Hyperthermic intraperitoneal chemotherapy is an independent risk factor for development of acute kidney injury

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Summary

Purpose: Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) or hyperthermic intrapleural chemotherapy (HIC) has been established as the new treatment modality for selected patients with peritoneal and pleural malignancies. The purpose of the study was to compare the development of acute kidney injury (AKI) in patients who received intravenous cisplatin alone, HIPEC and underwent surgery.

Methods: This retrospective study included 104 patients who underwent different therapeutic procedures including systemic cisplatin, surgery and HIPEC or HIC using cisplatin for the treatment of peritoneal carcinomatosis from a variety of primary tumors at Koc University Hospital and American Hospital between January 2015 to December 2017.

Results: AKI developed in 18 (17.3%) patients. Baseline creatinine was significantly increased in 3 groups after therapies. The development of AKI was highest in patients treated with HIPEC compared to patients treated with intravenous cisplatin and patients who underwent surgery. AKI developed 31.2% in the HIPEC group (10 of 32 patients), 11.7% in the surgery group (4 of 34 patients) and 10.5% in intravenous cisplatin group (4 of 38 patients), respectively (p=0.04).

Conclusion: HIPEC may not be so safe with regard to kidney function. Every attempt should be taken to decrease kidney damage during this procedure.

Key words: acute kidney injury, cisplatin, HIPEC

Introduction

Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) and less extensively hyperthermic intrapleural chemotherapy (HIC) has been emerged as new therapeutic approach to treat peritoneal carcinomatosis (PC) originating from different tumors including colorectal, ovarian and gastric cancers and primary peritoneal tumours (pseudomyxoma and peritoneal mesothelioma) and malignant pleural diseases [1-3].

HIPEC has been widely used for controlling ascites or microscopic peritoneal carcinomatosis following surgical resection of abdominal cancers [3]. In various centers there are different methodologies in using HIPEC, including "open" or "closed" technique, using mitomycin and/or platin-based, mono-chemotherapy or combination of chemotherapy regimens, temperature and duration of HIPEC [4]. In general, chemotherapeutic drugs are
introduced intraoperatively into the peritoneal cavity at temperatures 41-45°C. The abdominal cavity is perfused for about 60-90 min, thereby exposing potential microscopic residual cancer cells directly to the synergistic effects of hyperthermia and cytotoxic agents [5].

The summarized HIPEC-related morbidity and mortality is reported to range between 2.8% and 33.0%, respectively [4]. In another systematic review of morbidity and mortality for CRS+HIPEC Chua et al. showed that the mortality and morbidity ranged from 0.9% to 5.8% and 12% to 52%, respectively [6].

HIC has also been used in malignant pleural mesothelioma although the data is scarce in the literature [7]. In a recent study, HIC with cisplatin showed promising results [8]. Most patients are treated with tubectomy and sclerotherapy, although its success rate is around 64% [8,9].

Cisplatin is also commonly used in HIPEC for the management of PC. Cisplatin exerts its cytotoxic effect by binding and cross-linking DNA. The main side effect of cisplatin is nephrotoxicity and systemic cisplatin lowers creatinine clearance [10]. Thus one of the options is to give cisplatin locally instead of systematically. Since cisplatin is nephrotoxic, local cisplatin administration in the peritoneal cavity may seem protective regarding systemic toxicity of cisplatin. Furthermore, cisplatin penetration and cytotoxicity are augmented by heat, with a thermal enhancement ratio of 2.9 at 41.5°C [11]. Indeed, it has been used in many HIPEC protocols at variable doses for the treatment of tumors with PC, including primary peritoneal neoplasms, sarcomas and gynecological tumors [12,13].

However, with regard to renal effects of cisplatin, there are different findings, while it was shown that there was low incidence of renal function impairment with cisplatin use in HIPEC [14,15]. Recent data suggests that intraperitoneal cisplatin is absorbed into the circulation and thus systemic complications cannot be excluded [16].

