The effect of intraoperative fluid therapy on postoperative renal functions in patients undergoing hyperthermic intraperitoneal chemotherapy and cytoreductive surgery

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ABSTRACT

Aims: To present the effect of perioperative fluid management on postoperative renal functions in patients who underwent cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).
Study design: Retrospective observational study
Place and Duration of Study: Department of Anesthesiology and Reanimation, Faculty of Medicine, Osmangazi University, Eskişehir between between January 2018 and January 2021.
Methodology: Data of 18 patients were analyzed. Hearth rate, mean arterial blood pressure, and brain oxygeniation by near-infrared spectroscopy (NIRS) were evaluated in 3 CRS phases (at start, 1st hour and 2nd hour of CRS) and 4 HIPEC phases (at minute 15, 30, 45 and 60). Renal function, electrolyte balance, liver function, and full blood count were recorded preoperatively and at 2nd hour, 1st day, and 3rd day postoperatively. Postoperative renal failure was defined as a 1.5-fold increase in creatinin level according to the preoperative value.
Results: There were 14 (77.8%) women and 4 (22.2%) men, with a mean age of 53.3 years old. During both CRS and HIPEC phases, no patient's cerebral NIRS values dropped more than %20 compared with the baseline value. All of the patients received <15 litres of intravenous fluid throughout the surgery, with a mean fluid volume of 12 ml/kg/h. Serum creatinine levels increased 1.5-fold in two patients, which improved immediately in one and persisted until the 7th postoperative day in the other one.
Conclusion: There is a great variability in the intraoperative fluid therapy needs of patients with CRS and HIPEC. The type and amount of intraoperative fluid therapy have a significant effect on all clinical outcomes as well as renal functions. Although there is no optimal intraoperative fluid therapy, closed monitorization of haemodynamic parameters is the key factor for good outcomes.

Keywords: Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, intraoperative fluid therapy, renal function

1. INTRODUCTION

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is among the effective multimodal treatment options that have become increasingly popular in approciate patients with peritoneal carcinomatosis in the last two decads. CRS is a parietal and visceral peritonectomy procedure in which all intra-abdominal macroscopic tumors are removed. With this technique, life expectancy and quality of life increase in patients with peritoneal carcinomatosis caused by different cancers such as colorectal, gastric, ovarian and peritoneal mesothelioma. In the 6th workshop on peritoneal surface cancers held in 2008, CRS with HIPEC became the standard treatment modality for cases with peritoneal carcinomatosis in experienced centers. In this surgery, morbidity ranges from 12% to 67.6% while mortality is between 0% and 9% (1-2).

CRS and HIPEC is a high-risk surgical procedure with major perioperative metabolic and hemodynamic changes. Temperature control at all stages of surgery and providing normovolemia and tissue perfusion constitute difficulties in anesthesia management. As is well known, there is a direct correlation between the amount of fluid administered to the patient during the perioperative period and postoperative complication rate. In case of insufficient fluid administration, various unwanted situations such as acute kidney injury, hypotension, cardiac disrhythmia, and ischemia can occur. In contrast, prolonged mechanical ventilation, delayed wound healing and infection may develop if the patient is overloaded. Therefore, keeping the fluid status of the patient within proper margins throughout the perioperative period is critical for minimizing postoperative morbidity and mortality (3). However, there is little data on this issue, without a global consensus (3-5).

In the present study, we aimed to present our experience of the affect of perioperative fluid management on postoperative kidney functions in patients who underwent CRS and HIPEC.

2. MATERIAL AND METHODS

2.1 General data

Following the approval of ethics committee (30.12.2020/07), a total of 26 patients who underwent CRS with HIPEC for the treatment of peritonitis carcinomatoza between January 2018 and January 2021 were reviewed. This study was a retrospective evaluation of the perioperative anaesthetic management of patients undergoing CRS and HIPEC for different originated cancers. The primary end point of the study was the affect of the intraoperative fluid therapy on the renal functions.

