

Acute Kidney Injury Following Hyperthermic Intraperitoneal Chemotherapy With Cisplatin

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Abstract. *Background/Aim:* Cisplatin increases the risk of acute kidney injury (AKI) during systemic chemotherapy. However, little is known about its risk of inducing AKI when used during intraperitoneal chemotherapy. This study aimed to determine the incidence of AKI in patients undergoing cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) with cisplatin. *Patients and Methods:* A retrospective analysis of patients who received cisplatin-based HIPEC from November 2008 to March 2018 was undertaken to determine the incidence of AKI. *Results:* A total of 111 patients were identified. The incidence of AKI was 15.3% (17/111). Univariate analysis showed increased peritoneal cancer index (PCI), low intraoperative and post-operative urine output were significantly associated with the development of AKI. Multivariate analyses did not identify any significant predictors factors for AKI. *Conclusion:* Cisplatin-based HIPEC is associated with AKI. At our centre, the incidence of AKI was 15.3%. Risk factors that may influence its development include high PCI and low perioperative diuresis.

Cisplatin (cis-diamminedichloroplatinum) [II]) is an inorganic platinum compound commonly used as a systemic chemotherapeutic agent for various malignancies including lung, testicular and ovarian tumours (1). With the increasing use of cytoreductive surgery (CRS) and hyperthermic

intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis, cisplatin has also become widely used as an intraperitoneal chemotherapy agent (2). The instillation of cisplatin at temperatures exceeding 41.5 degrees Celsius into the open abdomen following CRS has resulted in significant improvements in our ability to deliver regionally high dose chemotherapy whilst limiting the risk of adverse effects (3).

Cisplatin nephrotoxicity is the major limiting factor for parenteral administration of cisplatin. Within days of treatment, up to 70% of patients experience cisplatin nephrotoxicity, which is characterised by a rise in serum creatinine and urea, glycosuria, proteinuria and electrolyte wasting (4). Cisplatin-induced nephrotoxicity may progress to permanent end stage renal failure despite preventative measures (5). However, the risk of developing acute kidney injury (AKI) following intraperitoneal cisplatin therapy remains unclear.

There is limited data in the literature regarding nephrotoxicity following cisplatin-based HIPEC. Evidence suggests cisplatin-based HIPEC is an independent risk factor for AKI compared to non-cisplatin-based HIPEC (2). However, the calculated incidence of AKI following cisplatin-based HIPEC varies widely, with figures ranging from 3.7% to 88.1% (6). The aim of this study was to determine the incidence of AKI in adult patients with peritoneal carcinomatosis who have undergone CRS and cisplatin-based HIPEC. Risk factors contributing to the development of AKI were evaluated as a secondary endpoint.

Patients and Methods

Patient selection. Patients who underwent CRS and cisplatin-based HIPEC from November 2008 to March 2018 at St George Hospital (Sydney, Australia) were identified. Data was collected retrospectively from a prospectively maintained database at the Peritonectomy Unit of St George Hospital. All patients were staged preoperatively with contrast-enhanced computer tomography (CT) of chest, abdomen and pelvis, fluorodeoxyglucose positron emission tomography (PET), and

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Key Words: Clinical study, cisplatin, hyperthermic intraperitoneal chemotherapy, incidence, acute kidney injury, peritoneal carcinomatosis.

Table I. RIFLE criteria.

Category	Creatinine/GFR criteria	UO criteria
Risk (R)	Increased serum creatinine $\times 1.5$ or GFR decrease $>25\%$	UO <0.5 ml/kg/h $\times 6$ h
Injury (I)	Increased serum creatinine $\times 2$ or GFR decrease $>50\%$	UO <0.5 ml/kg/h $\times 12$ h
Failure (F)	Increased serum creatinine $\times 3$ or GFR decrease $>75\%$ or serum creatinine level >4 mg/dl	UO <0.5 ml/kg/h $\times 24$ h Anuria $\times 12$ h
Loss (L)	Persistent acute renal failure of complete loss of renal function for >4 weeks	
ESKD (E)	ESKD for >3 months	

GFR: Glomerular filtration rate; UO: urine output; ESKD: end stage kidney disease.

gadodexate disodium-enhanced (Primovist™) magnetic resonance imaging (MRI). Suitability for surgery was determined for all patients at a multidisciplinary meeting that included radiologists, medical oncologists, surgeons and allied health staff.

