Annals of Medicine and Surgery 35 (2018) 163–168

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Acute kidney injury increases the rate of major morbidities in cytoreductive surgery and HIPEC☆

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ARTICLE INFO

Keywords:
CRS and HIPEC
AKI
Major morbidity

ABSTRACT

Introduction: Acute kidney injury (AKI) following cardiovascular surgery has been shown to increase costs and overall morbidity and mortality. The incidence, risk factors, and outcomes of AKI following other types of major surgeries have not been as well characterized. We sought to study the incidence of AKI following cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) per the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Materials and methods: Patients undergoing CRS and HIPEC between 2013 and 2015 were included. Demographic and perioperative data were compared between patients who experienced AKI versus controls using appropriate statistical analysis between categorical and continuous variables. AKI was recorded by a Certified Professional in Healthcare Quality (CPHQ) and defined as a rise in serum creatinine by ≥ 0.3 mg/dL within 48 h (KDIGO criteria).

Results: Fifty-eight consecutive patients undergoing CRS and HIPEC were included. Twelve (20.7%) patients were recorded to develop AKI. This was the most common complication recorded by the CPHQ member. There was one 30-day mortality secondary to cerebral infarction. AKI patients had a longer hospitalization period (14.2 ± 6.9 vs. 9.5 ± 3.3 days, p = 0.002), and a higher rate of major complications (50.00% vs. 15.21%; p = 0.018). Readmission rate was similar (p = 0.626). Multivariate regression identified excessive blood loss during surgery as a major predictor of AKI occurrence, and pre-existing comorbidities and postoperative AKI as predictors of major morbidities following CRS and HIPEC.

Conclusion: AKI following CRS and HIPEC appears to be a common complication which is associated with further major morbidities. Current quality improvement programs may be under-reporting this incidence.

1. Introduction

Acute kidney injury (AKI) has been increasingly recognized as a postoperative complication with potentially serious consequences [1,2]. About 30–40% of surgical patients suffer from AKI in the postoperative setting which is significantly higher than the 5–7.5% seen in all acute care hospitalizations [3]. Moreover, AKI accounts for up to 20% of admissions into intensive care units (ICU) [1,4]. A large proportion of our knowledge of the surgery-related AKI is derived from the cardiovascular literature [3,5] where the occurrence of AKI is estimated to reach 30% and has been associated with increased morbidity and mortality [6,7], higher costs [2], and worse survival [8].

To date, only a handful of studies evaluated the incidence of AKI in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal therapy (CRS and HIPEC) [9–11]. However, kidney injury related to cisplatin, a known nephrotoxic agent, was a major contributor to the occurrence of AKI. Nonetheless, the specific impact of AKI on the surgical outcomes was not assessed.

The lack of uniform measures and varying definitions of AKI has resulted in a wide discrepancy in reporting its postoperative incidence which ranges from 1 to 31% [12]. Since 2004, consensus criteria were developed to define AKI. To provide consistency at our institution, AKI is recorded on all inpatient admissions by a Certified Professional in Healthcare Quality (CPHQ) trained to capture the appropriate data. Whether AKI, as a sequela of CRS and HIPEC rather than an adverse event of the intraoperative chemotherapeutic agent, worsens the short-

☆ All authors have read and approved the manuscript. The authors have no financial disclosures nor conflicts of interest to report. This manuscript is not under consideration elsewhere.

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https://doi.org/10.1016/j.amsu.2018.09.036
Received 16 January 2018; Received in revised form 16 September 2018; Accepted 21 September 2018

and long-term outcomes remains unanswered, mainly due to the lack of well-established risk factors for AKI in the context of CRS and HIPEC surgery.

The scarcity of reports and the opportunity for improved standardization resulting from the international definition of AKI endorsed by Kidney Disease Improving Global Outcomes (KDIGO) in 2012 inspired us to evaluate our incidence of AKI in patients undergoing CRS and HIPEC at our community hospital as one of the complications associated with the procedure. With the aim of evaluating this group of individuals and understanding more thoroughly the risk factors associated with this perioperative morbidity in this patient population.

2. Methods

2.1. Study population

All patients prospectively identified with a variety of primary malignancies with peritoneal carcinomatosis or sarcomatosis that necessitated CRS and HIPEC between June 2013 and July 2015 at our institution were evaluated for inclusion in our study. Patients were excluded from this case cohort if they were identified to have chronic kidney disease as defined by our CPHQ. Our criteria for this diagnosis are established by a constant decrease in the glomerular filtration rate (GFR < 60 ml/min per 1.73 m^2) for > 3 months, irrespective of cause, and was classified into five stages based on the level of GFR according to the KDIGO definition [13]. These data were prospectively maintained under an approved Institutional Review Board (IRB) protocol and listed in the National Clinical Trial registry (NCT02082886).