Thus there are conflicting data regarding systemic and peritoneal renal toxic effects of cisplatin. Additionally, no comparative data exists regarding the renal toxic effects of cisplatin when given systemically or intraperitoneally named as HIPEC. With this background in mind, in this retrospective study we aimed to compare the development of acute kidney injury in patients who received intravenous cisplatin, HIPEC and underwent surgery.

Methods

This is a retrospective cohort study of 3 groups of patients who underwent different therapeutic procedures including systemic cisplatin alone, surgery and HIPEC/HIC using cisplatin for the treatment of PC and malignant pleural mesothelioma at Koc University Hospital and American Hospital between January 2015 to December 2017.

Exclusion criteria were defined as follows: age <18 years, patients with estimated glomerular filtration rate <45 mL/min/1.73m² or history of glomerular disease, history of peritonectomy, history of receiving chemotherapy, recent history of acute kidney injury within the last 4 weeks, contrast exposure within the last 2 weeks and acute infection in any organ. In addition, patients were ineligible for HIPEC with cisplatin if they had estimated glomerular filtration rate < 45 mL/min/1.73m², had end-stage renal disease or received renal replacement therapy. Patients whose performance status (PS) was 0-1 according to Eastern Cooperative Oncology Group (ECOG) were included to the study.

This study was in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and local regulatory requirements. The study was approved by the local ethics committee.

Data collection

Age, sex, weight, height, primary tumor type of the patients were obtained from the medical records. Body surface area (BSA) was calculated according to the Mosteller formula. Potential risk factors for nephrotoxicity were collected, including baseline comorbidities (hypertension, diabetes mellitus and chronic kidney disease (CKD)) and using nephrotoxic agents one week prior to one week following procedures. All patients were screened with intravenous radiology contrast media (gadolinium) and iodine) within the two weeks prior to surgery or one week after.

Intraoperative data

Intraoperative data including duration of operation, amounts of fluid loss and replacement, urine output and vasopressors administration were registered when available.

Chemotherapy

Patients received a standard chemotherapeutic regimen consisting of cisplatin 75 mg/m² (up to 150 mg).

HIPEC was performed immediately after surgery using the closed abdomen technique. When the target temperature (42°C) was reached in 3 liters saline solution, 75 mg/m² cisplatin was infused for 60 min, and intraperitoneal temperature at outflow was maintained between 42 and 43°C.

Definition of acute kidney injury

The Acute Kidney Injury Network (AKIN) classification is used to diagnose acute kidney injury. AKI is defined by the sudden decrease (in 48 hrs) of renal function, defined by an increase in absolute serum creatinine of at least 0.5 mg/dL or by a percent increase in SCR ≥50% (1.5× baseline value), or by a decrease in the urine output (documented oliguria <0.5 mL/kg/hr for more than 6 hrs) [19].
Statistics

Data analyses were performed by using SPSS for Windows, version 15 (SPSS, Inc., Chicago, IL). Whether the distributions of continuous variables were normal or not was determined with the use of the Shapiro Wilk test. Data are presented as mean ± standard deviation, or as percents. Differences in clinical and biochemical parameters were compared by the x² test for categorical variables, whereas the non-parametric Kruskal-Wallis test was used for continuous variables since parameters were non-normally distributed. A p value of <0.05 was considered statistically significant.

Results

This retrospective study included 104 patients (27 male, 77 female). Twenty seven were hypertensive, 6 had diabetes. Twenty two patients had lung cancer, 5 had mesothelioma, 51 had gynecological cancer and 26 had gastrointestinal system cancer. Thirty two patients were treated with HIPEC or HIC, 34 patients had surgery, 38 patients were treated with intravenous cisplatin. AKI developed in 18 (17.3%) patients. The demographic parameters are

