Fenoldopam use during Cardiopulmonary Bypass and Postoperative Rates of Acute Kidney Injury

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Objective: Acute kidney injury (AKI) is a complication following heart surgery that is associated with increased morbidity and mortality. Fenoldopam is a dopaminergic receptor agonist that has been successful in the prevention of cardiac surgery–associated AKI. We hypothesized that fenoldopam started preoperatively would reduce the risk of AKI in patients with chronic kidney disease (CKD), stage 3 or higher.

Methods: We conducted a retrospective study of adult patients admitted from 2015 to 2019 for cardiac surgery requiring cardiopulmonary bypass (CPB). Fenoldopam was started in the operating room 1 to 2 hours before the procedure and continued for up to 16 hours post-CPB at a rate of 0.3 mcg/kg/min. The primary outcome was the incidence of postoperative AKI with or without fenoldopam.

Results: A total of 203 patients with CKD stage 3 or higher were examined in this study, 35.5% of whom received fenoldopam. Of the patients who received fenoldopam, 41.67% developed AKI compared to 38.17% of those without fenoldopam. Being female had a small protective effect against AKI (OR 0.233, CI 0.108–0.502), as did having an adequate hematocrit level prior to surgery (OR 0.921, CI 0.871–0.974). Analysis revealed that a hematocrit level of 37.18% indicated anemia in the study population.

Conclusion: While the administration of fenoldopam prior to CPB in patients with CKD stage 3 or higher did not significantly reduce AKI after cardiac surgery or significantly reduce length of stay, possible renal protective properties were identified. Being female and having an adequate preoperative hematocrit level were identified as possible investigative points for future studies.

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Key words: Cardiac surgery, Pharmacotherapy, Cardiology

Acute kidney injury (AKI) is a complex clinical syndrome with a spectrum of clinical manifestations and outcomes (1); characterized by the deterioration of renal function over a period of hours to days, resulting in the failure of the kidney to eliminate nitrogenous waste products and to maintain fluid and electrolyte homeostasis (2). The Acute Dialysis Quality Initiative group developed a definition for AKI based on risk, injury, failure, loss of kidney function, and end-stage kidney disease, collectively known as the RIFLE criteria, which classify the stages of AKI disease (3,4).

The frequency of AKI among hospitalized patients is approximately 25%; however, it can reach 50% in adult patients who undergo cardiac surgery (8,9). Acute kidney injury has been noted to be associated with increased length of stay, admission to the intensive care unit, and a 2-fold increase in mortality (8,10). Vives et al (11) proposed that postoperative AKI is complex and multifactorial and that interventions relying on serum creatinine levels are often initiated too late.

Pharmacological and non-pharmacological interventions aimed at preventing postoperative AKI have been previously described. Pharmacological interventions to prevent cardiopulmonary bypass (CPB)-associated AKI have had limited success, whereas there are generally accepted non-pharmacological interventions. The non-pharmacological interventions, largely surgical and protective techniques, include the timing of transfused blood, maintaining baseline preoperative hemoglobin/hematocrit levels, and using pulsatile CPB (11). Current pharmacological interventions include the use of angiotensin-converting enzyme inhibitors, aspirin, statins, dexmedetomidine, erythropoietin, and diuretics (11). More commonly studied interventions are the use of N-acetylcysteine, dopamine, and fenoldopam (11–14).

Dopamine is believed to increase renal perfusion and glomerular filtration via stimulation of dopaminergic receptors in the kidney. However, dopamine does not always increase renal perfusion or glomerular filtration rate (GFR) when used in CPB patients (14). Fenoldopam is a potent dopamine-1 (D1)-specific agonist that selectively induces renal vasodilation and is 6 times more potent than dopamine at the D1 receptor (14,15). Fenoldopam works on the peripheral D1 receptors located in the kidneys to inhibit sodium-potassium adenosine triphosphatase (16,17). Theoretically, increased renal vasodilation enhances renal blood flow, glomerular filtration, and the renal oxygen supply. Fenoldopam can decrease peripheral vasculature resistance and

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increase urine flow rate and sodium excretion. The trials included in these analyses evaluated fenoldopam administration near the end of surgery or postoperatively, in the intensive care unit, but limited data exist regarding fenoldopam use prior to the initiation of CPB (17).

