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Do Early Non-Steroidal Anti-Inflammatory Drugs for Analgesia Worsen Acute Kidney Injury in Critically Ill Trauma Patients? An Inverse Probability of Treatment Weighted Analysis

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Abstract

Background: Administration of NSAIDs for acute post-traumatic analgesia is increasing in popularity as an alternative to opioids despite reservations regarding its potential impact on the development of acute kidney injury (AKI). We hypothesized that early NSAID administration for analgesia would be associated with worsened renal function in severely injured trauma patients.

Methods: A retrospective cohort study of severely injured adult (> 16 years) patients admitted to the intensive care unit with ≥ 1 rib fracture 2010–2017 was performed. The early NSAID group was defined by receipt of one or more doses of NSAID within the first 48 hours of hospitalization. AKI diagnosis and staging was defined by the Kidney Disease Improving Global Outcomes Guidelines. The primary outcome was a composite measure of two outcomes within the first week of hospitalization: (1) AKI progression (increase in AKI stage from arrival) or (2) death. Secondary outcomes included AKI progression, AKI improvement, AKI duration, and mortality. Inverse propensity of treatment weights were generated utilizing clinically sound covariates suspected to be associated with the decision to give early NSAIDs and the primary or secondary outcomes. Multivariable analyses were performed adjusting for inverse propensity of treatment weights, covariates, and length of stay.

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Results: Of 2,340 patients, 268 (11%) were administered early NSAIDs. When compared to the control group, patients who received early NSAIDs were less severely injured. Renal outcomes were worse in the control group. Standardized mean differences were minimal after weighting. On multivariable analysis, administration of early NSAIDs was not associated with worsened renal outcomes or increased mortality.

Conclusion: Although only 11% of patients received early NSAIDs after trauma for analgesia, early NSAID exposure was not associated with increased AKI progression, decreased AKI improvement, prolonged duration, or increased mortality. Given the lack of evidence showing harm, early NSAIDs for analgesia may be underutilized for severely injured patients.

Level of Evidence: 3, Prognostic

Keywords

Non-Steroidal Anti-Inflammatory Drugs; Acute Kidney Injury; Post-Traumatic Pain

Background:

Choice of analgesic for the critically ill trauma patient requires assessment of the risks and benefits of each agent. In an effort to decrease the short- and long-term consequences of opioid use for post-traumatic pain, many centers are increasing their use of non-steroidal anti-inflammatory drugs (NSAIDs) as part of a multimodal pain regimen (MMPR). (1–4) Acute pain is frequently treated with NSAIDs, which have shown to substantially reduce acute pain in both emergency and post-surgical populations. (5–8) Furthermore, MMPRs utilizing NSAIDs have consistently shown a reduction in opioid requirements and opioid-related complications. (4, 9–11) A systematic review of 33 placebo-controlled studies assessed the effects of NSAIDs on opioid use and complications in perioperative patients. (12) The authors reported a 26% decrease in opioid consumption, 30% decreased odds of nausea and vomiting, as well as a 47% decreased odds of sedation with NSAID use.

Pain relief from NSAIDs can be attributed to inhibition of prostaglandins, but prostaglandin inhibition may also lead to a wide range of side effects including renal toxicity. (13) Over 40% of severely injured trauma patients suffer AKI; nearly 70% of these patients have AKI on hospital arrival. (Hatton, unpublished data) (14) Because renal hypoperfusion may be exacerbated by NSAIDs, clinicians may avoid them in patients with AKI or at high risk of developing AKI, despite their known benefits in the treatment of pain.

Clinical data regarding the safety of NSAIDs for analgesia in the acute post-traumatic setting is lacking. Two meta-analyses have evaluated the effects of peri-procedural NSAID use on AKI, neither in the trauma setting. (15, 16) The first reported no evidence regarding withholding NSAIDs for coronary angiography and the second determined that NSAIDs have “uncertain effects” on the risk of post-operative AKI. Given the increase in the use of NSAIDs among critically injured trauma patients as a result of implementation and improved adherence to the MMPR at the study institution, the safety of this practice warrants investigation. (4) We hypothesized that early NSAID administration for analgesia would be associated with worsened renal function in severely injured trauma patients.

