Diclofenac--Acetaminophen Combination Induced Acute Kidney Injury In Postoperative Pain Relief

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ABSTRACT - Purpose: The objective of this study was to determine: 1) the incidence and the risk factors of diclofenac/acetaminophen combination as a single agent induced Acute Kidney Injury (AKI) in postoperative pain relief 2) the average cost and length of hospital stay for patients in AKI group and non-AKI group. Methods: All patients with no prior history of chronic kidney disease (CKD) and normal serum creatinine [44~130 μmol /l] who received diclofenac and acetaminophen combination as a single agent intramuscularly (IM) between January and December 2015 in The Second Xiangya Hospital, Changsha, Hunan, China were included in this retrospective own-control study. Baseline serum creatinine (SCr) and SCr during NSAID use were collected. AKI is defined as an increased of Scr over 1.5 times the baseline. Multivariate analyses were performed with a logistic regression model to assess the significant risk factors of AKI. **Results:** A total of 821 patients were included in the study with 63 [7.7%] patients had diclofenac/acetaminophen combination single agent induced AKI. Multivariate analysis confirmed that using diclofenac/acetaminophen combination after surgeries within 24 h were significantly associated with AKI [odds ratio, OR, 2.173; 95% CI, 1.113-4.243; P=0.023]. The average cost and length of hospitalization in AKI group was 1.87 times [p=0.000] and 1.2 times [p=0.043] comparison than non-AKI group, respectively. **Conclusions:** The incidence of diclofenac/acetaminophen combination single agent induced AKI in postoperative pain relief was 7.7%. Patients with hypertension or liver cirrhosis was more likely to develop AKI and using diclofenac/acetaminophen combination after surgeries within 24 h was significant risk factors for AKI. AKI prolonged the cost and length of hospitalization.

INTRODUCTION

Acute postoperative pain is defined as acute pain temporarily related to tissue injury that is resolved during appropriate healing time (1). The intensity of pain may initially present as severe pain but gradually subsides during the time of healing. It has been reported that the prevalence of acute postoperative pain is about 80 %, with 86 % are associated with moderate to severe pain (2). Adequate management of postoperative pain is an important component of the standard care of the surgical patients (3, 4). The guideline recommends that clinicians provide adults and children with acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in patients without contraindications (5). NSAIDs inhibit prostaglandin synthesis pathway results in a reduction in pain and inflammation and thereby reduce nociceptive stimuli (6). Acetaminophen is indicated for the short-term treatment of mild to moderate pain or fever (7). In addition, acetaminophen and NSAIDs have different mechanisms of action and research indicates that the combination of acetaminophen with NSAIDs might be more effective than either drug alone (8). Acute kidney injury (AKI) is defined as a rapid deterioration of renal function over a period of time. Progressive AKI may develop into chronic kidney disease in some patients (9). AKI is also known to

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induce distant organ damage, which in turn contributes further to morbidity and mortality (10). A study investigating patients after general surgery reported an eight-fold increase in mortality in patients with perioperative AKI (11). The use of NSAIDs is associated with series adverse effects such as renal failure (12). There is some evidence to support increased incidence of renal failure with increased dosing of selective and nonselective NSAIDs (13). Fayaz et al (14) found that the change serum creatinine (Scr) did not differ between diclofenac and acetaminophen, diclofenac and placebo or placebo and placebo groups after coronary artery bypass grafting (CABG). The meta-analysis of 1065 patients across 20 randomized controlled trials (RCTs) established that the risk of renal failure was not significantly higher with perioperative NSAIDs usage (15). Metesh Acharya et al (16) identified 11 studies, comprising one meta-analysis, seven RCTs, and three retrospective studies, and conclude that NSAIDs are not associated with an increased risk of renal failure after cardiac surgery when administered at normal doses. There were some case reports of AKI from NSAIDs such as ketorolac or ibuprofen when used for perioperative pain management (17). There were few studies showed that diclofenac and/or acetaminophen was associated with AKI in postoperative pain relief.

Currently, diclofenac 25 mg and acetaminophen 150 mg combination administered by intramuscular injection (IM) as a single agent is most frequently used for postoperative pain in Second Xiangya Hospital of Central South University (SXHCSU), Changsha, Hunan Province. The objective of this study was to determine: 1) the incidence and the risk factors of diclofenac/acetaminophen combination single agent induced AKI in postoperative pain, 2) the average cost and length of hospital stay for patients in AKI group and non-AKI group.