Given the pharmacokinetics and dynamics of fenoldopam, we endeavored to evaluate the potential of fenoldopam to reduce AKI when administered prior to CPB. We hypothesized that the use of fenoldopam, in addition to the usual care, would reduce the incidence of AKI after open-heart surgery (with CPB) in patients at increased risk for postoperative kidney injury (CKD stage 3 or higher) more than would standard care alone.

Materials and Methods

Study design, Participants, and Data collection

We conducted an institutional review board (IRB)–approved retrospective study of adults admitted to an HCA Healthcare hospital and who underwent cardiac surgery and utilized CPB from 2015 through 2019. The included patients underwent propensity matching for the control and intervention groups. Patients considered at increased risk for AKI, defined as those with preoperative baseline CKD stage 3 or higher and a GFR of 60 mL/min/1.73m^2 or lower, were initially included. A sub-group of this population had received intravenous fenoldopam at a rate of 0.3 µg/kg/min. The infusion was initiated in the operating room 1 to 2 hours prior to CPB. The control population consisted of patients with baseline CKD stage 3 or higher who had a creatinine result from the same admission but before the day of surgery. In contrast, the fenoldopam population included patients who had had a creatinine test within 14 days of the surgery if they did not have one during the admission before the day of surgery. The AKI risk was calculated using the RIFLE criteria, defined as a 50% increase in creatinine or 1.5 times the baseline value, comparing the preoperative creatinine closest to surgery and the highest creatinine within 2 weeks of having undergone surgery.

Patients under the age of 18 years; on hemodialysis, peritoneal dialysis, or continuous renal replacement prior to surgery; who met the definition of shock entering the operating room or undergoing surgery for aortic dissection repair; or with a known allergy to fenoldopam mesylate were excluded from the study. After applying the exclusion criteria, 203 patients were identified and their data extracted from a large multi-institutional database (HCA Enterprise Data Warehouse) and cross-matched with the local pharmacy database. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems codes were used to query the dataset. This study received an IRB exempt determination (#2019-428).

Data analyses

The primary endpoint of this study was the development of AKI, postoperatively. We sought to examine whether fenoldopam provided protection from AKI after open-heart surgery using CPB. The data were analyzed using SAS 9.4 (SAS Institute, Cary, NC). Logistic regression was used to predict the odds of association between AKI and factors including age, sex, the use of fenoldopam, hematocrit levels before surgery, and GFR in the population. Chi-square and Fisher's exact tests were used to analyze the associations between the categorical variables. The categorical variables were summarized using frequencies and percentages, while descriptive statistics for continuous variables included the mean (± standard deviation). An alpha level of .05 was used to define the type I error rate. Results showing a P value lower than .05 were considered statistically significant for analyses.

Results

We obtained information on 203 patients (Table 1), treated from 2015 through 2019, who had CKD stage 3 or higher (mean GFR of 47.5 ml/min/1.73m2 ± 9.7). There was a disproportionately higher percentage of males in the fenoldopam group than in the control group. Collectively, these patients had a mean preoperative creatinine of 1.51 mg/dL (±0.4), and preoperative hematocrit of 37.9% (±5.8). These patients spent a mean of 9 (±4.8) days in the hospital and had a mean postoperative creatinine of 1.79 (±0.8) mg/dL.

Table 1. Demographic description of the total population

Characteristic (n)	n = 203
Age (yr) (mean ± SD)	70.2 ± 7.6
Male	142
Female	61
Race	
Black	9
White	193
Other	1

The descriptive characteristics of the fenoldopam group (n = 72) and control group (n = 131) are shown in Table 2.

