney Injury Criteria in Pediatric Population, *MIVF* maintenance intravenous fluid

[a]Melphalan administered during hyperthermic intraperitoneal chemotherapy (HIPEC)

[b]Mitomycin C administered during HIPEC

[b]Repeat HIPEC

TABLE 4 Postoperative pain management

Patient	Postoperative epidural rate (mL/h)				Postoperative opioids (MED; mg/kg/day)			
	Agent	Fentanyl (μg/h)	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[a]	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

MED morphine equivalent dose (7 mg morphine equivalent to 1 mg hydromorphone), *Min* minimum, *Max* maximum

[a]Repeat hyperthermic intraperitoneal chemotherapy (HIPEC)

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.

In this series, the patients received approximately 133 ml/kg of crystalloids intraoperatively, which equaled 13 ml/kg/h. Blood loss was significant (15 ml/kg), however, and intraoperative urine output was adequate (∼ 2 ml/kg/h). Despite administration of what appears to be adequate intraoperative volume replacement for adults, in a younger population, however, it is possible that more vigorous fluid resuscitation may be necessary to avoid oliguria and to potentiate cisplatin-related nephrotoxicity. Owusu-Agyemang et al.[15] observed that intraoperative fluid administration at a rate of 6–15 ml/kg/h was necessary to maintain urine output at 3 ml/kg/h.

The incidence of grade 3 or 4 nephrotoxicity after CRS/HIPEC among adults is 6% and as high as 25% among children and young adults.[20,21] In a report of 50 patients who underwent CRS/HIPEC, Hayes-Jordan et al.[9] described two patients who experienced grade 3 AKI and three

patients who experienced grade 4 acute renal failure. Thong et al.,[22] in an adult study of 111 patients who underwent 113 CRS/HIPEC procedures, noted that six patients had renal impairment, with one patient experiencing AKI and two patients requiring hemodialysis.

In the current series, the postoperative serum creatinine level rose above the baseline in all but one patient, with two patients experiencing severe AKI. These two patients (patients 8 and 10) also were significantly under-resuscitated based on intraoperative urine output (Table 2). One required short-term hemodialysis, and both eventually recovered renal function. Whereas 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.[21] noted a reduction in the incidence of grades 3 and 4 nephrotoxicity, from 25 to 0%, after implementation of a renal protective protocol. Using 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 h after HIPEC and continued for 48 h after HIPEC.

In the current series, adoption of a formalized renal protective strategy may have minimized the degree of nephrotoxicity observed after HIPEC. Although 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 for children and young adults who undergo CRS/HIPEC has not been described previously. In the current study, eight patients received epidural analgesia, and there were no epidural related complications necessitating early removal. Thoracic epidural analgesia, an excellent option for postoperative pain management, is commonly used in many HIPEC centers.[26,27] Epidural analgesia use is associated with reduced opioid requirements, decreased need for postoperative mechanical ventilation, and shorter ICU stay. It 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 longer 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]

This study had several limitations. The results reflect a single-institution experience with a rare pathology involving a limited number of patients. Although the surgeons were the same, the 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 had an impact on cisplatin-associated nephrotoxicity. Finally, lack of a standard perioperative pain management regimen may have contributed to significant opioid use.

CONCLUSION

The use of CRS/HIPEC for DSRCT is associated with significant intravenous fluid requirements together 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.

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