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HIPEC group (n=32)</th>
<th>Surgery group (n=34)</th>
<th>Cisplatin group (n=38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>55.31 ± 10.69</td>
<td>54.76 ± 11.82</td>
<td>58.05 ± 11.18</td>
<td>0.80</td>
</tr>
<tr>
<td>BMI, kg/m² (mean±SD)</td>
<td>23.78 ± 3.89</td>
<td>21.25 ± 4.11</td>
<td>21.59 ± 1.63</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline creatinine mg/dl (mean±SD)</td>
<td>0.71 ± 0.20</td>
<td>0.70 ± 0.20</td>
<td>0.78 ± 0.26</td>
<td>0.46</td>
</tr>
<tr>
<td>Baseline urea (mg/dl) (mean±SD)</td>
<td>26.82 ± 10.14</td>
<td>23.03 ± 7.30</td>
<td>29.07 ± 11.39</td>
<td>0.59</td>
</tr>
<tr>
<td>Males (n,% )</td>
<td>6 (18.8)</td>
<td>4 (11.8)</td>
<td>17 (44.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension (n,% )</td>
<td>6 (18.8)</td>
<td>5 (14.7)</td>
<td>16 (42.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes (n,% )</td>
<td>1 (3.1)</td>
<td>3 (8.8)</td>
<td>2 (5.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>RAS blocker (n,% )</td>
<td>4 (12.5)</td>
<td>5 (14.7)</td>
<td>12 (31.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Beta blocker (n,% )</td>
<td>4 (12.5)</td>
<td>5 (8.8)</td>
<td>6 (15.8)</td>
<td>0.67</td>
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<tr>
<td>Diuretic (n,% )</td>
<td>0</td>
<td>2 (5.9)</td>
<td>5 (13.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>NSAID (n,% )</td>
<td>6 (18.8)</td>
<td>2 (5.9)</td>
<td>5 (13.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>AKI (n,% )</td>
<td>10 (31.2)</td>
<td>4 (11.7)</td>
<td>4 (10.5)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

BMI: body mass index, NSAID: non steroidal anti-inflammatory drugs, AKI: acute kidney injury

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AKI</th>
<th>No-AKI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte suspension (n,% )</td>
<td>3 (30)</td>
<td>2 (9)</td>
<td>0.29</td>
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<tr>
<td>Hypotension (n,% )</td>
<td>5 (50)</td>
<td>2 (9)</td>
<td>0.29</td>
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<tr>
<td>NSAID (n,% )</td>
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<td>0.27</td>
</tr>
<tr>
<td>Hypertension (n,% )</td>
<td>1 (10)</td>
<td>5 (22)</td>
<td>0.39</td>
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<tr>
<td>Diabetes (n,% )</td>
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<tr>
<td>RAS blocker (n,% )</td>
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<tr>
<td>Beta blocker (n,% )</td>
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<td>5 (15)</td>
<td>1</td>
</tr>
<tr>
<td>Diuretic (n,% )</td>
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</tr>
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</table>

Table 1. Comparative demographic parameters and AKI development among 3 groups of patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HIPEC (n=32)</th>
<th>Surgery (n=34)</th>
<th>Cisplatin (n=38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>8 (7.6)</td>
<td>8 (7.6)</td>
<td>6 (5.7)</td>
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<tr>
<td>Mesothelioma</td>
<td>2 (1.9)</td>
<td>1 (0.9)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Overian cancer</td>
<td>15 (14.4)</td>
<td>12 (11.5)</td>
<td>11 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>3 (2.8)</td>
<td>2 (1.9)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Cervix cancer</td>
<td>1 (0.9)</td>
<td>2 (1.9)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>9 (8.6)</td>
<td>9 (8.6)</td>
<td>8 (7.6)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Comparative clinical and demographic patient parameters with and without acute kidney injury (AKI) among 3 groups of patients