Preoperative hematocrit levels in patients without AKI were approximately 1% to 3% higher compared to those with AKI, as noted in Table 2. Age, GFR, and preoperative AKI were similar in all the groups (Table 2). Of the patients treated with fenoldopam, 41.7% (30/72) were found to have an AKI compared to 38.2% (50/131) who did not receive fenoldopam (Table 2 and Figure 1). Figure 1 highlights the differences in characteristics in the population. The population was made up mostly of males, who are believed to have lower rates of postoperative AKI compared to females.

Table 3 shows the descriptive statistics for patients with and without postoperative AKI. Patients who developed AKI were more likely to be male, have lower preoperative hematocrit levels, and have longer postoperative lengths of stay (Table 3). Patients with AKI had hospital stays that were 11.1 (±5.8) days longer than those without AKI, who had stays of 8.2 (±3.9) days. Patients treated with fenoldopam did experience shorter hospitalizations (approximately 1 day shorter), but this was not statistically significant.

Table 2. Descriptive statistics of variables considering the administration of Fenoldopam for the total population

Fenoldopam administration	Yes	No
Patients, n	72	131
By Sex		
Male	65	77
Female	7	54
By Diuretic		
Yes	67	105
No	5	26
By Pre-op CAD		
Yes	48	73
No	24	58
By Pre-op Dyslipidemia		
Yes	50	99
No	22	32
By Pre-op Unspecified Renal Failure		
Yes	32	49
No	40	82
Patients with AKI		
Age (yr) (mean ± SD)	71 ± 7	68 ± 9
Relative Discharge Day	9.6 ± 4.7	11 ± 5.8
GFR (mL/min/1.73m2)	49.5 ± 6.8	45.1±10.0
Pre-op Creatinine (mg/dL)	1.5 ± 0.2	1.63 ± 0.5
Post-op Creatinine (mg/dL)	2.0 ± 0.7	2.2 ± 1.1
Pre-op Hematocrit (%)	37.9 ± 5.5	35.9 ± 5.7
Patients without AKI		
Age (yr) (mean ±SD)	72 ± 5	70 ± 8.0
Relative Discharge Day	7.4 ± 4.4	8.2 ± 3.9
GFR (mL/min/1.73m2)	46.2 ± 10.8	49.0 ± 9.5
Pre-op Creatinine (mg/dL)	1.6 ± 0.56	1.4 ± 0.3
Post-op Creatinine (mg/dL)	1.7 ± 0.7	1.5 ± 0.4
Pre-op Hematocrit (%)	38.3 ± 5.8	39.1 ± 5.7

Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; GFR, glomerular filtration rate; pre-op, preoperative
Relative discharge day: patient's length of stay in days; post-op creatinine: postoperative creatinine (highest creatinine level within 14 days, post-surgery)

Table 4 shows the output for the logistic regression for AKI, calculated with age, sex, fenoldopam, hematocrit level, and GFR as covariates. Fenoldopam was not a significant predictor of AKI in the regression (Table 4). Instead, females had 4.3-fold lower odds of having an AKI (odds ratio [OR] 0.233, CI [0.108–0.502]; P value = .0002). In addition higher preoperative hematocrit levels (OR 0.921, CI [0.871–0.974]; P = .004) provided some protection from postoperative AKI after cardiac surgery (Table 4).

Our breakpoint for determining anemic versus non-anemic patients was a hematocrit level of 37.18%. For patients who developed AKI, baseline hematocrit levels were lower compared to those of patients who did not develop AKI (Table 2). Figure 2 illustrates the breakdown of patients (by sex) who were considered anemic versus non-anemic.