Cytoreductive surgery. All patients underwent CRS as described by Sugarbaker (3). The extent of disease was scored following laparotomy using the Peritoneal Cancer Index (PCI) (7). A score of 0 to 3, based on the size and confluence of tumour, is allocated in 13 regions of the abdomen to give a total score out of 39.

Hyperthermic intraperitoneal chemotherapy. HIPEC was administered to patients following CRS in a standardised manner. At our institution, the open method ("Coliseum technique") was used as described by Sugarbaker (8). The chemoperfusate was instilled into the abdomen and warmed up to $41-46^{\circ}\text{C}$ to achieve an intraperitoneal temperature exceeding 41.5°C . Cisplatin was delivered at doses of 100 mg/m^2 in 1000 ml of 0.9% normal saline for 90 min in all primary tumours except for gastric adenocarcinoma. In patients with gastric adenocarcinoma, a fixed dose of cisplatin (120 mg) and mitomycin C (30 mg) was delivered in 1000 ml of 0.9% normal saline for 90 min . Patients with peritoneal mesothelioma also received mitomycin C (12.5 g/m^2) within the chemoperfusate. In all patients, cisplatin dose reduction of 25% was applied in the event of prior chemotherapy >1 -line, prior CRS and HIPEC, or pre-existing renal impairment.

Data collection. Prior to surgery, baseline demographic data and anthropometrics were collected. Baseline blood tests including renal function parameters were also collected. Intraoperatively, intravenous hydration was given to titrate to urine output of 0.5 ml/kg/hr , and total intraoperative urine output data was collected. Post-operatively, all patients were admitted to the intensive care unit following CRS and HIPEC for monitoring. Strict fluid balance and urine output monitoring was conducted. Daily blood tests were conducted, including creatinine, urea, and electrolytes. AKI was defined using serum creatinine, GFR and urine output according to the RIFLE criteria (9) (Table I). Estimated GFR (eGFR) was calculated using the CKD-EPI equation. Hypomagnesaemia was defined as serum magnesium $<0.7\text{ mmol/l}$.

Statistical analysis. Descriptive statistics were reported as median (interquartile range) for continuous data, and frequency (percentage) for categorical data. Univariate analysis was undertaken using student's T-tests and Mann-Whitney U-tests for continuous variables or χ^2 and Fisher Exact tests as appropriate. Multivariate

analysis was performed using a logistic regression model to determine risk factors for developing AKI following cisplatin-based HIPEC. The model incorporated significant variables identified on univariate analysis and those which were considered clinically relevant. All p -values were two-sided and values of <0.05 were considered significant. All statistical analyses were carried out in SPSS (release version 26.0; IBM; Chicago, IL, USA).

Results

Patient and surgical characteristics. A total of 111 patients were identified, including 73 (65.8%) women and 38 (34.2%) men. Median age at operation was 51 years old. Primary tumour origins included mesothelioma (36.9%), ovarian (26.1%), gastric (9.9%), sarcoma (6.3%), appendiceal (1.8%) and other (18.9%). Full baseline demographic characteristics are provided in Table II.

Incidence of acute kidney injury. AKI was identified in 15.3% of patients ($n=17$), whilst 84.7% of patients ($n=94$) retained normal baseline renal function following cisplatin-based HIPEC. Of the 17 patients with AKI, 52.9% (9/17) were classified as Risk, 29.4% (5/17) as Injury and 17.6% (3/17) as Failure according to the RIFLE criteria.

Univariate analysis was conducted to determine differences between patients with AKI and patients without AKI (Table III). There were no statistically significant differences in baseline characteristics prior to CRS and HIPEC. Intraoperatively-measured PCI was significantly higher in patients who developed AKI compared to patients without AKI, with median PCI of 22.0 (IQR=16.0-37.0) vs. 15.5 (IQR=7.0-29.3), $p=0.04$. Intraoperative urine output was significantly lower in patients who developed AKI compared to those without AKI, with a median of $1,350.0\text{ ml}$ (IQR=1,000.0-2065.0) vs. $1,770.0\text{ ml}$ (IQR=1,155.0-2,792.5), $p=0.01$. Median post-operative urine output in the first 24 h was also significantly lower in patients with AKI, $2,175.0\text{ ml}$ (IQR=1,420.0-2,988.5) vs. 2800.0 ml (IQR=2,163.0-3,716.3), $p=0.03$.