There were no specific exclusion criteria; however, six patients were evaluated inoperable, two patients were excluded as their paper charts (hardcopy medical records) were missing. As a result, data of 18 patients were analyzed. Medical charts obtained from the hospital records were used to collect anaesthetic and perioperative data, including patient demographics, intraoperative medication and fluid administration, blood loss, urine output, postoperative pain management, and anesthesia-related complications.

2.2 Haemodynamic and surgical parameters

The hemodynamic and clinical parameters, including hearth rate (HR), mean arterial blood pressure (MAP), were evaluated in 3 CRS phases (C0 at start of CRS, C1 at the 1st hour of CRS, and C2 at the 2nd hour of CRS) and 4 HIPEC phases (H1 at minute 15, H2 at minute 30, and H3 at minute 45 and H4 at minute 60). Results for renal function, electrolyte balance, liver function, full blood count and clotting profile were recorded preoperatively and at 2nd hour, 1st day, and 3rd day postoperatively. Haemoglobin (Hb) concentrations at 2nd hour, 1st day, and 3rd day postoperatively were used to assess the ongoing postoperative blood loss.

2.3 Anesthetic management

All operations were performed under general anesthesia with standart techniques. Due to the complexity of the surgical interventions, intravenous/arterial accesses were established via large bore peripheral intravenous cannulas, arterial and central venous lines. In the induction of anesthesia, propofol or pentothal sodium was used as an intravenous anesthetic agent. Thereafter, endotracheal intubation was performed with the aid of a muscle relaxant rocuronium. Anaesthesia was maintained with intravenous remifentanil infusion and with desflurane as volatile anaesthetic agents with %50 O_2/%50 air in total 1 lt/min gas flow. In addition to standard anaesthetic monitoring utilised in our department (electrocardiography, continuous capillary oxygen saturation, inspiratory and expiratory gas analyses), central venous and invasive intra-arterial blood pressure monitoring was established in all patients. Central venous pressure (CVP) monitoring was done through a preexisting or newly placed central line. Brain oxygeniation was followed with near-infrared spectroscopy (NIRS) (INVOS 5100 Cerebral Oximeter, Somanetics Corporation) throughout the operation as follows: in 3 CRS phases (C0 at start of CRS, C1 at the 1st hour of CRS, and C2 2nd hour of CRS) and 4 HIPEC phases (H1 at minute 15, H2 at minute 30, and H3 at minute 45 and H4 at minute 60). All patients underwent temperature monitoring with a probe placed in the distal esophagus.

Intraoperative monitoring of metabolic status and haemoglobin concentration was achieved through regular arterial blood gas analysis. All patients had an indwelling urinary catheter inserted prior to the commencement of surgery. During HIPEC, the patient was closely followed with blood gas and heat monitorization. Liquids given to patients (crystalloid and colloid) were noted. Urine output and metabolic status of the patients were hourly followed and recorded. Parasetamol (1 g) and tramadol (1mg/kg) were administered to all patients for postoperative pain. Renal function (albumin, creatinine, and urea), Hb concentration, platelet count, International Normalized Ratio (INR), prothrombin time, and activated partial thromboplastin time (APTT) were recorded both preoperatively and postoperatively (2nd hour, 1st day, and 3rd day). After surgery, all patients were transferred to the post-anaesthesia care unit (PACU) and then general surgery intensive care.

2.4 Statistical analysis

All data were evaluated using SPSS version 22.0. The continuous values were expressed as mean ± standard deviation (SD) and the categorical variables were obtained as number and percentages (%). $P < .05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Results

Eighteen patients with a mean age of 53.3±11.8 (37-75) years old were included in the study. There were 14 (77.8%) women and 4 (22.2%) men. Fourteen (77.8%) patients were preoperatively classified as American Society of Anesthesiology (ASA) 2 physical status while the remaining four (22.2%) cases were ASA 3 physical status. The mean BMI score was 28.9±4.0 (24-36). Colorectal cancer (44.4%) was the most common tumor type in the study population (Table 1). The entire anesthesia time lasted an average of 6.2±1.7 hours.

