CLINICAL RESEARCH STUDY

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Prior Exposure to Nonsteroidal Anti-inflammatory Drugs Reduces the Rate of Organ Failure and In-Hospital Mortality in Acute Pancreatitis

Antonio Mendoza Ladd, MD,[a,1] Darwin Conwell, MD, MSc,[b] Thomas E. Burroughs, PhD,[c] Munigala Satish, MBBS, MPH[c]

[a]Department of Internal Medicine, Division of Gastroenterology, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas; [b]Division of Gastroenterology, Hepatology and Nutrition. The Ohio State Universtiy Wexner Medical Center, Columbus, Ohio; [c]Saint Louis University Center for Health Outcomes Research, St. Louis, Missouri.

ABSTRACT

BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been linked recently to a lower expression of pro-inflammatory cytokines in humans with acute pancreatitis. Because it is unclear if this effect results in clinical benefits, the aim of this study was to determine if prior NSAID exposure improves immediate clinical outcomes.

METHODS: Retrospective medical record review of adult patients admitted with acute pancreatitis. Cases were extracted from a national Veterans Affairs database using International Classification of Diseases, Ninth Revision codes. Prior NSAIDs use was determined through pharmacy data claims. The rates of acute kidney injury, respiratory failure, cardiovascular failure, and in-hospital mortality were compared between those with prior NSAID use (AP+NSAID) and those without it (AP−NSAID) using univariate and multivariate analysis.

RESULTS: A total of 31,340 patients were identified: 28,364 AP+NSAID and 2976 AP−NSAID. The median age was 60 years, 68% were white, and the median hospital stay was 4 days. Approximately 2% of patients died during the hospitalization. After adjusting for demographics and other covariates, patients in the AP+NSAID arm had lower rates of acute kidney injury, $P = .0002$), cardiovascular failure ($P = .025$), any organ failure ($P \leq .0001$), and in-hospital mortality ($P < .0001$).

CONCLUSION: Prior use of NSAIDs is associated with a lower incidence of organ failure and in-hospital mortality in adult patients with acute pancreatitis. The role of NSAIDs as therapeutic agents in this condition should be evaluated in interventional trials.

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KEYWORDS: Acute pancreatitis; Clinical outcomes; In-hospital mortality; Inflammations; NSAIDs; Organ failure

INTRODUCTION

Acute pancreatitis remains a public health concern worldwide. In the United States alone it accounts for >290,000 admissions annually with a cost of $2.5 billion.[1] During severe acute pancreatitis, pro-inflammatory cytokines set in motion the systemic inflammatory response syndrome, which is responsible for the development of organ failure in the early phases of the disease.[2] Development of organ failure defined as the presence of acute kidney injury, cardiovascular failure, or respiratory failure—either alone or in

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Requests for reprints should be addressed to Antonio Mendoza Ladd, MD, Department of Medicine, Division of Gastroenterology, University of New Mexico School of Medicine, Albuquerque, NM 87131.

E-mail address: dr_ladd25@yahoo.com

[1] Present Affiliation: Department of Internal Medicine, Division of Gastroenterology, University of New Mexico Health Sciences Center, Albuquerque.

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combination—is the main factor driving the high mortality rate of severe cases.[2,3]

Animal models and, most importantly, a recent human clinical trial, have demonstrated that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the expression of pro-inflammatory cytokines[4-9] in acute pancreatitis. Unfortunately, whether this reduction translates into improved immediate clinical outcomes remains unknown. Using the available data to date, we hypothesized that NSAIDs have anti-inflammatory effects in humans with acute pancreatitis that result in improved immediate clinical outcomes. To test our hypothesis, we carried out this large-scale retrospective cohort study utilizing the rates of organ failure and in-hospital mortality as primary outcomes.

CLINICAL SIGNIFICANCE

- First-time nonsteroidal anti-inflammatory drugs (NSAIDs) or any drug is associated with improved immediate clinical outcomes in acute pancreatitis.
- The benefit of NSAIDs seems to be a class effect, rather than characteristic of individual agents within it.
- Interventional trials should explore NSAIDs as treatment for acute pancreatitis.