METHODS

A retrospective own-control chart review of all patients from the Second Xiangya hospital, Changsha, Hunan, China between January 2015 and December 2015 who met the following inclusion and exclusion criteria were collected. All patients with normal renal function [SCr: 44~130 μmol /l as hospital laboratory determination] received diclofenac/acetaminophen combination single agent administered by IM for postoperative pain were included. Exclusion criteria: 1) patients did not have a baseline Scr before using diclofenac/acetaminophen combination single agent, 2) patients with preoperative chronic kidney disease (CKD) defined by estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (18), [eGFR was calculated by the CKD-EPI formula (19)], 3) Patients underwent kidney surgeries or kidney transplants. The study was approved by the Second Xiangya Hospital of Central South University Research and Ethics Committee [ID: yxb-lcys-201501].

Data collection

Patient data were reviewed and extracted from electronic medical records at the Second Xiangya Hospital of Central South University. Information collected included demographics, NSAID use which included dose, frequency and duration of use, SCr and eGFR at baseline and within 7 days after surgery (20), length of hospitalization and cost of hospitalization. The demographics included gender, age, past medical history such as diabetes, hypertension [not divided into stages], cirrhosis, hyperlipidemia and arteriosclerosis. It has been shown that comorbidity such as diabetes, hypertension, cirrhosis, hyperlipidemia or arteriosclerosis associates with increased risk of AKI in general population (21, 22). Medications that are known to cause AKI used concomitantly with NSAID were recorded. AKI is defined as an increased of Scr over 1.5 times the baseline (19).

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel spreadsheet and was then imported to SPSS Statistics 18.0 [IBM Corp., China] which was used for all statistical analysis. All the variables included gender, older age [>60 years], the total doses of using NSAID, the interval between surgery and NSAID use, number of patients with preoperative comorbidity and concomitant drugs related to AKI were presented as percentages. Differences in renal function were analyzed using Mann-Whitney U tests and Wilcoxon tests. Statistical significance was defined as $p < 0.05$. All variables were entered in the Logistics regression analysis. Odds ratio (OR) and 95% Confidence Interval (CI) of each variable were reported.

RESULTS

A total of 821 patients were included in the study with 468 [57.0%] patients were men, mean age of the patients was 50 years [range 4–84 years]. The average duration of diclofenac/acetaminophen use was 2 days [range = 1 – 25 days]. Demographic characteristics of patients are presented in Table 1. A total of 63 [7.7%] patients developed AKI. Of the 821 patients, 226 [27.5%] patients had at least one predisposing comorbidity. Hypertension was most prevalent in 115 [14.0%] of the patients.

Table 2 showed the SCr before and during NSAID use. The baseline Scr [mean, 66.6 vs 67.4 μmol/L] and eGFR [mean, 104.7 vs 101.3 mL/min/1.73 m^2] between AKI group and non-AKI group were not statistically different [p=0.742, p=0.922]. Postoperative Scr [mean, 204.9 vs 62.1 μmol/L] and eGFR [mean, 44.6 vs 106.4 mL/min/1.73 m^2] between AKI group and non-AKI group were statistically significant [p<0.05, p<0.05]. Table 3 showed that the baseline SCr and eGFR of all patients were normal. And the SCr and eGFR of all patients during NSAID use were significantly different from the baseline [p<0.001]. Especially, the SCr and eGFR of AKI-group during NSAID use were abnormal.

The differences of the average hospitalization cost and length between AKI group and non-AKI group was presented in Table 4. The average hospitalization cost with AKI was 1.94 times higher when compared with patients without AKI [mean, 38850.7$ vs 19992.3$; p=0.000]. The average length of hospital stay in AKI group was 1.20 times as long as in non-AKI group [mean, 29.8 days vs 24.8 days; p=0.043].

Table 5 showed the AKI incidence and the average cost and length of hospitalization of every type of surgeries. Patients with general surgery had the highest incidence of AKI [11.7%], and the incidence of AKI of patient with cardiovascular surgery was 9.9%. The incidence of AKI of these two surgeries were higher than overall AKI [7.7%] in this study. The average cost of hospitalization of general surgery [p=0.002], neurosurgery surgery [p=0.031] and cardiovascular surgery [p<0.001] were significant difference between AKI group and non-AKI group.

Table 6 is a summary of the predictive risk factors by logistics regression. Patients using NSAID after surgeries within 24 h were more likely to had AKI [OR, 2.173; 95% CI, 1.113~4.243; P=0.023]. Gender, older age, the total doses of NSAID, and concomitant drugs related to AKI were not statistically significant. Preoperative comorbidities in AKI group after using NSAID for postoperative pain relief were significant risk factors. Only two comorbidities, hypertension [OR, 2.541, 95%CI, 1.316~4.909; P=0.005] and liver cirrhosis [OR, 4.323, 95%CI, 1.650~11.328; P=0.003] show statistical significance. Patients [22.2%] with preoperative liver cirrhosis had the highest incidence of AKI.

