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Kidney Function Modifies the Effect of Intraoperative Opioid Dosage on Postoperative Delirium

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Abstract

Background: There are few studies demonstrating how kidney function affects the risk of developing delirium in older adult surgical patients administered opioids. This study determined whether baseline kidney function influences the relationship between morphine equivalent dose and the development of delirium on postoperative day (POD) 2 in patients with hip fracture.

Methods: This retrospective study analyzed emergency department (ED) estimated glomerular filtration rate (eGFR), perioperative serum creatinine, intravenous morphine equivalents and POD2 delirium assessment by the Confusion Assessment Method in 652 patients age ≥ 65 years without preoperative delirium. ED eGFR was used to divide subjects into groups by presence or absence

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of chronic kidney disease (CKD) and associations of opioid dose with POD2 delirium were compared using multivariable logistic regression.

Results: POD2 delirium incidence was 29.8% (N=194). Intraoperative and post anesthesia care unit (PACU) morphine equivalent dosage as well as ED eGFR was similar comparing patients with and without POD2 delirium. Age, American Society of Anesthesiologist (ASA) status, and dementia were associated with delirium on POD2. The odds of POD2 delirium increased significantly with increase of intraoperative opioid in patients with CKD (OR=1.6, 95% CI: 1.2-2.2), but not in patients without CKD (p-interaction=0.04). PACU or POD1 opioid doses were not associated with POD2 delirium after covariate adjustment.

Conclusion: This study suggests that incremental increases in intraoperative opioids combined with CKD increase odds of POD2 delirium after hip fracture repair, compared to patients without CKD..

Keywords

delirium; postoperative; hip fracture; analgesics; opioids; kidney

Background

Delirium is the most common complication after hip fracture surgery.[1] Postoperative delirium is associated with poorer cognitive outcomes, increased length of stay, increased complications and nursing home placement.[2] Therefore, it is imperative to optimize management strategies to prevent delirium.

One controversy in delirium prevention is opioid administration for pain management. There is evidence that opioids can predispose to delirium in a dose dependent manner.[3] Alternatively, undertreating pain can increase the chance of developing delirium.[4] Individualized opioid dosing strategies must take into account age and organ function such as kidney function. Chronic kidney disease (CKD) is a recognized risk factor for postoperative delirium.[5] Since some opioids and their metabolites are excreted by the kidney,[6] decreases in baseline kidney function with age and co-morbidity[7] as well as changes in kidney function during the perioperative period[8] could contribute to delirium onset.

CKD is common in hip fracture patients. Reduced kidney function was present on admission in approximately one-third of patients with hip fracture and is a risk factor for postoperative complications and increased mortality.[9-11] Currently, there are few studies demonstrating how CKD affects the risk of developing delirium in older surgical patients administered opioids.

The primary aim of this study was to determine whether CKD influences the relationship between opioid dose and the development of postoperative delirium in patients with hip fracture. In addition, we sought to determine whether perioperative changes in kidney function affect the relationship between opioid dose and the onset of postoperative delirium.

Methods

The study was approved by the Institutional Review Board for Johns Hopkins University. Between 1999 and 2019, patients admitted to the hip fracture service were consented for collection of perioperative data. The hip fracture service is multidisciplinary[12] and includes geriatric co-management, in which patients are assessed for delirium pre and postoperatively. Baseline demographics, at-home medications, intraoperative characteristics and postoperative outcomes are collected on all consenting individuals. Preoperative "probable dementia" was diagnosed if the patient had no delirium by Confusion Assessment Method (CAM) and either Mini Mental State Examination (MMSE) cutoff score <24 or clinical diagnosis of dementia by a geriatrician during the pre-hip fracture repair evaluation.[13] Exclusion criteria for the analysis included preoperative delirium, age less than 65 years, and incomplete data on opioid dosing and/or kidney function.

Delirium:

The presence of delirium was assessed preoperatively and on postoperative day 2 using the Confusion Assessment Method[14] as performed by either the attending geriatrician or a trained research assistant.

