The potential effect of iopamidol contrast on renal function in patients infected with SARS-CoV-2 virus: A retrospective cohort study

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ABSTRACT

Background: Many types of computed tomography (CT) scans require the use of contrast. Acute kidney injury (AKI) is a known adverse effect of intravenous contrast administration. To our knowledge, the effects of low-osmolar contrast agents such as iopamidol on renal function in patients infected with the SARS-CoV-2 virus have never been studied. This study investigates the incidence of AKI following iopamidol contrast administration in patients infected with the SARS-CoV-2 virus.

Methods: This retrospective cohort study included two groups: patients who received CT pulmonary angiography who were infected with SARS-CoV-2 virus and those who tested negative for SARS-CoV-2. Data were collected from the electronic medical record of a single hospital from January 1, 2020, to September 15, 2020. AKI was defined using the Kidney Disease: Improving Global Outcomes definition: increase in serum creatinine by ≥0.3 mg/dL (≥26.5 mcmol/L) within 48 h, or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or urine volume <0.5 mL/kg/h for 6 h.

Results: AKI occurred in 13.51% of patients in the SARS-CoV-2 positive group and 16.92% of patients in the negative group. Using a two-sample test to compare the equality of proportions (with continuity correction factor), we found there is no significant difference in the two proportions (P = 0.3735).

Conclusion: There was no significant difference in the incidence of AKI between SARS-CoV-2 positive and negative groups. Given the limitations of this study, further work must be done on this topic.

Key Words: Acute kidney injury, contrast, COVID-19, iopamidol, severe acute respiratory syndrome-coronavirus-2

INTRODUCTION

Computed tomography (CT) is one of the most commonly administered diagnostic tests in the United States. Health-care providers must decide whether to order either oral or intravenous contrast when referring patients for a CT scan. There are some known side effects of iodinated intravenous contrast that are routinely explained to patients when obtaining consent for such a test. These side effects include, but are not limited to,
nausea, vomiting, headache, hives, and importantly contrast-induced nephropathy. Acute kidney injury (AKI) in hospitalized patients is a major contributor to morbidity and mortality across the world. Thus, it is important to decrease the incidence of contrast-induced nephropathy to improve patient outcomes. Optimization of patients receiving intravenous contrast includes intravenous hydration, sodium bicarbonate, withholding of nephrotoxic agents, and use of low or iso-osmolar contrast media.

Patients with a history of severely impaired baseline kidney function and those with AKI have an increased risk of contrast-induced nephropathy following the administration of intravenous contrast. The current guidelines suggest that patients with normal or mild to moderately impaired kidney function, i.e., an estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73 m², do not require any special precautions before CT with contrast. If a patient has a GFR <30 mL/min/1.73 m² or has AKI, they may be at risk for contrast-induced nephropathy. The exception to this guideline is if a patient is anuric and on chronic hemodialysis, in which case contrast would not be contraindicated.

All modern intravenous contrast used for CT is iodine-based. There are three broad classifications of iodine-based contrast media: low-osmolality contrast media, iso-osmolality contrast media, or high-osmolality contrast media. High-osmolality contrast is no longer in use today due to deleterious effects such as vasodilation, increased heat production, and pain. Both low and iso-osmolality contrasts are still regularly used in hospitals. Low-osmolality contrast is approximately 600–850 mOsm/kg H₂O, whereas iso-osmolality contrast is approximately 290 mOsm/kg H₂O. Thus, low osmolality agents are “low” when compared to high osmolality agents but have a higher osmolality when compared with plasma. Low-osmolality contrast agents include iohexol, ioversol, and iopamidol. Only one iso-osmolar agent is currently available for use: iodixanol.

It has been hypothesized that iso-osmolar agents may have a decreased risk in regards to AKI when compared with low-osmolar agents. There is at least one study from 1991 that demonstrated that the ionic low-osmolar agent ioxaglate was less toxic when compared with ionic hyperosmolar agents. A meta-analysis published in the *Annals of Internal Medicine* in 2016 included 25 randomized trials comparing the iso-osmolar iodixanol with a diverse group of low-osmolar agents. This study reported a modest reduction in AKI risk with iodixanol. It is debatable how clinically meaningful this risk reduction is, even though it was marginally statistically significant.

