The effect of intraoperative fluid therapy on postoperative renal functions in patients undergoing hyperthermic intraperitoneal chemotherapy and cytoreductive surgery: A retrospective observational study

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ABSTRACT

Aims: To investigate 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, Türkiye between January 2018 and January 2021.

Methodology: Data of 18 patients were analyzed. Hearth rate, mean arterial blood pressure, and brain oxygenation 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 and hepatic functions, and full blood count were recorded preoperatively and at 2nd hour, 1st day, and 3rd day postoperatively. Acute kidney injury (AKI) was defined as a 1.5-fold increase in serum creatinine 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 ml/kg/h of intravenous fluid throughout the surgery (mean fluid volume was 12 ml/kg/h). AKI was developed in two patients.

Conclusion: The cornerstone of our fluid management in these patients was to adjust the amount of fluid under the guidance of urinary output and other hemodynamic indicators. In addition, excessive fluid administration was prevented with fluid infusion not exceeding 15 ml/kg/h. Although there is no evidence on optimal intraoperative fluid administration due to the limited number of studies, we hope that our study will contribute to the futher Large scale, prospective, and randomized controlled trials.

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

1. INTRODUCTION

In recent decads, cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has become an effective multimodal treatment in appropriate patients with peritoneal carcinomatosis caused by various cancers such as colorectal, gastric, ovarian cancers and mesotheliomas. CRS is a parietal and visceral peritonectomy procedure in which all intraabdominal macroscopic tumors are removed. Thanks to this

technique, life expectancy and quality of life increase in these patients. 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 reported up to 9% (1-2).

CRS and HIPEC is a high-risk surgical procedure with major perioperative metabolic and hemodynamic changes. Temperature control and providing normovolemia and tissue perfusion at all stages of surgery constitute difficulties in anesthesia management. The task of the anesthesiologist is to know the pathophysiological changes occurring in each phase. It is essential to provide and maintain normovolaemia in the SRC phase due to the large fluid shifts, and to take precautions regarding increased metabolic activity and developing coagulation changes in the HIPEC phase. 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 (AKI), 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 safe margins throughout the perioperative period is critical for minimizing postoperative morbidity and mortality (3). In particular, keeping renal functions (such as urinary output and serum creatinine level) within normal limits is a priority necessity for positive intraoperative and postoperative outcomes. However, there is not a global consensus regarding the fluid therapy in patients undergoing CRS and HIPEC, due to small number of clinical studies on this issue (3-5).

In the present study, we aimed to present our experience regarding the effect of perioperative fluid management on postoperative renal 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), data 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 endpoint of the study was the effect of the intraoperative fluid therapy on the renal functions including hourly urinary output and serum creatinine level. Secondary endpoint was the potential relationship between fluid therapy and postoperative morbidity and mortality.

There were no specific exclusion criteria. However, a total of 8 patients (six were accepted inoperable intraoperatively and two had incomplete medical records) were excluded from the study. 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. AKI was defined as a 1.5-fold increase in serum creatinine level according to the preoperative baseline value" (6).

2.3 Anesthetic management

All operations were performed under general anesthesia with standard 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 intravenous (IV) anesthetic agent. Thereafter, endotracheal intubation was performed with the aid of a muscle relaxant rocuronium. Anaesthesia was maintained with IV remifentanil infusion and desflurane volatile agent, with %50 O2/%50 air in total 1 lt/min gas flow. In addition to standard anaesthetic monitoring utilized 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 oxygenation 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 (Hb) concentration was achieved through regular arterial blood gas analyses. 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 functions (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 had ASA 3 physical status. The mean body mass

index (BMI) score was 28.9±4 (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 ml/kg/h of IV fluid (mean fluid volume was 12±2.6 ml/kg/h) throughout the surgery. A total of 11 patients were given gelofusin, of whom 5 also received 5% albumin (Table 4). 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 product was transfused to any patient. In all cases, urine output was followed hourly, and fluid-urine balance was tried to be maintained. Postoperative AKI was defined as a 1.5-fold increase in creatinine level according to the preoperative baseline value. AKI was developed in two patients. One of these patients had solitary kidney and high ASA score. This patient had multiple hemodialysis after the surgery. The other patient had a moderate elevation in serum creatinine level with normal GFR, and her values improved on postoperative 3th day. Inotrope agent was administered to five patients, and noradrenaline infusion was given to three of those.