Table 3. Kinds of cancer and their treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HIPEC and HIC group (n=32)</th>
<th>Chemotherapy group (n=38)</th>
<th>Surgery group (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>8 (7.6)</td>
<td>8 (7.6)</td>
<td>6 (5.7)</td>
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<tr>
<td>Mesothelioma</td>
<td>2 (1.9)</td>
<td>1 (0.9)</td>
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<td>2 (1.9)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Cervix cancer</td>
<td>1 (0.9)</td>
<td>2 (1.9)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>9 (8.6)</td>
<td>9 (8.6)</td>
<td>8 (7.6)</td>
</tr>
</tbody>
</table>

JBUON 2018; 23(5): 1530
given in Tables 1 and 2. The kinds of cancers and their treatments are shown in Table 3. As expected, in all 3 groups baseline creatinine was significantly increased after the procedures. The development of AKI was highest in patients treated with HIPEC and HIC compared to patients treated with intravenous cisplatin and patients with surgery (Table 1). AKI developed 31.2% in the HIPEC group (10 of 32 patients), 11.7% in surgery group (4 of 34 patients) and 10.5% in intravenous cisplatin group (4 of 38 patients), respectively (p=0.04; Table 1).

Discussion

In this retrospective study, we investigated and compared the incidence of development of AKI among 3 groups of patients, namely HIPEC group, surgery group and cisplatin group. What it was demonstrated was that AKI development was higher in the HIPEC group compared to surgery and cisplatin groups. To the best of our knowledge this is the first study comparing 3 groups of patients with respect to development of AKI in the literature.

HIPEC and HIC were used in various tumor types. The logic behind this was the effect of heat which increases the effects of cytotoxic drugs by a variety of mechanisms including increased membrane permeability, improved membrane transport and increase of drug penetration in tissue in a temperature-dependent manner [20,21]. Heat alters cellular metabolism (inhibits RNA synthesis and arrests mitosis, increases the number of unstable lysosomes with increased destructive capacity) and changes drug pharmacokinetics and excretion [21,22]. Indeed, malignant cells are selectively killed by hyperthermia in the range of 41 to 42°C [23] and in addition, malignant cells become more sensitive to heat compared to the normal cells and undergo apoptosis at 41 to 43°C, while normal cells are capable to survive [24]. However, heat may also change drug pharmacokinetics and can increase the cytotoxicity of certain chemotherapeutic agents [21,22]. One of the most used chemotherapeutic agent in HIPEC and HIC is cisplatin. This is due to the fact that cisplatin is a large, water soluble, ionized compound that does not easily cross the peritoneal barrier into the systemic circulation thus potentially limits the major side effect, namely nephrotoxicity. It was suggested that the incidence of cisplatin-induced nephrotoxicity following HIPEC may be lower compared to systemic administration. This could also be attributed to the local administration of cisplatin in HIPEC [25,26]. This makes it an ideal agent for intraperitoneal and intrapleural chemoperfusion. Indeed, it has been shown that intraperitoneal concentrations have been found to be 10-30-fold higher in peritoneal fluid than in plasma in previous studies [27,28].

Cisplatin nephrotoxicity involves direct tubular damage and the following inflammatory reaction, resulting in fibrosis and increased apoptosis [26,29]. Even more important is that some patients who develop AKI with cisplatin could progress to CKD [25]. Thus, giving cisplatin locally (intrapleural or intraperitoneal) seems plausible in preventing systemic side effects, especially nephrotoxic effects. However, despite this initial enthusiasm, cisplatin - even given locally - may be related with notable systemic toxicity. Kusamura et al. showed that cisplatin doses ≥240 mg delivered intraperitoneally, correlated with grade III-V systemic toxicity and his cohort had a 5.7% rate of nephrotoxicity [30].