Discussion

Based on our retrospective analysis of data from 203 patients who underwent CPB surgery, the infusion of fenoldopam at a rate of 0.3 mcg/kg/min starting just before surgery did not reduce the postoperative rate of AKI in patients with CKD stage 3 or higher. Patients who did not receive fenoldopam had an incidence of AKI of 38.2% compared to 41.7% in fenoldopam-treated patients, a difference that was not statistically significant. Fenoldopam was also not a significant predictor of AKI in our logistic regression. The incidence of AKI in our study was somewhat higher than has appeared in recent reports. Cogliati et al reported an average AKI incidence rate of 30% in all their patients who underwent CPB (18). The higher rate of AKI in our series likely reflects the use of a 50% deflection in creatinine as the metric for AKI, as well as the increased-risk population we chose to study.

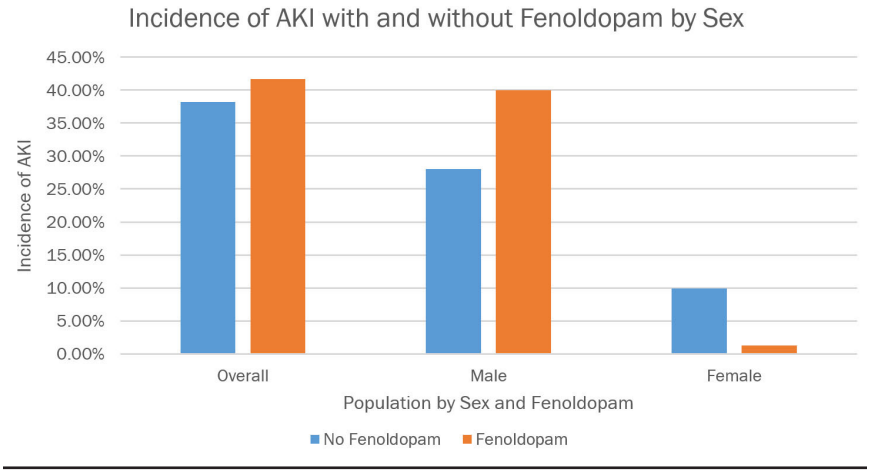
Given that fenoldopam has been reported to increase blood flow in the cortical and medullary areas of the kidney (17,18), the thought was that the timing of the intervention would impact outcomes. Peak fenoldopam response is observed within 15 minutes of initiating the drip, with effects continuing for 60 minutes after the drip has been discontinued (19,20). If administered later during the operation, peak onset may not have time to substantially increase blood flow. If administered prior to the operation as a continuous infusion, the thought was, outcomes would be improved if blood flow was increased for as long as possible.

Previous studies, such as the one completed by Bove et al, used different endpoints to determine their efficacy (14). For example, those studies used a 25% increase in serum creatinine as their definition of AKI, whereas our study used a 50% increase in serum creatinine. Rates of infusion are another noted difference between our study and others that have been completed. Some studies used 0.05 mcg/kg/min as their infusion rate.

Fenoldopam remains an intriguing and theoretically plausible therapeutic agent with regard to renal protection. As a selective dopaminergic receptor agonist, fenoldopam can increase glomerular filtration, a mechanism that can minimize tubular slugging after an ischemic insult, provided it does not increase oxidative stress (21). Adequate blood volume must be maintained through fluid administration, similar to the approach used in the diuretic renal-clamp method for mitigating AKI. Unfortunately, our small retrospective study did not adequately control for the multifactorial nature of cardiac surgery-associated AKI, including factors such as time on CPB, blood and fluid administration, and the administration of diuretics and other nephrotoxic agents.

The findings on the utility of fenoldopam are inconclusive. In a meta-analysis of 6 randomized controlled studies, Gillies et al reported that fenoldopam was associated with a significant reduction in AKI after surgery; however, there was no impact on renal replacement therapy or hospital mortality (21). There are published studies in support of this, with 1 randomized controlled study on 667 patients revealing that fenoldopam treatment resulted in a higher incidence of hypotension (22). Another meta-analysis reported that fenoldopam was beneficial in reducing AKI, the

Figure 1. Incidence of AKI patients with and without Fenoldopam by sex



need for renal replacement therapy, length of stay, and mortality in critically ill patients; however, it was limited by the inclusion of both surgical and nonsurgical patients (21,23).