Table 1. The type of cancers in the study population

	n	%
Colorectal cancer	8	44.4
Ovarian cancer	5	27.8
Gastric cancer	3	16.7
Ovarian+endometrial cancer	1	5.6
Meshotelioma	1	5.6

The hemodynamic and clinical parameters, including HR, MAP, and NIRS, were recorded in 3 CRS phases (at the beginning, 1st, and 2nd hour of CRS) and 4 HIPEC phases (at 15th, 30th, 45th, and 60th minutes) (Table 2). During both CRS and HIPEC phases, no patient's cerebral NIRS values dropped more than %20 compared with the baseline value.

Table 2. HR, MAP, and NIRS (left and right) values of the patients throughout the surgery

	HR	**MAP**	**NIRS-left**	**NIRS-right**
CRS beginning	84.3±9,9	96.7±14.7	73.65±8.7	73.1±8.7
CRS 1st h	79±14,1	78.1±17.2	75.6±9.9	75.6±8.1
CRS 2nd h	77.5±12,2	82.1±11.3	76.8±8	76.1±9
HIPEC 15th min	85.3±12.8	74.1±10	76.9±7.6	77.8±9.2
HIPEC 30th min	88.9±14,4	69.6±6.9	77.7±11.9	78.6±8.3
HIPEC 45th min	91.5±14.7	73.3±8.4	77.8±12	79.6±9
HIPEC 60th min	94.1±14.1	77.5±12.8	79.1±9.1	82.1±8.9

Basic laboratuar tests including Hb, hemotocrite, platelet count, AST, ALT, BUN, creatinine, and GFR were measured both preoperatively and postoperatively (2nd hour, 1st day, and 3rd day) (Table 3).

Table 3: Preoperative and postoperative basic laboratuar tests

	Hb	Htc	Plt	AST	ALT	BUN	cr	GFR
preop	12.5±1.4	39.7±6.5	237.5±96.2	22.5±10.3	20.5±12.9	14.3±4.8	0.7±0.1	86.9±7.6
Postop 2nd h	12.1±2	37.5±5.7	287.8±99.4	179.4±193.8	133.1±142.1	11.8±4.4	0.7±0.1	84.2±11.8
Postop 1st d	11.1±1.8	33.5±5.9	233.2±73	86.3±80.2	72.7±65.1	13.5±5.6	0.8±0.2	81.3±15
Postop 3rd d	9.8±0.6	29.3±2.2	198.1±100	34.9±20.6	29.3±17.8	13.9±6.4	0.8±0.8	80.1±22.5

All of the patients received <15 litres of intravenous fluid (mean fluid volume of 12±2.6 ml/kg/h) throughout the surgery. A total of 10 patients were given gelofusin, of whom 5 also received 5% albumin. Mean total urine output was 1.8 ml/kg/h (ranging from 0.5 to 4.1ml/kg/h). Mean urine output in HIPEC period was 3.4 ml/kg/h (ranging from 0.4 to 11 ml/kg/h). Renal function was monitored with arterial blood gas analysis and routine blood tests (Table 3). No blood transfusion was done to any patient. In all cases, urine extraction was followed hourly, and fluid-urine balance was tried to be maintained. Postoperative renal failure was defined as a 1.5-fold increase in creatinin level according to the preoperative value. Serum creatinine levels increased 1.5-fold in two patients, which improved immediately in one and persisted until the 7th postoperative day in the other. Inotrope agent was administered to five patients, and noradrenaline infusion was initiated to three of those.

The highest temperature in the HIPEC period was 38.9 degree. As emphasized in the Enhanced Recovery After Surgery (ERAS) guidelines, we tried to prevent hypo and hyperthermia. The highest intraoperative lactate value is 7.10 mmol/l.