Table 4: Data of fluid therapy and vasopressor administration

parameters	n (%)
Colloid infusion	11 (61.1%)
Albumin (5%) infusion	5 (27.8%)
Blood product transfusion*	0
Need of vasopressor	5 (27.8%)

The amount of IV fluid was presented as mean±standard deviation (minimum-maximum); the other parameters were presented as number (percentage).
* Erythrocyte suspension and fresh frozen plasma

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.
Complications including arrhythmia and anaphylaxis occured in two patients. The majority of the patients were suitable to be extubated at the end of the procedure. Three patients were not extubated (one due to very long operation time, one due to anaphylactic reaction, one due to noradrenaline support) and were taken to the general surgery intensive care unit 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. In our study, the mean anesthesia time was 6.2 hours, similar to the previous reports in the literature" (7). Extensive fluid shift is a potential problem in such surgeries. Therefore, fluid status, renal and cardiac functions should be 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 outcomes. As known, hypovolemia, hypotension, major surgery, nephrotoxic drugs, blood transfusions, and systemic inflammation are the leading risk factors for AKI. Hence, hemodynamic optimization including optimizing cardiac output, tissue perfusion, and oxygenation is highly recommended to prevent renal injury" (8).
In the literature, there is a great variability in the administration of intraoperative fluid therapy in these patients (3-5, 9, 10). 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. The need for colloid administration and vasopressor was evaluated according to the varying intraoperative hemodynamic data of the patients, urine output, and presence of fluid shift such as blood loss and ascites drained. 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 recommended liberal fluid regimens in the past years (9, 10). However, recently, goal-directed fluid therapy (GDT) with HES restriction and the use of human albumin when needed have been recommended. As known, HES administration has a negative impact on renal function, especially in younger patients (11,12). In parallel, we did not use HES in our patients.
"Optimising intravascular volume, cardiac output, and oxygen delivery by hemodynamic monitoring and GDT is likely the best method of preventing and/or treating nephrotoxicity"

(13). “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 closed monitoring and GDT protocol in CRS and HIPEC makes it possible to individually adjust the fluid therapy and vasoactive drug use, avoiding overhydration and ensuring hemodynamic stability in all surgery phases” (3). With this approach, intravascular volume status can be safely ensured in most of the patients, without adding vasopressor therapy to achieve optimal blood pressure. Although GDT appears superior to traditional liberal or fixed-volume approaches, there are limited data comparing GDT to the restrictive approaches. The most important 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 crystalloids and gelafusin-based colloids, maintaining a urine output of greater than 0.5 ml/kg/h. AKI, defined as at least 1.5-fold increase in creatinine level in comparison to basaeline value, was observed in two patients of whom one was mild and self-limited and progressive in other patient.

HIPEC-associated AKI incidence was reported between 0 and 18.6%, due to the 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 case series” (10,15). Cotte et al. reported “a 29 % incidence of renal toxicity with acute renal failure when cisplatin alone was used” (14).

Restrictive strategy is described as a restrictive zero-balance approach, and the fluid that is lost during surgery 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 should be a standard procedure for both the surgical and the anaesthesia team to assess and estimate blood loss at during the surgery. Blood transfusion requirement is variable, depending on the extent and nature of the peritoneal disease. The decrease in hemoglobin concentration can be used as an indicator for blood loss. It should be also kept in mind that exposure to blood transfusions is associated with an increased perioperative morbidity and mortality. In our study, none of the patients required any blood product transfusions. During the postoperative period, mortality was not observed in any patient.

In such operations, the patients are usually exposed to extreme changes in body temperature and may suffer from metabolic acidosis. Preventation of hypothermia and hyperthermia is strongly recommended in the Enhanced Recovery After Surgery (ERAS) guidelines (16). Some increase in core temperature ranging between 36 and 41 degree is often allowed in the most of the centers performing CRS and HIPEC. As known, significant effects occur on metabolic rates including increased oxygen demand, heart rate, end tidal CO2 levels and metabolic acidosis/increased lactate values, as a result of increased body temperature. In the present case series, closed monitorization of body temperature was standard, and abnormal heat changes were not observed.

The patients undergoing long and complicated surgical procedures have also increased intraabdominal pressure which may lead to an increase in the intracranial pressure and a decrease in the cerebral perfusion pressure (17). The results reported by Sawoszy et al (17) were consistent with reports observing the relationship between intracranial pressure and intraarterial pressure. 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 (18). “Abdominal filling with saline solution enriched with chemotherapeutics causes an

increase in intraabdominal pressure with cranial shift of the diaphragm. This situation leads a reduction in the functional residual capacity and an increase in airway pressure" (19). 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 agent, 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 conducted in rats, desflurane was shown to protect the kidney against ischemia and reperfusion (20). On the other hand, sevoflurane is metabolized to compound A and fluoride, which carry a hypothetical risk of nephrotoxicity. However, a clinically significant association between sevoflurane use and AKI has not been established in humans (21).
In the ERAS guideline, early extubation of these patients is a strong recommandation (16). 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.
This study has several limitations. First, it was conducted in a single center, which may limit the generalizability of the statistical results. The smaller sample size may be another limitation. However, considering that there is limited number of studies in this field, the present study can provide important scientific contributions to the current literature and may be supportive for the future works.

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. The cornerstone of our fluid management in these patients was to adjust the amount of fluid under the guidance of urinary output and other hemodynamic indicators. In addition, excessive fluid administration was prevented with fluid infusion not exceeding 15 ml/kg/h. Although there is no evidence on optimal intraoperative fluid administration due to the limited number of studies, we hope that our study will contribute to the futher Large scale, prospective, and randomized controlled trials

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.

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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