Individuals infected with SARS-CoV-2 have many abnormalities across multiple organs, which are the subject of ongoing study worldwide. The novel SARS-CoV-2 virus is hypothesized to cause a hypercoagulable state and autopsies of some individuals have demonstrated microvascular thrombosis including renal capillaries. The effects of low-osmolar contrast agents such as iopamidol on renal function in patients infected with the SARS-CoV-2 virus have never been studied. Our study aims to explore the potential impact of the SARS-CoV-2 virus on kidney function. Given the limited previous research on this topic, we hope this study will provide some insight into the impact of the SARS-CoV-2 virus and how to better optimize this patient population in the future before undergoing key diagnostic tests such as CT pulmonary angiograms. We hypothesize that patients infected with the SARS-CoV-2 virus receiving the intravenous contrast iopamidol have an increased risk of developing AKI. As such, the objective and aim of this study are to determine if infection with the SARS-CoV-2 virus is a risk factor for AKI in patients receiving iopamidol contrast.

**METHODS**

This retrospective cohort study was initially presented to the local Institutional Review Board (IRB). The study was approved by the IRB, which granted a waiver of consent. To test our hypothesis, the retrospective cohort study was then performed on adults hospitalized at St. Joseph’s Medical Center Stockton, California. Iopamidol is currently the contrast agent used for all patients at St. Joseph’s Medical Center for CT angiography. This study was limited to those receiving CT pulmonary angiography to control for variation in contrast volume used for the various indications of radiocontrast CT.

An initial list was obtained from the St. Joseph’s Medical Center radiology department, which included all adult patients who received iopamidol contrast between January 1, 2020 and September 15, 2020. The initial list was derived from information accessed in Cerner® (Cerner Corp., North Kansas City, USA). All patients who specifically received CT pulmonary angiography were selected for further analysis. Upon obtaining this list, a preliminary review was used to place patients into two cohorts for comparison: adults with confirmed infection of the SARS-CoV-2 virus and adults that tested negative for SARS-CoV-2. A total of 78 patients were in the SARS-CoV-2 positive group for the given timeframe, which determined our sample size. A random number generator was then used to select patients from the SARS-CoV-2 negative group who also received iopamidol contrast for CT pulmonary angiography. A total of 75 patients were in this group.

Using patient’s medical record numbers, charts were accessed in Cerner® (Cerner Corp., North Kansas City,
Data were collected directly from the electronic health record in a categorical, yes or no fashion (yes AKI vs. no AKI). The use of predetermined inclusion and exclusion criteria was used to control for confounding variables. Confounding factors that were considered included age, diabetes, chronic kidney disease (CKD), and certain medications. These confounding factors were used to develop exclusion criteria, which included: anuric patients, patients with CKD requiring hemodialysis, or patients with diabetic nephropathy. Patients who received the following medications within 24 h of their contrast study were also excluded from the study, as these medications are known to alter kidney function: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs).[16,17] Furthermore, patients with known intrinsic renal vascular disease including thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and scleroderma were also excluded. Those with atheroembolic disease, malignant hypertension, known intrinsic glomerular disease, or obstructive nephropathy were also excluded. Finally, patients with incomplete or missing data were excluded.

Once patients who met exclusion criteria were eliminated, basic demographic information was obtained. Such information included patient’s age, length of hospital stay, admission location, and gender [Table 1]. Additional information regarding patient disposition following hospitalization was also collected [Table 2]. Furthermore, patient’s baseline health status was investigated by calculating the Charlson Comorbidity Index (CCI). All patient’s admission history and physical notes were used to calculate the comorbidity index. Similarly, admission notes were used to calculate the National Early Warning Score (NEWS) and assess illness severity. Patient’s data were subsequently de-identified, organized, and sent to a hospital statistician for analysis.

RESULTS

Initially, 78 patients were screened for contrast nephropathy in the SARS-CoV-2 positive group and 79 patients were screened in the negative group. Of note, a handful of patients did not have repeat laboratories after receiving iopamidol contrast. This included two patients in the SARS-CoV-2 positive group and 24 of the SARS-CoV-2 negative group. This data was considered incomplete, and the patients were not included in the study. A random number generator was used on the remaining uncollected data to replace these patients in the control group. This additional data contained ten patients without repeat laboratories after receiving contrast of which were subsequently excluded from the final data set.

After initial screening, a total of four patients were excluded from the SARS-CoV-2 positive group based on our exclusion criteria: two patients had end-stage renal disease (ESRD) on hemodialysis, one patient received lisinopril, and one patient received ibuprofen within 24 h of CTA. A total of ten patients were excluded from the SARS-CoV-2 negative group: two patients had ESRD on hemodialysis, five patients received lisinopril, two patients received losartan, and one patient received NSAIDs within 24 h of CTA. The final sample sizes were 74 patients for the SARS-CoV-2 positive group and 65 for the SARS-CoV-2 negative group.