Opioid dose:

All opioid doses were converted to intravenous morphine equivalents in milligrams divided by weight in kilograms. Morphine equivalent dose was calculated as per standard ratio[15] of:

IV Morphine: IV Hydromorphone of 10:1.5

IV Morphine: IV Fentanyl of 1mg: 10mcg

IV Morphine: PO Morphine of 1:3

PO Morphine: PO Oxycodone of 1.5:1

PO Morphine: PO Tramadol of 1:4

The cumulative opioid dose in intravenous morphine equivalents was calculated by adding intraoperative opioid + PACU opioid + POD1 opioid. Intraoperative opioid included opioids administered from entry to operating room exit. PACU opioid included opioids administered from entry until PACU exit. POD1 opioid included opioids administered from 7am the day after surgery until 7am the following day. Total morphine equivalents for each time period included both pro re nata (prn) and regular scheduled dosing.

Kidney function:

Serum creatinine values were obtained on routine perioperative blood draws including arrival in the Emergency Department (ED), as the baseline, POD1 and POD2. The eGFR in the ED was calculated using the patient's age, sex, race and creatinine using the Chronic Kidney Disease Epidemiology Collaboration Equation.[16]

Statistical Analysis

Participants were divided into two groups based on presence or absence of CKD. CKD was defined as eGFR <60mL/min/1.73m^2. Frequency data between presence or absence of CKD were compared using Fisher's exact test, continuous data were analyzed with 2-sample t-test. Unless otherwise indicated, frequency data are reported as number and percentage, and continuous data are reported as mean with standard deviation. Pearson Correlation was performed between creatinine values obtained from the ED and creatinine values that were obtained within six months prior to the patient's index hospitalization in order to determine if baseline ED creatinine was reflective of the patient's true baseline kidney function or if the circumstances that led to a hip fracture also may have affected kidney function

Multivariable logistic regression was performed to test the interaction of CKD and morphine equivalents given intraoperatively, in the PACU and on POD1, on the odds of delirium on POD2. To examine impact of dosing across time periods on the outcome, incremental changes based on one standard deviation of dosing amount for each time period were used as the measurement units rather than using the absolute amounts in multivariable modeling. The regression model evaluated effect modification by level of ED eGFR above or below the CKD cutoff, through inclusion of the morphine equivalent variables, presence or absence of CKD, and their cross-product interaction terms, adjusting for relevant confounders including age, ASA status and probable dementia at baseline and change in creatinine from the ED to POD1.

All p values reported are two-tailed and a $p < 0.05$ is considered statistically significant. Statistical analyses were carried out using SAS version 9.4.

Results

From 1999 to 2019, 1,924 patients underwent hip fracture repair at Johns Hopkins Bayview Medical Center. Of this group, 711 patients provided written consent to be included in our database, among them 652 had information on kidney function, delirium and opioid administration.

Pearson Correlation between ED creatinine and creatinine values obtained within six months prior to the patients index hospitalization was 0.747 ($p<0.0001$).

Table 1 shows baseline demographics and clinical characteristics grouped according to CKD. Patients with CKD were older with higher ASA status. Patients with CKD were more likely to have coronary artery disease, congestive heart failure, peripheral vascular disease, and higher ED creatinine.

Table 2 shows perioperative characteristics grouped by CKD. Patients with CKD received lower cumulative opioid doses and had higher mortality in hospital. Patients with CKD received a significantly lower amount of midazolam but not propofol intraoperatively compared to patients without CKD.

The incidence of delirium on POD2 was 29.8% (N=194). The baseline (ED) eGFR was similar in patients with and without delirium on POD2 (eGFR: 59.0 ± 24.1 vs 61.6 ± 22.7 mL/min, p=0.18). Patients with delirium on POD2 received similar amounts of morphine equivalents intraoperatively and in the PACU, but lower amounts of morphine equivalents on POD1, as compared to their counterparts who were delirium free on POD2 (morphine equivalents: intraoperative 0.19 ± 0.21 vs 0.16 ± 0.21 mg/kg, p=0.09; PACU 0.017 ± 0.049 vs 0.021 ± 0.057 mg/kg, p=0.47; POD1 0.13 ± 0.17 vs 0.18 ± 0.22 mg/kg, p=0.03). Cumulative opioid dose, intraoperative + PACU + POD1, was similar between these two groups of patients (morphine equivalents: 0.35 ± 0.31 vs 0.35 ± 0.34 mg/kg, p=0.99).