METHODS

Study Design and Data Source

This was a retrospective study of medical records of adult (>18 years of age) patients with acute pancreatitis hospitalized from September 1999 through December 2015. The dataset was compiled using inpatient and outpatient records maintained electronically by the US Department of Veterans Affairs (VA) health care system. Variables of interest were extracted using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes.

Identifying Index Case of Acute Pancreatitis

All cases (n = 46,655), were identified using ICD-9 code 577.0 for acute pancreatitis (primary inpatient diagnosis code). To maximize identification of first-episode cases, a 2-year washout period was applied to exclude patients with recurrent acute pancreatitis and those diagnosed within 2 years of entry into the database (n = 12,529).

Primary Predictor

The primary predictor variable of interest was any NSAIDs use prior to the index acute pancreatitis admission. Prior use of NSAIDs was defined as the filling of at least one ≥30-day prescription of any NSAIDs prior to the index admission as evidenced by pharmacy claims. The NSAIDs exposure duration was arbitrarily defined as either <1 year (≥1 day but <1 year) or >1 year. A list of the NSAIDs evaluated in this study is available in Appendix 1 (available online).

Outcomes of Interest

The outcomes of interest were organ failure and in-hospital mortality. Organ failure was defined as the presence of acute kidney injury (ICD-9 code 584.9), respiratory failure (ICD-9 code 518.81), or cardiovascular failure (ICD-9 code 458.9), either alone or in combination during the index admission. Death during the index admission was considered as in-hospital mortality.

Etiology of Acute Pancreatitis

Cases with associated ICD-9 codes for gallstones (ICD codes 574, 574.1, 574.3, 574.5, 574.7, 574.8, 574.9) were classified as gallstone related and the rest as non-gallstone-related cases.

Covariates

These included demographic information such as age, sex, and race. Presence of gallstones, alcohol use, smoking status, diabetes mellitus, pancreatic cancer, chronic pancreatitis; as well as procedures such as cholecystectomy, endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous and open biliary procedures were also evaluated.

Exclusion Criteria

All patients who filled a ≥30-day prescription for NSAIDs for the first time after the index admission (n = 2786) were excluded.

Statistical Analysis

Patients were divided into 2 groups: those with prior NSAIDs use (AP+NSAID) and those without it (AP−NSAID). Data analysis was performed using SAS software version 9.3 (SAS Inc, Cary, NC). Patient characteristics in both groups were compared using frequencies, median, and interquartile ranges. Significance was tested using univariate analysis (chi-square test, Fisher exact test, or Wilcoxon signed-rank test where appropriate). All variables with a P-value < .05 on univariate analysis were included in the final multivariate logistic regression model for evaluating the independent predictors of outcomes. Significance tests were performed using 2-tailed hypothesis, and the level of significance (α) was set to 0.05. This study was approved by the St. Louis Veterans Affairs Medical Center institutional review board.

RESULTS

Overall Cohort

A total of 31,340 patients entered the final analysis. The patient selection process is illustrated in Figure 1, and their