Upon initial analysis of the data, ten of the 74 patients (13.51%) in the SARS-CoV-2 positive group had an AKI, as defined by KDIGO criteria. AKI also occurred in eleven of the 65 patients (16.92%) in the

| Table 1: Intergroup comparison of demographic information including age, length of hospital stay, admission location, and gender |
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| **Groups** | **Age (Years)** | **Average Length of Hospital Stay (Days)** | **Admission Location** | **Gender (Male/Female)** |
| SARS-CoV-2 Positive | 56.3 ± 15.8 | 12.6 ± 9.8 | 51 Wards | 31 Female/43 Male |
| SARS-CoV-2 Negative | 62.8 ± 17.9 | 8.9 ± 5.2 | 48 Wards | 40 Female/25 Male |

ICU: Intensive care unit, ED: Emergency department, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

| Table 2: Comparison of patient disposition following hospitalization including SNF, Home/Self-Care, Home Health, Hospice, Transferred to Another Hospital, Expired, or LTAC Facility |
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| **Groups** | **SNF** | **Home Self-Care** | **Home Health** | **Hospice** | **Another Hospital** | **Expired** | **LTAC Facility** |
| SARS-CoV-2 Positive | 7 | 39 | 3 | 1 | 1 | 19 | 4 |
| SARS-CoV-2 Negative | 11 | 39 | 6 | 1 | 2 | 6 | 0 |

SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2, SNF: Skilled nursing facility, LTAC: Long term acute care facility
It was theorized that the contrast agent for CT pulmonary angiography study. The original hypothesis was that COVID-19 patients would have an increased risk of contrast nephropathy after exposure to iopamidol contrast. Our findings indicated that there was no significant difference in the incidence of contrast nephropathy between the control group and the COVID-19 group. Based on the findings of our study, it appears that there is not a significantly increased risk of contrast nephropathy among COVID-19 patients.

COVID-19 patients are at an increased risk for thrombosis, with an increased risk of both microvascular and larger thrombus formation and AKI is also associated with severe cases of COVID-19. It was theorized that the nephrotoxic effects of contrast agents combined with the increased risk of AKI in COVID-19 patients would lead to an increased risk in contrast nephropathy in COVID-19 patients. The results of our study do not support this conclusion, but our study also had fairly low power. This warrants further study into the risk of contrast nephropathy on COVID-19 patients, especially not only because of the low power of our study but also because we focused on just one type of contrast agent.

It would be difficult to assess the external validity of our study, especially given the limited pool of COVID-19 patients we were able to select from. Various demographic factors were not possible to control in the formation of our experimental group since, after exclusion criteria, we only had a relatively narrow group of COVID-19 patients who had received iopamidol contrast agent for CT pulmonary angiography study.

**Future study directions**

Although the results showed no significant difference, this study can be improved in future analyses. To increase the power of this study, a larger sample size derived across multiple hospital systems could be beneficial. The current study was examining a single 355-bed hospital, thus contributing to the low sample size. A multicenter trial would also provide the benefit of increasing the external validity of our study.

In addition, considering the possibility of low statistical power with categorical data, we propose proceeding with numerical data. Of the patients that did have an AKI following iopamidol contrast, data could be re-analyzed with a focus on the change of creatinine from baseline and/or highest absolute creatinine value. Not only would this provide our study with increased statistical power, but it would also allow for a deeper analysis. More specifically, a change in creatinine could be used to compare the severity of AKI in these patients. Such data would give further insight into the effects of iopamidol contrast in patients affected with SARS-CoV-2.

In the current study, the only CKD patients that were excluded were those who had ESRD and required hemodialysis. Due to CKD being an established clear risk factor for AKI, to increase the internal validity of this study, patients with CKD can be excluded from the study or stratified into a separate group. Furthermore, the clinical severity of patients in the SARS-CoV-2 positive group varied greatly. Some patients in this group required minimal amounts of supplemental oxygen, whereas others were critically ill. Therefore, it would also be beneficial to stratify these patients into different groups. Given that some of the COVID-19 patients were critically ill and commonly admitted to the intensive care unit (ICU); in future studies, it would be the best to select control group patients who are similarly admitted to the ICU to further control for confounding factors related to a patient being in a critically ill condition.

**CONCLUSION**

There was no significant difference in the incidence of AKI between the SARS-CoV-2 positive and negative groups. However, with the limitations of this study, further work must be done to determine the implications of these findings. Future directions may include numerical data, larger sample sizes, and/or stricter inclusion and exclusion criteria. While these limitations may have affected the outcome of our results, the importance of the study remains. Understanding the effect of SARS-CoV-2 infection on the incidence of AKI following iopamidol contrast will surely alter the management of such patients.

**Research quality and ethics statement**

This study was approved by the Institutional Review Board/Ethics Committee at St. Joseph’s Medical Center (Approval No. CANV DHRB-2020-640; Approval date September 26, 2021). The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the STROBE Guidelines, during the conduct of this research project.
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Conflicts of interest
There are no conflicts of interest.

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