In multivariable analyses, older age, elevated ASA status and having a probable dementia diagnosis at baseline were associated with significantly increased odds of delirium on POD2 independent of kidney function at baseline and opioid dosing perioperatively in all 4 models. Change in creatinine from ED to POD1 was not associated with odds of delirium on POD2 (Supplementary Table S1). One SD increase of intraoperative morphine equivalent dose was associated with a 35% increase in odds of delirium on POD2 in patients with CKD, compared to patients without CKD where odds of delirium was not associated with opioid dose (Supplementary Table S1, Model 1). However, this effect modification of opioid dosage on the odds of delirium by CKD was not found with PACU or POD1 dosages (Supplementary Table S1, Models 2 and 3) where opioid dosage was not associated with odds of delirium regardless of presence or absence of CKD. Similar results were observed using the data from only patients who had all 3 measurements of intravenous morphine equivalents perioperatively (Supplementary Table S1, Model 4 and Figure 1), where the odds ratio of delirium on POD2 associated with 1 SD increase in morphine equivalents received intraoperatively was estimated as 1.60 (95% Confidence Interval (CI): 1.19 to 2.15) for patients with CKD, compared to the odds ratio of 1.06 (95% CI: 0.82 to 1.38) in patients without CKD (p-interaction = 0.04).

Discussion

This study shows that in hip fracture patients, CKD has a modifying effect on the relationship between intraoperative opioid dose and risk of delirium on POD2. No modifying effect was found with either PACU or POD1 opioid dose. In addition, perioperative changes in kidney function were not associated with development of delirium on POD2. These results emphasize the importance of considering baseline kidney function for intraoperative opioid dosing in preventing early postoperative delirium.

Previous studies report an association between intraoperative opioid doses and postoperative delirium in orthopedic patients.[3] Similarly, intraoperative opioid dose has been related to PACU symptoms of delirium.[17] The current study found POD2 delirium associated with intraoperative dose to be specific in older patients with CKD undergoing hip fracture repair, but did not find associations or effect modification by CKD of opioid dose in PACU or on POD1. These findings are most likely related to variations in opioid dose between the intraoperative, PACU, and POD1 time periods. The PACU dose is much lower than intraoperatively and therefore less likely to have effect. Patients who had delirium receive

significantly less opioid on POD1 compared to those without delirium. This would tend to negate the opioid effect at this timepoint.

Kidney function decreases after hip fracture repair in approximately 13% of patients.[18] We found no association between creatinine changes from ED to POD1 and delirium on POD2. Whether changes in creatinine after POD 1 affect delirium is still unclear. However, data from cardiac surgery suggests that acute kidney injury in the two days postoperatively increases the risk of delirium.[19]

Although opioids are primarily metabolized in the liver, kidney function affects opioid pharmacokinetics and removal of some metabolites.[6] Patients with reduced kidney function are at higher risk for delirium following opioid administration.[20,21] Adverse opioid effects when administered for pain management can be avoided by decreasing the opioid dosage based on the severity of kidney disease.[22] In the current study, the SD for intraoperative opioid is 0.21 mg/kg so the odds ratio reported for intraoperative opioid is associated with such a dosing increase. In clinical terms this roughly equates to intravenous doses of 150 mcg fentanyl or 2.2mg hydromorphone in a 70 kg individual with CKD during the intraoperative period.

Advantages of this study include the large sample size with complete intraoperative and postoperative data on kidney function and opioid dosage. Limitations include that the effects after POD2 were not analyzed. Different opioids were converted to intravenous morphine equivalents and lumped together in the analysis, yet we did not account for differences in pharmacokinetics. Even though the morphine equivalent calculations were originally obtained as outlined in the methods section, our database contains only total morphine equivalents calculations and not data concerning the specific opioid administered. Our analysis included hip fractures occurring over a 20-year period, prohibiting the ascertainment of specifics concerning type of opioid administered in older cases occurring prior to electronic medical records. Our database does contain information on postoperative complications. However, it does not allow us to establish the temporal relationship between the occurrence of these complications and delirium on POD2. Since the health status of those with lower kidney function is in general worse, there are likely other factors in this group that could contribute to delirium. Complete data concerning known risk factors for delirium in an older adult population are not available in our dataset. Given this, the variables chosen for the final model are limited and residual confounding cannot be ruled out.