Median serum urea on day 3 post-operatively was significantly elevated in patients with AKI compared to those without AKI, 6.4 mmol/l (IQR=4.5-10.1) vs. 3.9 mmol/l

Table II. Patient demographics and clinical characteristics.

Variable	All n=111
Pre-operative	
Age at operation (years)	51.0 (39.0-0.0)
Gender	
Female	73 (65.8)
Male	38 (34.2)
Weight (kg)	70.0 (61.0-88.0)
Baseline Cr (umol/l)	65.0 (55.0-76.0)
Baseline Urea (mmol/l)	4.6 (3.5-4.6)
Baseline Mg (mmol/l)	0.8 (0.7-0.9)
eGFR (ml/min/1.73 m ²)	90.0 (82.5-90.0)
Primary tumour origin	
Mesothelioma	41 (36.9)
Ovarian	29 (26.1)
Gastric	11 (9.9)
Sarcoma	7 (6.3)
Appendiceal	2 (1.8)
Other	21 (18.9)
Intra-operative	
PCI	17 (8-30)
Operative time (h)	8.6 (6.6-10.0)
Intraoperative urine output (m)	1,590.0 (1,130.0-2,560.0)
Post-operative	
AKI	17 (15.3)
Urine output first 24 h (m)	2,640.0 (2,085.0-3,618.0)
ICU length of stay (days)	2.0 (2.0-4.0)
Total hospital stay (days)	19.0 (12.0-30.0)

Data expressed as n (%) or median (IQR: interquartile range) unless otherwise stated.

(IQR=2.8-5.0), $p<0.005$. Median serum urea on day 7 post-operatively was also significantly elevated in patients with AKI, 9.6 mmol/l (IQR=5.4-19.8) vs. 3.9 mmol/l (IQR=2.6-5.4), $p<0.005$. Median serum magnesium remained above 0.7 mmol/l in both groups at all time-points. Median serum magnesium on day 3 post-operatively was significantly higher in patients with AKI compared to those without AKI, 0.9 mmol/l (IQR=0.80-0.99) vs. 0.75 mmol/l (IQR=0.66-0.87), $p=0.01$.

Multivariate analysis was performed using direct logistic regression with the factors as per Table IV. None of the included variables were found to be significant predictive factors of AKI in the final model.

Discussion

Cisplatin nephrotoxicity is the result of multiple complex signalling pathways causing proximal renal tubular injury, oxidative stress, inflammation and ischaemic injury (10). Cisplatin can trigger various apoptotic pathways, including

the direct activation of the extrinsic death receptor pathway, the intrinsic mitochondria, and the endoplasmic reticulum stress pathway (4, 11). These induce the production of pro-inflammatory cytokines such as TNF-alpha and IL-1b. Necrosis may also occur secondary to severe toxic injury or the post-apoptotic cellular milieu (10). Evidence suggests high doses of cisplatin results in a predominant necrosis response, whilst lower doses of cisplatin result in dominant apoptosis response (12). Finally, cisplatin may also cause renovascular injury, and contribute to nephrotoxicity through further ischaemic insult to the kidney (10).

The incidence of AKI following CRS and cisplatin-based HIPEC in our study population was 15.3% (17/111), as defined by the RIFLE criteria. Comparison with the literature reveals significant variation in the reported incidence rates of cisplatin-induced AKI. La Manna *et al.* reported the highest incidence of AKI with rates of 88.1% (37/42) (13). Sin *et al.* reported an AKI incidence of 40% (19/47) (14), and Angeles *et al.* found an AKI incidence of 48% (30/66) (15). Hakeam *et al.* reported the lowest AKI incidence in the literature, with rates of 3.7% (2/53) (6). The multiple different criteria used to define AKI in the literature likely contribute to the varying findings. Of note, Maeda *et al.* found urinary biomarkers such as NAG, Kim-1, and NGAL may be more sensitive than serum creatinine in detecting AKI in patients treated with cisplatin (16). Measurement of these urinary biomarkers should be considered in future studies to accurately identify all cases of AKI following cisplatin therapy. Other study factors contributing to heterogeneity in the literature includes differences in HIPEC protocols, cisplatin dosages, and inclusion of multiple primary tumours.