The condition known as CSA-AKI has multiple etiologies, including microembolization, neurohormonal activation, preoperative metabolic abnormalities, and ischemia-related injury (11). Described risk factors include advanced age, female sex, diabetes, lower GFR, preoperative anemia, hypothermia during surgery, red blood cell transfusion during surgery, aortic cross-clamp time, and the duration of the CPB. The median or lowest hematocrit level during surgery is a widely known and accepted risk factor for AKI in patients undergoing CPB surgery. Although females may be at increased risk for hemodilution due to smaller blood volumes and are therefore traditionally thought to be more likely to suffer from AKI, our study suggests that a low rate of AKI in females could be protective. This is consistent with emerging evidence regarding lower rates of AKI in female CPB patients (24,25). In a retrospective study, Mehta et al (28) found that females had decreased rates of AKI and mortality, perhaps due to better tolerance of hemodilution while on CPB (26). One theory that has been mentioned to explain the difference in the sexes is adaptive mechanisms. It has been proposed that females can tolerate lower hemoglobin and hematocrit levels better than males can due to adaptations linked to cyclic blood loss through menstruation (26). These adaptations may involve increased levels of 2,3 diphosphoglycerate in the blood of females, which could enhance the capacity of these patients to tolerate lower hemoglobin and hematocrit levels. This compound competes with oxygen for binding to hemoglobin (26). Past literature has shown that women with high amounts of 2,3 diphosphoglycerate in circulation could allow for greater delivery of oxygen to tissues (26).

Finally, there is not a consensus about the benefits of using fenoldopam in cardiac surgery with CPB for kidney protection. While there are studies showing the advantages of its use (27),

Table 3. Descriptive statistics of different variables considering patients with AKI versus those without AKI for the total population

Postoperative AKI Status (n)	Yes	No
Patients	80	123
By Sex		
Male	66	76
Female	14	47
By Race		
Black	5	4
White	75	118
Other	0	1
By Pre-op Diuretic		
Yes	71	101
No	9	22
By Pre-op CAD		
Yes	49	72
No	31	51
By Pre-op Dyslipidemia		
Yes	55	94
No	25	29
By Unspecified Renal Failure		
Yes	40	41
No	40	82

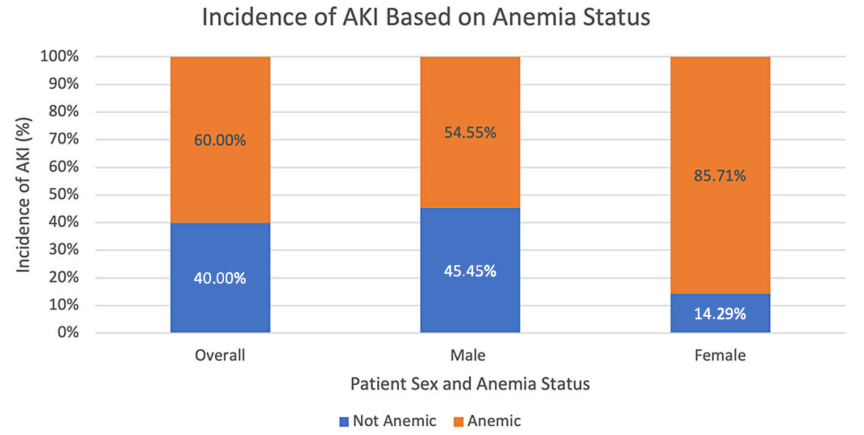
All diagnoses present on admission.