Hakeem et al. in a retrospective study investigated the incidence of nephrotoxicity post-HIPEC using cisplatin 50 mg/m² plus doxorubicin 15 mg/m². RIFLE classification was used to assess the development of nephrotoxicity. Variables, such as comorbidities and nephrotoxic medications were obtained. Renal function parameters were also collected, including serum creatinine levels and serum magnesium levels at baseline and at days 3, 7 and 30 after HIPEC. Perioperative urine output was also recorded. Among 55 patients, 2 (5.7%) developed AKI following HIPEC with cisplatin. One patient met the criteria for renal failure and progressed to chronic renal failure. The other patient had renal injury. The incidence of hypomagnesemia increased to 24.5% by day 7 (p=0.041) and 30.1% by day 30 (p<0.001) following HIPEC. Low intraoperative urine output, angiotensin II receptor antagonist use and hypertension were associated with development of AKI. The authors concluded that although nephrotoxicity can complicate cisplatin-based HIPEC, permanent renal dysfunction may rarely occur. More attention should be paid toward monitoring magnesium levels after cisplatin use with HIPEC [26]. In another retrospective study, Sanchez et al. reported much higher AKI incidence (30.5%) by using RIFLE criteria [31]. In another study involving 50 women with ovarian cancer using cisplatin dosage between 100-150 mg/m² with HIPEC showed 6% incidence of nephrotoxicity. In 16 of these patients, cisplatin was combined with systemic infusion of thiosulfate [15].

Boisen et al. studied the role of HIPEC in epithelial ovarian cancers in 34 patients. The majority of patients (21 of 34 patients, 62%) received mitomycin C. The other drugs administered included cisplatin (10 of 34 patients, 29%), oxaliplatin (2 of 34 patients, 6%), and carboplatin (1 of 34 pa-
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tients, 3%). Seven (21%) patients developed transient renal dysfunction, and this was seen almost exclusively in the patients who received cisplatin [32]. Thus, it is important to note that cisplatin, although given locally during HIPEC or HIC, may be associated with kidney injury in a considerable number of patients. This necessitates continuous monitoring of perioperative renal function, as well as early detection of AKI during HIPEC [31]. Proposed algorithms for the preventive measures include holding a urine output at least of 2 ml/kg/h by aggressive hydration [33], avoiding inotropes and hypotension episodes [34] and using agents that increase renal cisplatin tolerance such as amifostine [35]. The suggested mechanisms of action are binding free radicals, transfer of hydrogen to DNA groups, depletion of oxygen close to DNA and an increase in the biochemical DNA repair mechanisms [35].

In our study, we showed that patients with HIPEC experienced more AKI than other patients who underwent surgery or treated with cisplatin. In the light of our results, cisplatin, even given locally, may be related with systemic side effects. Indeed, in a chemotherapeutic regimen that is combined with cisplatin (50 mg/m²) with doxorubicin (15 mg/m²), infused over 90 min showed a cisplatin perfusate to blood area under the curve ratio of 6.28 [16]. These data indicates the absorption of cisplatin into the circulation during HIPEC, hence systemic complications cannot be excluded. In this respect the total doses of cisplatin given in HIPEC and systemic cisplatin may be different. Another factor may be procedure itself. In HIPEC patients cytoreductive surgery and local cisplatin are performed concomitantly and both anesthesia [36] and major abdominal surgery [37] have been related with AKI. The combination of anaesthesia, major abdominal surgery and cisplatin (although given locally) may play a synergistic role in the development of AKI.

As this study is retrospective, it has various limitations. First, due to the nature of the study we could not control all the variables. Second, the study group was very heterogeneous with different characteristics. Third, hypomagnesemia plays an important note in development of AKI [38]. However, hypomagnesemia was not specifically addressed in this study. The sample size of the study was relatively low. To report an adverse effect of a medication usually requires a study with a higher number of subjects. However, due to the type of the diseases treated with HIPEC and surgically fit patients to undergo this procedure made it difficult to conduct such a study on a large number of subjects.

In conclusion, HIPEC may not be so safe with regard to kidney function and every attempt should be taken to decrease kidney damage during this procedure. We wish to alert the physicians to keep in mind AKI complication during HIPEC. More studies are needed to highlight these issues.

Conflict of interests

The authors declare no conflict of interests.

References

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