Methods:

This was a retrospective cohort study of adult (> 16 years) trauma patients with one or more rib fractures admitted to the intensive care unit between 2010 and 2017 at a single institution. The study cohort was limited to patients with one or more rib fractures as all patients with rib fractures at the study institution receive a multimodal pain regimen. At the study institution, a MMAP was instituted in 2013. (4) The MMAP consisted of the following medications administered in a scheduled fashion: acetaminophen (24h intravenous followed by oral), gabapentinoids (48h pregabalin followed by gabapentin), NSAIDs (48h celecoxib followed by naproxen), lidocaine patches, and tramadol. Supplemental opioids were administered on an as-needed basis. Departure from the MMAP regimen was based on clinical judgement. Patients were excluded if the primary injury was due to burns, the patient was dialysis dependent prior to admission, the patient died within the first 24 hours after admission, or the patient was transferred directly to the ICU from an outside hospital. Demographic and clinical data were extracted from the trauma registry and supplemented by laboratory results and medication data from the electronic medical record. Arrival verbal Glasgow Coma Scale (GCS) was excluded from the data due to inconsistencies in the definitions applied to the registry. Patients with missing creatinine data were also excluded from the analysis. Medication data was converted from milligrams to doses, according to an *a priori* defined dose scale [Table 1]. Early NSAID exposure was defined as ≥ 1 dose of NSAID medication for analgesia within the first 48 hours from admission. This study was approved by the institutional review board at McGovern Medical School at UTHealth.

Outcome Measures

AKI was defined according to the Kidney Disease Improving Global Outcomes Guidelines. The baseline creatinine was imputed by the Modification of Diet in Renal Diseases equation based on age, race, and sex with an assumed average baseline glomerular filtration rate of 75ml/min. (14) The primary outcome was a composite of AKI progression or death within 7 days of admission. (17) Secondary outcome measures included AKI progression, AKI improvement, AKI duration, and in-hospital mortality. AKI progression was defined by an increase in AKI stage after arrival. (18) Improvement was defined as a decrease in AKI stage after arrival. AKI duration was defined as the number of days the patient met criteria of AKI at any stage. All outcomes were considered through the 7th hospital day in order to restrict our definition to include both potential NSAID-associated AKI and injury, shock, and resuscitation-related AKI. (17)

Statistical Analysis

Missing data was considered missing at random and imputed using Multivariable Imputation by Chained Equations with five iterations (19). Propensity scores for receipt of 1 or more doses of NSAID within 48 hours from admission were created for all patients using a logistic regression model using the following variables: age, sex, race, mechanism of injury, abbreviated injury scores, arrival systolic blood pressure (SBP), arrival heart rate (HR), arrival motor and eye GCS, transfer from an outside hospital, initial emergency room disposition, and admission creatinine. Propensity scores were converted to inverse probability of treatment weights.

Descriptive analyses were performed to compare baseline demographic and clinical data. Median values with interquartile range were used to describe continuous data and discrete data is reported as a total and frequency. Variables of interest were compared using the Chi-squared test or a Wilcoxon rank-sum test for categorical and continuous variables, respectively. Standardized mean differences were also generated to compare group differences before and after weighting. Multivariable Poisson regression with robust standard errors, weighted for the inverse probability of treatment and adjusted for patient length of stay was utilized to assess the relationship between early NSAID use and the composite primary outcome. Similar models were fit separately for the secondary non-composite outcomes AKI progression, AKI improvement, AKI duration, and mortality. To evaluate for a dose-dependent response, models were similarly fit using 48-hour NSAID dose in place of early NSAID exposure. All associations were reported as incidence risk ratios with robust confidence intervals. All data analyses were completed using R version 3.53 (R Core Team. 2013. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria).

Results:

Of 2,531 patients meeting inclusion criteria, 123 were excluded for death prior to 24 hours, 1 was excluded for end-stage renal disease, 0 were excluded for burn as the primary injury cause, 47 were excluded for direct ICU admission from an outside hospital, and 20 were excluded for missing creatinine data. (Figure 1) Age was missing in 3 (0.1%), race in 6 (0.2%), arrival SBP in 31 (1%), arrival HR 39 (2%), arrival GCS in 23 (1%). Other variables had no missing data.