Table 4. Odds ratio (AKI) with Age, Sex, Fenoldopam, Hematocrit Before Surgery, and GFR as Covariates

AKI diagnosis	OR	95% CI	P Value
Age (yr)	0.964	0.925–1.004	.07
Sex (F vs M)	0.233	0.108–0.502	.0002
Fenoldopam (No vs Yes)	1.189	0.618–2.286	.60
Hematocrit	0.921	0.871–0.974	.004
GFR	0.987	0.955–1.020	.44

Abbreviation: OR, odds ratio

Figure 2. Incidence of AKI base on anemia status



there are still others that show inconsistent data on this drug (28). Further studies should be considered in order to clarify these points.

Limitation

The first limiting factor was that this was a retrospective study, and some data could not be retrieved, limiting our sample population. We were also not able to differentiate the types of cardiac surgery our patient population had undergone. Some studies reported that valvular su rgery had a higher risk of AKI than did a coronary artery bypass graft (29). Our study was also limited in that it looked only at stage 1 AKI (based on the RIFLE criteria). We were unable to evaluate severe AKI and so unable to extrapolate whether fenoldopam was able to reduce AKI in severe cases. We also had limited information regarding the number of units of red blood cells transfused, whether hypotension occurred, and aortic cross-clamp time during surgery. We were also unable to extrapolate postoperative urine output in the fenoldopam and control groups. Thus, although we were not able to demonstrate a generalized utility of fenoldopam in patients with CKD stage 3 or higher, a more focused and better controlled randomized trial of fenoldopam may be useful. Male patients with very low GFR, anemia, and adequate perioperative fluid repletion may demonstrate a benefit in a carefully controlled study.

Conclusions

In our retrospective analysis of patients with CKD stage 3 or higher, fenoldopam did not have a significant impact on renal function. There was no difference in postoperative renal function, nor did this medication affect length of stay during hospitalization. There did appear to be possible protective factors, including being female, which may be due to a better tolerance of hemodilution while on CPB and higher baseline hematocrit levels prior to surgery. Baseline hematocrit levels should be maximized prior to open-heart surgery, and special considerations should be taken to evaluate female patients. Further studies are needed to justify the use of fenoldopam in patients undergoing cardiac surgery.

Resumen

La lesión renal aguda (LRA) es una complicación después de una cirugía cardíaca asociada con una mayor morbilidad y mortalidad. Fenoldopam es un agonista del receptor dopaminérgico que tiene éxito en la prevención de la LRA asociada a la cirugía cardíaca. Presumimos que el fenoldopam iniciado antes de la operación reduciría el riesgo de LRA en pacientes con enfermedad renal crónica (ERC) en estadio avanzado. Realizamos un estudio retrospectivo de pacientes adultos ingresados entre 2015 y 2019 para cirugía cardíaca que requirió bypass-cardiopulmonar. El fenoldopam se inició en el quirófano una o dos horas antes del preoperatorio y se continuó hasta 16 horas después de la bypass-cardiopulmonar a una velocidad de 0.3 μg /kg/min. La variable de resultado principal en este estudio fue la incidencia de LRA posoperatoria con o sin fenoldopam. En este estudio se examinó a un total de 203 pacientes con ERC en estadio tres o superior, de los cuales el 35.5% recibió fenoldopam. Entre los pacientes que recibieron fenoldopam, el 41.67% desarrolló LRA en comparación con el 38.17% sin fenoldopam. Las mujeres (razon de momios (RM) 0.233, intervalo de confianza [IC] 0.108–0.502) y hematocrito adecuado antes de la cirugía (RM)0.921, IC 0.871–0.974) parecieron tener un pequeño efecto protector contra la LRA. El análisis reveló un hematocrito del 37.18% para determinar el estado de anemia en la población de estudio. La administración de fenoldopam antes de la bypass-cardiopulmonar, a pacientes con ERC III o superior, no redujo significativamente la LRA después de la cirugía cardíaca. Fenoldopam tampoco se asoció con una mejora significativa en la duración de la estancia hospitalaria. El sexo femenino y un hematocrito preoperatorio más alto pueden tener efectos protectores contra la lesión renal.

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