In summary, CKD in older patients with hip fracture has a modifying effect on intraoperative opioid dose such that incremental dose increases have significantly greater odds of precipitating POD2 delirium in patients with than without CKD. Further study is required to determine whether adjusting intraoperative opioid dose in hip fracture patients with CKD is a possible intervention to prevent early postoperative delirium.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

Conflict of Interest

Arman B. Davani: none

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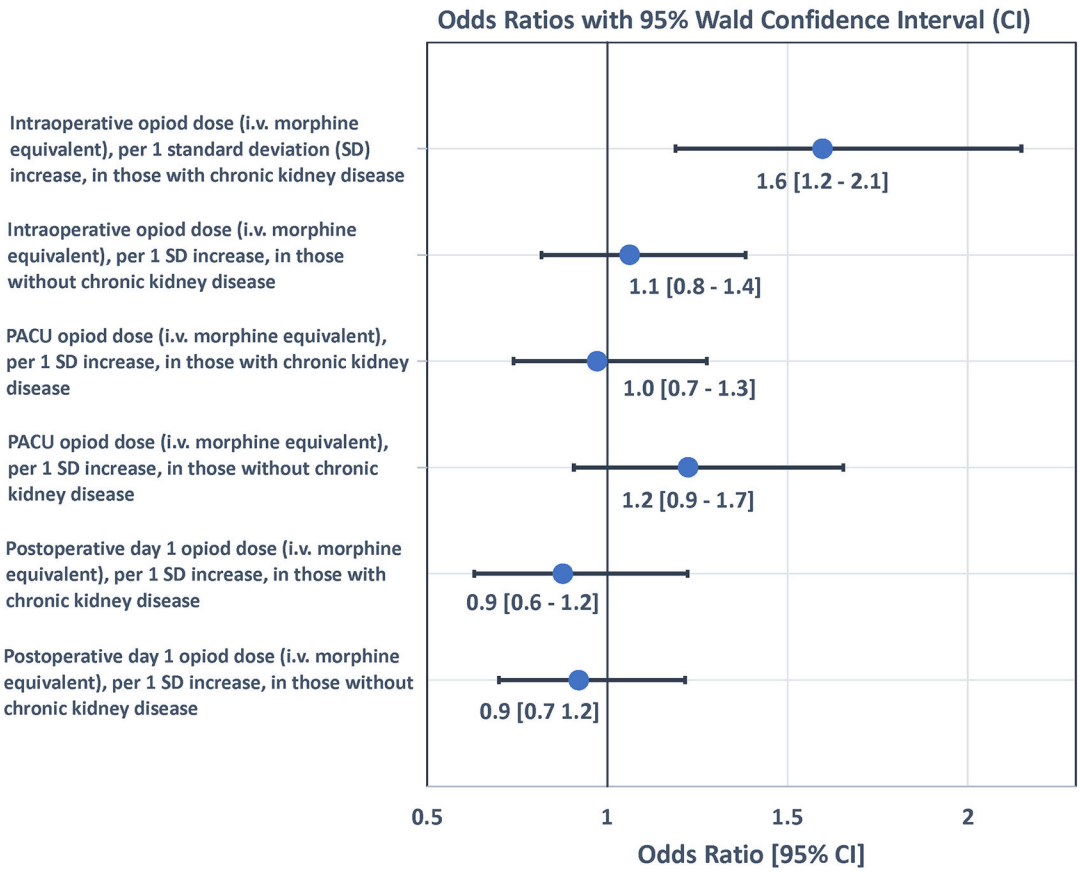

Figure 1:

Forrest plot of odds ratios for opioid dose for prediction of delirium on postoperative day 2 by presence or absence of chronic kidney disease. OR = Odds Ratio. Odds Ratio adjusted for age, ASA, dementia status, and change in creatinine from ED to POD1. SD=standard deviation. PACU=post anesthesia care unit. POD=postoperative day.