Included patients were primarily male (73%) who had been injured by blunt mechanism (93%), with a median age of 44 years. Patients were severely injured with a median injury severity score of 25. Of 2,340 patients, 268 (11%) patients received early NSAIDs. On arrival, 809 (35%) of patients met criteria for AKI diagnosis. Those who received early NSAIDs were more likely to be admitted in 2017, be less severely injured, have a higher arrival SBP, and a higher arrival GCS score. (Table 2). Patients who received early NSAIDs received an average of 4 (IQR 2–6) doses within the first 48 hours after admission and the majority received at least one dose of ketorolac. Other demographic data were similar between groups. Before inverse probability of treatment weighting, patients who received early NSAIDs were less likely to meet the primary outcome of worsening AKI or mortality and were less likely to die. Receipt of early NSAIDs were associated with shorter AKI duration. There was no difference in AKI improvement. (Table 3)

Propensity scores for early NSAID administration revealed a low overall probability of treatment. The median propensity score in patients who received early NSAIDs was 14% (IQR 10–19%) and the median propensity score in patients who did not receive early NSAIDs was 10% (IQR 7–15%). Before weighting, there were differences primarily in arrival motor and eye score, head abbreviated injury scale, and SBP. After weighting, the covariates were similar between treatment groups with all standardized mean differences less than 0.2. (Supplemental Figure 1)

On multivariable Poisson regression, early NSAID administration was not related to the composite primary outcome of AKI progression or death within the first 7 days from admission. (Figure 2) Additionally, early NSAID administration was not related to the secondary outcomes of AKI progression, AKI improvement, AKI duration, and mortality. When NSAID doses instead of exposure was used in the multivariable models, no dose-dependent effect was identified (data not shown).

Discussion:

In the present study, although only 11% of patients were treated with early NSAIDs for analgesia after trauma, early exposure was not associated with the primary composite outcome of AKI progression or mortality. Furthermore, early NSAID exposure was not associated with increased AKI progression, decreased AKI improvement, prolonged duration, or increased mortality. Given the lack of evidence showing harm, early NSAIDs for analgesia may be underutilized for severely injured patients.

The relationship between AKI and poor outcomes after trauma have been well-described (20–24), but it is unknown to what degree AKI development may be prevented. (25) NSAIDs are known to have nephrotoxic effects, but have not previously been proven to be a risk factor for AKI when used acutely after severe trauma. Given that NSAIDs are frequently utilized in increasingly common MMPRs for post-traumatic pain, assessing the safety of NSAID use in critically ill trauma patients becomes more imperative. (1, 3, 4, 26) In a recent study by Wei *et al.* highlighting the implementation of a MMPR at the study institution, NSAID doses increased significantly after implementation of the MMPR in 2013. (4) Not only did in-hospital milligram morphine equivalents (MME) decrease by 31%, but pain scores improved. ICU patients in their study had a higher MME requirement per day and a higher average pain score, highlighting the potential benefit of a MMPR that includes NSAIDs to decrease opioid use in this population. (4) Similarly, in the present study, the proportion of ICU patients receiving early NSAID administration increased throughout the study period from 12% in 2010 to 30% in 2017. This is likely due to continued maturation and adherence to the MMPR at the study institution.

Risk of AKI is thought to be varied based on the level of inhibition of cyclooxygenase enzyme 1 (COX-1). (27, 28) The proposed mechanism of renal injury from NSAIDs is primarily due to hemodynamically-mediated nephritis, which results from inhibition of COX-1 and subsequent reduction in prostaglandin synthesis. (29) In a healthy patient, prostaglandins do not significantly alter renal hemodynamics. (30) However, in the setting of renal vasoconstriction from intravascular volume depletion, prostaglandins play a critical role in preserving renal blood flow. (31, 32) Several studies have found that risk of AKI increases significantly when NSAIDs are combined with another medication that alters renal hemodynamics, such as diuretics. (27, 28) It is reasonable to suspect that patients recovering from hemorrhage, as frequently seen in the critically ill trauma population, would be at an elevated risk of renal hypoperfusion and NSAID-associated AKI. However, the predominant mechanism of post-traumatic AKI remains unknown and may develop from a diverse series of insults including ischemia-reperfusion injury, excessive resuscitation and subsequent

intracapsular hypertension, post-traumatic systemic inflammation, rhabdomyolysis, and direct kidney trauma. (20, 33–35)