Complication occured in two patients as arrhythmia and anaphylaxis. The majority of the patients were suitable to be extubated at the end of the procedure whereas three patients were transferred to the general surgery intensive care unit as intubated. Nine patients needed reversal of the muscle relaxant effect. During the postoperative 30 days, no mortality was observed in the study population.

3.2 Discussion

CRS with HIPEC is a long-lasting abdominal surgical procedure with additional hyperthermia and intraoperative chemotherapy. In our study, the mean anesthesia time was 6.2 hours, similar to the literature (6). Extensive fluid shift is a potential problem in such surgeries. Therefore, fluid status, renal and cardiac functions should be continuously assessed with closed hemodynamic monitoring to maintain euvolemia with adequate tissue perfusion.

In particular, maintaining renal function within normal limits is critical for obtaining best perioperative outcome. As known, hypovolemia, hypotension, major surgery, nephrotoxic drugs, blood transfusions, and systemic inflammation are the leading risk factors for acute renal injury. Hence, hemodynamic optimization including optimizing cardiac output, tissue perfusion, and oxygenation is highly recommended to prevent renal injury (7).

In the literature, there is a great variability in the administration of intraoperative fluid therapy in these patients (3-5, 8, 9). The fluid management in our practice consisted of both crystalloids and colloids, and HES was not used in any of the patients. When colloid was needed, gelofusin with or without albumin was used in 11 patients. Our patients received approximately 12 ml/kg/h of fluids, and mean urine output was 1.8 ml/kg/h. The amount of fluids given was guided by hemodynamic parameters, blood gas analyses, and urinary output. Five patients were given vasopressors to maintain MAP.

In fact, there is no evidence that a single pharmacological intervention during surgery protects the kidneys from damage. Most authors recommend liberal fluid regimens (8, 9) in the past years. However, recently, goal-directed fluid management has been recommended HES restriction and the use of human albumin have been suggested. As known, HES administration had a significant negative impact on renal function, especially in younger patients (10,11). In parallel, we did not use HES in our patients.

Optimising intravascular volume, cardiac output, and oxygen delivery by haemodynamic monitoring and goal-directed therapy fluid resuscitation in the operating room is likely the best method of preventing and/or treating nephrotoxicity (12).

Goal-directed approach to fluid therapy (GDT) is recommended as optimal approach in patients undergoing major invasive surgery with expected blood loss >500 mL and/or other significant perioperative fluid shifts. The use of a monitoring and hemodynamic GDT anesthetic protocol in CRS and HIPEC makes it possible to individually adjust the fluid therapy and vasoactive drugs use, avoiding over-hydration and ensuring hemodynamic stability in all surgery phases (3). With this approach, intravascular volume status ensured and this is optimal before adding vasopressor therapy to achieve optimal blood pressure. While GDT appears superior to traditional liberal or fixed-volume approaches, there are limited data comparing GDT to the restrictive approach. One disadvantage of GDT is that it requires invasive monitoring of hemodynamic parameters. Excessive perioperative administration of intravenous fluid, which was common in traditional liberal or fixed-volume approaches to fluid therapy, should be also avoided. The patients in our study were administered intraoperative crystalloid and gelatin based colloid intravenous fluid to maintain a urine output of greater than 0.5 ml/kg/hour. Renal failure, defined as a ≥ 1.5-fold increase over basal creatinine, occurred in two patients of whom one was mild and self-limited and prograssive in other patient.

HIPEC-associated acute kidney injury (AKI) incidence is described between 0 and 18.6%, with a great variability in the definition criteria (3) Cisplatin use is associated with a greater AKI risk between 3.7 and 5.8% depending on the series. The nephroprotective measures used are based on preoperative hydration and the administration of neutralizing substances. However, there is a low evidence level of their efficacy based on clinical observations and cases series (9,14). Cotte et al. reported a 29 % incidence of renal toxicity with acute renal failure when cisplatin alone was used in their study of adult patients undergoing HIPEC (13).