Table 1:

Baseline Demographics and Clinical Characteristics

Variable	No Chronic Kidney Disease (N = 321)	Chronic Kidney Disease (N = 331)	p
Age in years, Mean (SD)	79 (8)	83 (7)	0.000
Female	224 (70%)	251 (76%)	0.094
Caucasian *	310 (97%)	313 (95%)	0.266
ASA Status *			0.014
2	90 (28%)	62 (19%)	
3	203 (63%)	228 (69%)	
4	28 (9%)	40 (12%)	
Diagnoses			
Coronary Artery Disease *	59 (18%)	91 (28%)	0.007
Congestive Heart Failure *	32 (10%)	70 (21%)	0.000
Stroke *	51 (16%)	66 (20%)	0.185
Diabetes *	67 (21%)	82 (25)%	0.263
Peripheral Vascular Disease (N=292/304)	21 (7%)	40 (13)%	0.021
Dementia	59 (18%)	%74 (22%)	0.243
Depression (N=291/203)	47 (16%)	47 (16%)	0.911
COPD *	72 (22%)	60 (18%)	0.205
At-home Medications			
Antipsychotics (N=247/273)	14 (6%)	16 (6%)	0.999
Benzodiazepines (N=247/274)	20 (8%)	14 (5%)	0.214
Antidepressants (N=247/274)	38 (15%)	39 (14%)	0.713
Statins (N=247/274)	36 (15%)	32 (12%)	0.363
Opioids (N=276/300)	122 (44%)	127 (42%)	0.674
ED Creatinine	0.8 (0.2)	1.5 (1.0)	0.000
Femoral Neck Fracture *	154 (48%)	151 (46%)	0.313

* N = 1 or 2 with missing value

ASA=American Society of Anesthesiologists. SD=standard deviation.

Table 2:

Perioperative variables

Variable	No Chronic Kidney Disease (N = 321)	Chronic Kidney Disease (N = 331)	p
Intraoperative			
Surgical Procedure *			0.234
Bipolar or Monopolar	119 (37%)	127 (38%)	
Nail	116 (36%)	133 (40%)	
Length of Surgery in Minutes (N=317/330)	113 (50)	108 (52)	0.225
Regional Anesthesia	184 (57%)	203 (61%)	0.196
Midazolam (mg/kg) (N=314/326)	0.007(0.015)	0.004 (0.012)	0.013
Propofol (mg/kg) (N=286/287)	5 (5)	5 (5)	0.911
Postoperative			
Delirium on POD2	91 (28%)	103 (31%)	0.442
Change in creatinine from ED to POD1, per mg/dl increase (N=307/325)	−0.04 (0.17)	−0.16 (0.36)	0.000
Time to Aldrete Score of 9 or Greater (min) (N=234/262)	25 (44)	29 (57)	0.479
Average Pain Score on PACU, No (%)Discharge (N=246/270)	1 (2)	1 (2)	0.955
Average Pain Score on POD1 (N=268/280)	4 (3)	3 (3)	0.137
Average Pain Score on POD2 (N=255/271)	3 (3)	3 (3)	0.902
Cumulative Opioid Dose (INTRAOP + PACU + POD1) mg/kg morphine equivalents (n=282/301)	0.5 (0.5)	0.4 (0.4)	0.021
ICU Days Postop (N=248/267)	1 (3)	1 (2)	0.613
RBC Units Transfused, No (%) perioperatively (N=283/297)	1 (2)	1 (2)	0.952
Hospital Length of Stay Days, Mean (SD) (N=315/326)	6 (4)	6 (4)	0.751
Discharge from Hospital Alive *	316 (99%)	316 (95%)	0.012
Discharge Location (N=306/310)			0.880
Home	23 (7%)	14 (5%)	
Skilled Rehabilitation	275 (84%)	251 (85%)	

* N = 1 or 2 had missing value

** N = 316 in the upper half and N = 327 in the **chronic kidney disease** group had data.

RBC= red blood cell. ICU= intensive care unit. PACU= post anesthesia care unit. POD= postoperative day. Intraop= intraoperative or intraoperatively. UTI= Urinary Tract Infection. Postop = postoperative or postoperatively. No =Number.