There are multiple well-known patient factors that can potentiate or synergise nephrotoxicity in patients receiving cisplatin-based HIPEC. Potentiating factors may include any cause of AKI, such as hypovolaemia, nephrotoxic medications including ACE inhibitors and IV contrast, or malignant post-renal obstruction (17).

In our study, we found patients with AKI were more likely to have reduced urine output intraoperatively and in the first 24 h post-operatively compared to patients without AKI.

These results are consistent with findings by Angeles *et al.* and Hakeam *et al.* who also demonstrated an association between low intraoperative urine output and AKI (6, 15). Low perioperative diuresis in patients undergoing cisplatin-based HIPEC suggests inadequate intravenous fluid hydration and resultant hypovolaemia. Hypovolaemia exacerbates the nephrotoxic effects of cisplatin by reducing its renal clearance, and further contributes to AKI by also causing reduced renal perfusion. Adequate perioperative hydration has therefore been shown to be an effective renoprotective strategy (18). Schmidt *et al.* found that adequate intraoperative fluid turnover during CRS and HIPEC exceeded the standard 6-8 ml/kg/h suggested

Table III. Comparison between patients with AKI and those without AKI.

Variable	Patients with AKI n=17	Patients without AKI n=94	p-Value
Pre-operative			
Age at operation (years)	53.0 (37.5-64.0)	50.5 (39.0-59.3)	0.74
Female gender	9 (52.9)	64 (68.1)	0.23
Male gender	8 (47.1)	30 (31.9)	0.23
Weight (kg)	76.0 (58.0-95.0)	69.0 (61.0-87.3)	0.56
Baseline Cr ($\mu\text{mol/l}$)	56.0 (50.5-82.0)	66.0 (57.0-75.8)	0.45
Baseline Urea (mmol/l)	4.6 (3.3-5.4)	4.6 (3.5-5.6)	0.80
Baseline Mg (mmol/l)	0.78 (0.69-0.86)	0.80 (0.74-0.87)	0.46
eGFR (ml/min/1.73 m ²)	90.0 (77.0-90.0)	90.0 (83.0-90.0)	0.62
Primary tumour origin			
Mesothelioma	9 (52.9)	32 (34.0)	0.14
Ovarian	4 (23.5)	25 (26.6)	0.79
Gastric	1 (5.9)	10 (10.6)	0.56
Sarcoma	1 (5.9)	6 (6.4)	0.94
Appendiceal	0 (0)	2 (2.1)	-
Other	2 (11.8)	19 (20.3)	0.32
Intra-operative			
PCI	22.0 (16.0-37.0)	15.5 (7.0-29.3)	0.04
Operative time (h)	9.4 (8.2-11.5)	8.5 (6.5-10.0)	0.06
Intraoperative urine output (ml)	1,350.0 (1,000.0-2,065.0)	1,770.0 (1,155.0-2,792.5)	0.01
Post-operative			
Urine output first 24 h (ml)	2,175.0 (1,420.0-2,988.5)	2,800.0 (2,163.0-3,716.3)	0.03
Urea D1 (mmol/l)	5.0 (4.0-6.6)	3.3 (2.7-4.2)	0.05
Urea D3 (mmol/l)	6.4 (4.5-10.1)	3.9 (2.8-5.0)	<0.005
Urea D7 (mmol/l)	9.6 (5.4-19.8)	3.9 (2.6-5.4)	<0.005
Magnesium D1 (mmol/l)	1.1 (0.82-1.21)	0.96 (0.82-1.16)	0.52
Magnesium D3 (mmol/l)	0.90 (0.80-0.99)	0.75 (0.66-0.87)	0.01
Magnesium D7 (mmol/l)	0.77 (0.72-0.87)	0.72 (0.65-0.82)	0.13
ICU length of stay (days)	5.0 (2.0-8.5)	2.0 (1.8-3.0)	0.09
Total hospital stay (days)	30.0 (18.0-52.5)	18.0 (11.0-28.3)	0.05

Data expressed as n (%) or median (IQR interquartile range) unless otherwise stated. Significant p-Values are shown in bold.

for most major abdominal surgeries (19). This is supported by Owusu-Agyemang *et al.*'s findings, who found 6-15 ml/kg/h of fluid administration was required to maintain adequate urine output in paediatric patients undergoing CRS with cisplatin-based HIPEC (20).