Restrictive strategy is restrictive zero-balance approach, only the fluid that is lost during surgery which is assaciated with a higher rate of acute kidney injury compared with a liberal fluid regimen. Perioperative fluid management strategies have begun to shift in clinical practice, from traditionally liberal to more restrictive, as randomized trials have consistently demonstrated reductions in morbidity with a restrictive approach. While GDT appears superior to traditional liberal or fixed-volume approaches, there are limited data comparing GDT to the restrictive approach described above.

It is standard procedure for both the surgical and the anaesthesia team to assess and estimate blood loss at during the surgery. Blood transfusion requirements were variable, and depended on the extent and nature of the peritoneal disease. The decrease in hemoglobin concentration can be used as an indicator for blood loss. Exposure to blood transfusions is associated with an increased morbidity and mortality in surgical oncology. None of the

patients required platelet transfusions or fresh frozen plasma. During the postoperative 30 days, mortality was not observed in any patient.
The patients are also exposed to extreme changes in body temperature both hypo- and hyperthermia, suffer from metabolic acidosis. Preventation of hypothermia and hyperthermia is strongly recommendation in the Enhanced Recovery After Surgery (ERAS) guidelines (15). All centres allowed some increase in core temperature; range of 36-41 degree. With increased body temperature there is corresponding effects on metabolic rate including increased oxygen demand, heart rate, end tidal CO_2 levels and metabolic acidosis/increased lactate values. In the present case series, closed monitorization of body temperature was standard, and abnormal heat changes were not observed.
Patients with long and complicated surgical procedures have also increased intra-abdominal pressure which may lead to an increase in the intracranial pressure and a decrease in the cerebral perfusion pressure (16). The results reported by Sawoszy et al (16) were consistent with reports observing the relationship between ICP and IAP. The NIRS-based technique, which is noninvasive and easy to apply at the bedside, allows to study these relationships indirectly. It was hypothesized that these NIRS probes would accurately reflect early changes in mesenteric and systemic perfusion (17). Abdominal filling with saline solution enriched with chemotherapeutics causes an increase in intraabdominal pressure with cranial shift of the diaphragm resulting in a reduction in the functional residual capacity and an increase in airway pressure (18). In our study, no patient's cerebral NIRS values dropped more than %20 during both CRS and HIPEC phases, compared with the baseline values.
In the study population, desflurane was used as volatile anaesthetic agents with %50 O2/%50 air in total 1 lt/min gas flow. Desflurane may be a good choice in patients during CRS with HIPEC, because of its nephroprotective effects. The explanation of this nephroprotective effect may be related to the cardioprotective mechanisms of desflurane. In a study in rats, desflurane was shown to protect the kidney against ischemia and reperfusion (19). On the other hand, sevoflurane is metabolized to compound A and fluoride, which carries a hypothetical risk of nephrotoxicity. However, a clinically significant association between sevoflurane use and acute kidney injury in humans has not been established (20).
In the ERAS guideline, early extubation of these patients was a strong recommandation (15). The majority of our patients were stable enough to be extubated at the end of the procedure. Some of these needed vasopressor support to maintain their haemodynamics. Therefore, we routinely monitored these patients for at least 30 minutes to ensure that they were stable after extubation.

4. CONCLUSION

Maintenance of normothermia, normovolaemia, and tissue perfusion constitute the major difficulties in anesthesia management of CRS and HIPEC. There is a great variability in the intraoperative fluid therapy needs of these patients. We think that the type and amount of fluids used have a significant effect on all clinical outcomes as well as renal functions. There is no evidence on optimal intraoperative fluid administration due to the limited number of studies, mostly retrospective. Large scale, prospective, and randomized controlled trials are highly required in this field. We hope that our study will contribute to the future researches.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee (date: 30.12.2020, protocol number: 07) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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