Patient-specific comorbidities that may hinder renal function in the perioperative period were accounted for such as the established diagnoses of hypertension, diabetes mellitus, cardiac disease, or systemic autoimmune diseases such as systemic lupus erythematous. The presence of any of these conditions would reflect in the patient receiving a Charlson comorbidity score of ≥ 1 as a metric to quantitatively measure the impact of existing diseases on the outcome. The Charlson index assesses patients' risk of 10-year mortality based on existing controlled or uncontrolled chronic illnesses [14,15]. We used the Clavien-Dindo classification system to grade the postoperative complications. Grades I (any deviation from the normal postoperative course without the need for surgical, endoscopic, and radiological interventions, or within the allowed pharmacological treatments) and II (requiring pharmacological treatment with drugs other than such allowed for grade I, blood transfusion, or parenteral nutrition) were regarded as minor complications, whereas grades III (requiring a surgical, endoscopic, or radiological intervention), IV (a life-threatening complication requiring critical care management), and V (mortality) were considered to be major events [16].

2.2. Surgical technique

Our treatment consisted of tumor resection and removal of the involved organs and peritoneum, as deemed safe [17]. HIPEC was performed using the closed abdomen technique at 42–43 °C. Intraperitoneal chemotherapy regimens used included Mitomycin C (40 mg); Cisplatin (45 mg/L) ± Doxorubicin (15 mg/L); or, Melphalan (50 mg/m2). Peritoneal Carcinomatosis Index (PCI) was used to score the extent of peritoneal involvement at the time of surgery as reported in the 13-region and lesion size system [18]. Completeness of cytoreduction score (CC) was reported as CC0 for no residual disease, CC1 for microscopic residual disease (< 0.25 cm), CC2 for macroscopic residual disease (0.25–2.5 cm), and CC3 for gross residual disease (> 2.5 cm).

Our fluid management protocol is applied to maintain end-organ perfusion. Intra-operative fluid management included a continuous baseline infusion of crystalloids, aiming at a urinary output of at least 0.5 cc/kg/hr. If necessary, norepinephrine was started to keep mean arterial blood pressure at ± 20% of baseline values per the anesthesiologist. Arterial blood gas analyses were checked as needed to monitor signs of tissue hypoperfusion and volume trials were initiated if defined urinary output was not achieved and/or signs of impaired microcirculation were present. Post-operative fluid management was goal-directed at urine output of at least 0.5 cc/kg/hr.

2.3. AKI diagnostic criteria

Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI diagnosis are used at our institution per our CPHQ member. Occurrence of AKI was defined as a rise is serum creatinine (sCr) of ≥ 0.3 mg/dL within 48 h of surgery. Laboratory tests, including hematology and basic chemistry panels, were drawn immediately post-operatively and on daily basis until the day of discharge. Since our aim is to examine the immediate impact of AKI on the surgical morbidity, our follow up period was limited to the main admission during which the patients received the CRS and HIPEC.

2.4. Statistical analysis

In this study, the primary endpoint was to describe the AKI incidence in a single institution's cohort of CRS and HIPEC, and its correlation with the occurrence of other major morbidities. Our secondary endpoint was the identification of perioperative factors that would predict the occurrence of AKI. Continuous variables are presented as the means ± standard deviations and were compared using Student's *t*-test, or the non-parametric Mann–Whitney test for 2 groups or using the ANOVA for > 2 groups. Categorical variables are presented as numbers (percentages) and were compared across groups using the χ^2 or Fisher's exact test, as appropriate. All statistical analyses were conducted by IBM SPSS software version 23 for Windows (Armonk, NY: IBM Corp). P values ≤ 0.05 were considered significant statistically. Renal recovery was classified as complete when sCr returned to a level less than 50% above baseline at discharge.

Regarding the power of the study, the initial prediction was that 50–60 patients would be needed to achieve $> 80\%$ power if a predicted 25% of the patients would demonstrate > 0.3 mg/dL change in their baseline creatinine within 48 h of surgery compared to the non-AKI patients. The estimated percentage of AKI occurrence was derived from the published literature addressing AKI occurrence following major surgical intervention.

3. Results

The initial fifty-eight consecutive patients who underwent CRS and HIPEC and met the inclusion criteria between June 2013 and July 2015 at Edward Hospital were included in this study. After collecting data on 58 patients between June 2013 and July 2015, we documented that 20% of the sample's (12 patients) creatinine drifted into the AKI range (≥ 0.3 mg/dL within 48 h of surgery). The change in the creatinine between the baseline and postop values (within 48 h post-operatively) in the AKI group was 0.52 ± 0.46 compared to the non-AKI group which was 0.13 ± 0.15 (N = 46). The calculated power of our study as reported in the fifty-eight patients was 82.6%, thus deemed satisfactory for further statistical analysis. None of the reported patients had an underlying chronic kidney disease at the time of the CRS and HIPEC. Their characteristics are summarized in Table 1. There were 39 females (67.2%) and 19 males (32.8%). Baseline serum creatinine was 0.81 ± 0.27 (range, 0.29–1.5). Mean BMI was 28.76 ± 7.43 (range, 18–49). Thirty-three patients (56.9%) had a Charlson score ≥ 1. Mean PCI was 17.91 ± 9.12 (range, 0–39). Complete cytoreduction (CC0/1) was achieved in 48 patients (82.7%). The mean length of stay (LOS) was 10.47 ± 4.53 days (range, 5–33). Our CPHQ recorded morbidity in 30 (51.7%) of patients; AKI was the most common and occurred in 12 (20.7%) of patients. Other adverse events included infection/sepsis