There is some evidence that celecoxib, a selective COX-2 inhibitor, is associated with lower risk of AKI when compared to nonselective NSAIDs, including the other medications evaluated in the present study: naproxen, ibuprofen, and ketorolac. (28, 36) Unfortunately, the present study was underpowered to evaluate AKI risk by individual NSAID medication types. Furthermore, it is unknown if increased NSAID doses are associated with increased risk of AKI. A cohort study of patients receiving care from the Veterans Affairs health care system by Lafrance, *et al.*, observed no dose-dependent relationship between AKI and either naproxen or celecoxib. (27) However, there was a notable increase in AKI risk in patients who utilized multiple different NSAID medications at the same time or who switched between one medication and another. (27) The present study found no dose-dependent relationship during the first 48 hours between NSAID and AKI risk.

While this study failed to show harm from early NSAID exposure in severely-injured trauma patients, it is likely that the inverse probability of treatment weighting incompletely accounted for physician selection of patients who would be administered NSAIDs. The data reveal significant difference in baseline characteristics of patients given early NSAIDs when compared to those not given early NSAIDs, as highlighted in Table 2. While included variables were appropriately balanced after inverse probability of treatment weighting, early NSAID administration appeared to have an imprecise, protective effect for AKI progression and mortality. It is suspected that NSAIDs were avoided in patients whose physiology was more altered than could be ascertained by factors available for analysis.

There are multiple potential reasons for treatment selection bias. Common relative contraindications for NSAID administration include a history of chronic kidney disease, cardiovascular disease, peptic ulcer disease, asthma, or prior NSAID allergy. Only pre-existing ESRD, which can be suspected based on presence of a dialysis catheter or an arteriovenous fistula, was considered in this study because prior medical history is frequently unknown to the physician writing medication orders during the acute post-injury period. At the study institution, neurosurgeons frequently request withholding of NSAIDs for analgesia due to theoretical bleeding risk, which may explain some of the observed selection of patients with higher GCS and lower head abbreviated injury scale in the early NSAID group. The evidence supporting this practice is limited and based primarily on mixed reports of poor outcomes observed in patients who sustain traumatic brain injury on anti-platelet therapy. (37–39) Patients who require multiple procedures and imaging studies are likely to miss scheduled medications, regardless of if the physician deemed the patient appropriate for NSAID administration. (40, 41) Duration of time away from the intensive care unit was not accounted for in this study. Finally, high osmolar contrast media is a known nephrotoxin and may be required for repair of a traumatic vascular injury. (42) This exposure was also not accounted for in this study. Despite the inverse probability of treatment weighted analysis presented in this study, a randomized-controlled trial of early NSAID administration in severely injured trauma patients is warranted to address the unadjusted confounders suspected to remain. While a double-blinded, placebo-controlled trial of early NSAID administration may be the most robust study design, this would be a

resource-intensive undertaking. A more feasible and efficient design would favor a multicenter, open-label, cluster-randomized, multiple crossover, randomized, controlled trial to assess the impact of early NSAID administration on AKI in critically ill trauma patients while minimizing the bias of unknown confounders.

This study has several limitations, in addition to those previously discussed. First, there is no equivalency of NSAID doses as there is with the opioid conversion to morphine milligram equivalents. Therefore, NSAIDs were converted to doses based on institutional practices, which may not be generalizable to other sites. Second, aspirin was not included in this analysis. At the present institution, aspirin is not utilized for pain control. Therefore, although patients on aspirin were included in the study, aspirin was not considered in the analysis. Aspirin is a medication in the NSAID class and has known nephrotoxic effects and should therefore be included in future studies. Third, cohort limitation to those with one or more rib fractures may limit generalizability. Fourth, the duration of NSAID exposure was limited to the first 48-hours. Finally, other potential harms such as gastrointestinal bleeding and ulcer formation were not assessed, which may also influence the decision to treat post-traumatic pain in an ICU with NSAIDs.