Our study also found an association of AKI with higher PCI. Higher PCI is likely related to longer operative time, resulting in a longer duration of time the abdomen is open. An open abdomen with exteriorised bowel causes hypovolaemia, with up to 32 g/m² body surface area/hr or 1 ml/kg/h of fluid loss from evaporation and radiation (21). Additionally, a higher PCI is indicative of higher tumour burden. Higher burden of disease, particularly pelvic disease or tumour which encases the post-renal urinary system, is more likely to contribute to obstructive causes of AKI. Higher PCI therefore may be a surrogate marker of potential pre- and post-renal factors increasing the likelihood of AKI.

Table IV. Multivariate analysis to identify predictive variables for AKI.

Variable	OR (95%CI)	p-Value
Primary gastric cancer	0.36 (0.02-5.60)	0.464
Intraoperative urine output (ml)	1.00 (0.99-1.00)	0.932
PCI	1.00 (0.91-1.09)	0.946
Operative time (h)	0.87 (0.53-1.42)	0.573
Urine output first 24 h post-operative (ml)	1.00 (0.99-1.00)	0.238
Serum magnesium	0.56 (0.14-2.28)	0.416
Hypomagnesaemia ⁺		
Normal		
Urea D3 (mmol/l)	1.12 (0.78-1.62)	0.529
Urea D7 (mmol/l)	1.31 (1.00-1.72)	0.052
ICU stay (days)	1.10 (0.85-1.42)	0.474
Total stay (days)	1.01 (0.96-1.07)	0.615

OR: Odds ratio; CI: confidence interval; PCI: peritoneal cancer index.
⁺Hypomagnesaemia in first 7 days post-operatively; p-value <0.05 was considered statistically significant.

Cisplatin nephrotoxicity is characterised by increased blood urea nitrogen levels as well as electrolyte imbalance such as hypomagnesaemia (4). This was consistent with our findings, which demonstrated increased serum urea on days 3 and 7 post-operatively in patients with AKI. Hypomagnesaemia affects up to 90% of patients and may occur in the absence of AKI (17, 22). We did not find an association between hypomagnesaemia and AKI.

The authors recognise our study has several limitations. The retrospective nature of our study does not account for all confounding factors, and does not allow us to establish a causative relationship. Possible confounding factors that were not collected included methods used to reduce the incidence of AKI such as perioperative intravenous fluids, sodium thiosulfate and cessation of usual nephrotoxic medications (*e.g.* ACE inhibitors, metformin). Use of essential nephrotoxic medications in the first 7 days post-operatively, such as vasopressors, antibiotics, and intravenous contrast were also not collected. Future prospective studies should include data collection on such factors. Additionally, data was collected from a single centre, and hence selective bias may affect our findings. Finally, our data demonstrated a heterogeneous population with multiple primary tumours. This was due to the rarity of disseminated peritoneal disease, however in future studies, analysis should be stratified according to primary tumour.

Conclusion

Cisplatin-based HIPEC is associated with a clinically significant incidence of AKI. Possible risk factors for its development include increased PCI and low perioperative diuresis. The use of a standardised definition of AKI such as the RIFLE criteria allows for better comparison with current evidence. Future prospective studies are needed to better delineate, and therefore address predictive factors for cisplatin nephrotoxicity and ascertain long-term outcomes.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

NA and DM oversaw the collection of data; KC performed statistical analysis and wrote the original draft of the manuscript; KC, RS, JK, NA and DM revised subsequent drafts and approved the final draft for submission. All Authors have read and agreed to the published version of the manuscript.

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Received January 27, 2021

Revised February 8, 2021

Accepted February 9, 2021