Table 1. Demographic characteristics on patients used NSAID for postoperative pain relief

	n (%)
Gender	
male	468(57.0)
female	353(43.0)
Age, years	
≤18	20(2.4)
19-45	217(26.4)
46-60	387(47.1)
>60	197(24.1)
Pre-operative comorbidity	
Hypertension	115(14.0)
Arteriosclerosis	49(.0)
Diabetes	45(5.5)
Cirrhosis	27(3.3)
Hyperlipidemia	7(0.9)

Table 2. The difference of the Scr and eGFR between AKI group and non-AKI group

	AKI n=63 Mean（SD）	Non-AKI n=758 Mean(SD)	p
Preoperative Scr, μmol/L	66.6(21.7)	67.4 (16.5)	0.774
Scr during NSAID use, μmol/L	204.9(141.4)	62.1(18.6)	0.000*
Preoperative eGFR, mL/min/1.73 m^2	104.7(28.2)	101.3(18.6)	0.813
eGFR during NSAID use, mL/min/1.73 m^2	44.6(29.5)	106.4(22.8)	0.000*

* P<0.05 is statistically significant. Analyzed by Mann-Whitney U tests.

Table 3. The comparison between the baseline of renal function and renal function during NSAID use

	The baseline Scr, μmol/L	Scr during NSAID use, μmol/L	p	The eGFR, mL/min/1.73 m^2	eGFR during NSAID use, mL/min/1.73 m^2	p
	Mean（SD）	Mean(SD)		Mean(SD)	Mean(SD)	
All patients	67.3(17.0)	73.0(57.3)	<0.001*	101.6(19.5)	101.6(28.6)	<0.001*
AKI group	66.6(21.7)	204.9(141.4)	<0.001*	104.7(28.2)	44.6(29.5)	<0.001*
Non-AKI group	67.4 (16.5)	62.1(18.6)	<0.001*	101.3(18.6)	106.4(22.8)	<0.001*

* P<0.05 is statistically significant. Analyzed by Wilcoxon tests.

Table 4. Cost and length of hospitalization with using NSAID in postoperative pain relief

	Mean(SD)	p
The average cost of hospitalization, USD,$		
AKI	38850.7(29897.3)	0.000*
Non- AKI	19992.3(14759.7)	
The average length of hospitalization, days		
AKI	29.8 (19.5)	0.043*
Non- AKI	24.8 (16.3)	

Table 6. Risk factors of AKI on patients using NSAID for postoperative pain control by Logistics regression

	AKI incidence (%)	OR	95%CI	p
Gender, female	5.7	0.646	0.371,1.127	0.124
Age, >60 years	8.5	1.157	0.653,2.049	0.618
Interval between surgery and using NSAID， <24 h	13.8	2.173	1.113,4.243	0.023*
Days of using NSAID, >2 days	6.0	0.675	0.333,1.368	0.275
Patients with preoperative comorbidity [a]				
Hypertension	14.0	2.541	1.316,4.909	0.005*
Live Cirrhosis	22.2	4.323	1.650,11.328	0.003*
Diabetes	13.3	1.576	0.609,4.079	0.348
Arteriosclerosis	8.2	0.656	0.208,2.066	0.472
Hyperlipidemia	14.3	1.280	0.145,11.338	0.824
Concomitant vancomycin [b]	11.0	1.684	0.891,3.185	0.109

a、All Comorbidity which all people were recorded in this study and hypertension, Arteriosclerosis, Diabetes, Cirrhosis and Hyperlipidemia were referred to be high risk to AKI.

b、Only vancomycin of all concomitant drugs which all people were recorded in this study was referred to be associated with AKI by its instruction.

* P<0.05 is statistically significant.

DISCUSSION

NSAID and/or acetaminophen are commonly used in mild to moderate pain management. These agents are usually given as two single agents and in oral formulation. Very seldom are the two drugs given as a combination single agent IM. This is the first study to show IM diclofenac/acetaminophen combination induced AKI in postoperative pain management.

NSAID alone causes about 15% of all cases of drug induced nephrotoxicity or 1 -5% of all NSAID users (23, 24). In a case report, a geriatric patient

with decompensated heart failure received oral diclofenac 25 mg/day resulted in nephrotoxicity (25). A study assessed pain control using oral ibuprofen and acetaminophen in patients after wisdom teeth extraction did not report incidents of AKI after 48-hour use (26).