The present study failed to show that early NSAID exposure for analgesia was associated with the primary composite outcome of AKI progression or mortality. Furthermore, early NSAID exposure was not associated with increased AKI progression decreased AKI improvement, prolonged duration, or increased mortality. Given the lack of evidence showing harm and the fact that only 11% of patients received early NSAIDs, this treatment for analgesia may be underutilized in severely injured patients. However, a randomized trial evaluating the safety and effectiveness of NSAIDs in this population is warranted given the inability to completely account for selection bias in an observational study design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Flow chart of patients included in analysis

Figure 2:
Relationship between NSAIDs and Outcomes

Figure 3:
Adjusted relationship between NSAIDs and outcomes

Table 1:

Dose conversion for NSAIDs

Medication	One dose equivalent
Ibuprofen	400 mg
Ketorolac	15 mg
Naproxen	250 mg
Celecoxib	200 mg

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Table 2:

Demographic Data

All Patients (n=2,340)	No Early NSAIDs (n=2,072)	Early NSAIDs (n=268)	p Value
Age, years	44 (28–59)	44 (33–56)	0.90
Year			
2010	231 (11%)	30 (11%)	<0.001
2011	284 (14%)	39 (15%)	
2012	322 (16%)	32 (12%)	
2013	322 (16%)	34 (13%)	
2014	325 (16%)	33 (12%)	
2015	194 (9%)	21 (8%)	
2016	217 (11%)	24 (9%)	
2017	177 (9%)	55 (21%)	
Male Sex	1493 (72%)	198 (74%)	0.60
Race/Ethnicity			
White	1143 (55%)	153 (57%)	0.20
Black	275 (13%)	45 (17%)	
Hispanic	494 (24%)	47 (18%)	
Asian	33 (2%)	6 (2%)	
Blunt Mechanism of Injury	1917 (93%)	246 (92%)	0.80
Transferred from Another Emergency Room	413 (20%)	57 (21%)	0.70
Initial Disposition			
ICU	1487 (72%)	204 (76%)	0.20
OR or IR	585 (28%)	64 (24%)	
Injury Severity Score	26 (18–34)	22 (14–29)	<0.001
Arrival Systolic Blood Pressure, mmHG	118 (97–138)	125 (108–142)	<0.001
Arrival Heart Rate	99 (84–118)	98 (84–111)	0.30
Arrival Glasgow Coma Scale	14 (3–15)	15 (8–15)	<0.001
Admission Creatinine	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.30
AKI Day of Arrival	718 (35%)	91 (34%)	0.60
Mechanical Ventilation Day of Arrival	1,457 (70%)	131 (49%)	<0.001
48-hour NSAID Doses	N/A	4 (2–6)	N/A
Receipt 1 doses within 48 hours			
Ibuprofen	N/A	19%	N/A
Naproxen		10%	

All Patients (n=2,340)	No Early NSAIDs (n=2,072)	Early NSAIDs (n=268)	p Value
<i>Celecoxib</i>		10%	
<i>Ketorolac</i>		79%	

Continuous data presented as: median (IQR) ICU – Intensive Care Unit, OR – Operating Room, IR – Interventional Radiology

Table 3:

Outcome Measures

All Patients (n=2,340)	No Early NSAIDs (n=2,072)	Early NSAIDs (n=268)	p Value
Composite Primary Outcome: Progression or Mortality within 7 days	382 (18%)	25 (9%)	<0.001
AKI Progression	221 (11%)	15 (6%)	0.01
AKI Improvement	673 (33%)	87 (33%)	1.0
AKI Duration	0 (0–1) Mean 1.0	0 (0–1) Mean 0.8	0.05
Mortality	138 (9%)	10 (4%)	0.006

Continuous data presented as: median (IQR) AKI – Acute Kidney Injury