It has been well established that acetaminophen causes liver cirrhosis in overdose or long-term use above recommended therapeutic dose (27). At therapeutic doses, acetaminophen is metabolized via glucuronidation and sulfation reactions occurring primarily in the liver which result in the water-soluble metabolites that are excreted via the kidney. In overdoses, a rapid depletion of glutathione and toxic metabolites production induce nephrotoxicity by triggering apoptosis or programmed cell death, resulting in tissue necrosis and organ dysfunction (28). Nephrotoxicity occurs about 1 – 2% in acetaminophen overdose (27). However, there has been no report of nephrotoxicity in therapeutic dose of acetaminophen use. A case report suggests that it is safe to use acetaminophen at therapeutic dose in patients with NSAID induced-nephropathy (29).

In this study, the use of diclofenac/acetaminophen single agent combination after surgeries within 24 h was independent significant risk factor. NSAIDs inhibit prostaglandin synthesis which antagonize the vasoconstrictor effects of angiotensin II. In every major operation, we postulated that hypoperfusion is not corrected after surgeries within 24 h, angiotensin II resulted in vasoconstriction of both the afferent and the efferent arterioles, and as a consequence, reduces GFR (30, 31). There is no published study about the mechanism of nephrotoxicity cause by the diclofenac/acetaminophen combination agents given IM. A future prospective study will be conducted to determine the safety of IM diclofenac/acetaminophen combination in postoperative patients with hypoperfusion.

This study showed that patients with hypertension or liver cirrhosis were more likely to develop AKI and are independent risk factors than other risk predisposing comorbidities for AKI. In all risk comorbidities for AKI, patients with hypertension or liver cirrhosis should avoid using diclofenac/acetaminophen combination single agent in postoperative pain relief. The surgeries of general surgery such as Liver transplantation and bile duct exploration and cardiovascular surgery were found to be develop AKI in our study compared with other surgeries. A single-center study involving 424 adult liver transplant recipients (32) reported that AKI occurred in 52% of patients. In cardiovascular surgery, AKI is a common complication after CABG (33). Other surgeries were not reported to be associated with AKI before.

The results from this study showed that the cost and length of hospitalization were higher in AKI group compared with non-AKI group, especially in cardiovascular surgery, general surgery and neurosurgery surgery. There were numerous studies reported that AKI had physiological and psychological consequences that were associated with morbidity and complications such as delayed wound healing, prolonged hospitalization and risk of chronic pain (34). The economic burden of AKI warrants further attention from hospitals and policymakers to improve the management of postoperative pain to prevent or ameliorate AKI and processes of care.

Limitation

This study has some limitations that merit a discussion. First, this was a single center study, the results may not be generalizable to patients with different risk profiles or centers with different surgical practice. Second, this is a retrospective chart review. As electronic medical records in SXHCSU is sometimes incomplete for some patients. As a result, some data such as blood loss, fluids and blood pressure during surgeries were not available. Third, unfortunately, the investigators do not have access to all patients who received surgery at the hospital. The patients in this study were identified by using the pharmacy database with the search term that included the medication “diclofenac”. Also, almost all of the post-surgical patients received diclofenac/acetaminophen combination agent for pain control. It would be difficult to compare patients using diclofenac/acetaminophen combination agent vs non-users. Finally, urine output was not available for all patients to clinically assess kidney function. Since this is a retrospective chart review, pain control could not be assessed as most of the time it was not documented. A prospective study is being conducting to collect all necessary data and to investigate the number of AKI in the users of the combination and non-users after surgeries.

CONCLUSION

The incidence of diclofenac/acetaminophen combination induced AKI in postoperative pain relief was 7.7%. Patients with hypertension or liver

cirrhosis was more likely to develop AKI and using diclofenac/acetaminophen combination after surgeries within 24h was significant risk factors for AKI. AKI prolonged the cost and length of hospitalization.

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Table 5. the AKI incidence and the average cost and length of hospitalization of every type of surgeries

Department	AKI incidence (%)	The average cost of hospitalization [a], USD,$			The average length of hospitalization [a], days		
		AKI group	Non-AKI group	p	AKI group	Non-AKI group	p
General Surgery	11.7	37428.3(26284.0)	22311.6(17802.2)	0.002*	30.9(19.8)	26.5(19.3)	0.257
Cardiovascular surgery	9.9	47343.0(37101.2)	19211.2(9796.1)	<0.001*	29.2(22.0)	21.3(11.2)	0.118
Urology surgery	6.7	20270.2(17381.4)	11581.8(7081.2)	0.263	31.5(29.0)	26.8(20.7)	0.763
Neurosurgery surgery	3.8	24601.2(6099.0)	21342.4(16598.0)	0.031*	28.3(12.6)	27.2(17.2)	0.514

[a] The average cost of hospitalization and the average length of hospitalization were shown by mean(standard deviation).

***** P<0.05 is statistically significant. Analyzed by Mann-Whitney U tests.