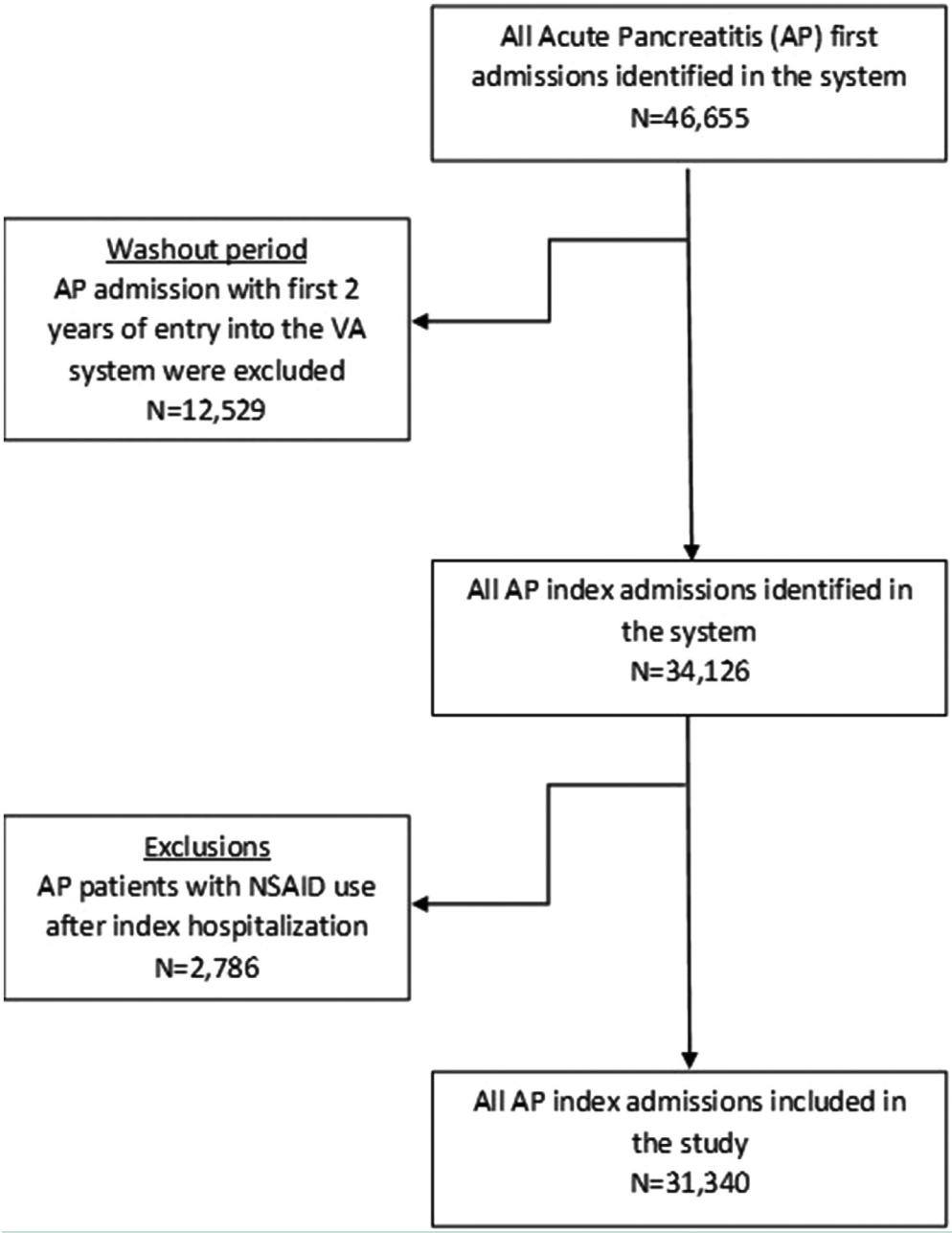

Figure 1 Patient selection process. AP = acute pancreatitis; NSAID = non-steroidal anti-inflammatory drug; VA = veterans administration.

main demographic characteristics are summarized in Table 1. The median age was 60 years, 95% were male, and 68% were white. The median length of hospital stay was 4 days (interquartile range 2-7 days) and 2.2% of patients died during the index admission. Overall, acute kidney injury was noted in 10.1%, respiratory failure in 3.6%, and cardiovascular failure in 0.7% of the entire cohort.

Characteristics and Outcomes by NSAIDs Use

A total of 28,364 (90.5%) and 2976 (9.5%) patients were included in the AP+NSAID and AP−NSAID arms, respectively. Diabetes mellitus, smoking, and alcohol consumption were significantly higher in the AP+NSAID group; while age, gallstone etiology, rate of ERCP, and pancreatic cancer were significantly higher in the AP−NSAID group ($P < .05$) (Table 1). Univariate analysis revealed an overall significantly lower rate of acute kidney injury (10% vs 12%; $P = .001$), cardiovascular failure (0.7% vs 1.1%; $P = .006$), respiratory failure (3.6% vs 4.5%; $P = .011$), any organ failure (12.3% vs 14.5%; $P \leq .001$), and in-hospital mortality (1.9% vs 4.9%; $P \leq .001$) in the AP+NSAID group (Figure 2).

After adjusting for covariates, multivariate analysis revealed that the AP+NSAID group had a significantly lower rate of acute kidney injury (odds ratio [OR] 0.79;

Table 1 Patient Demographics

	All AP Patients N = 31,340 n (%)	AP -NSAID, n = 2976 n (%)	AP +NSAID, n = 28,364 n (%)	*P* Value
Age in years (median, IQR)	60 (53-68)	62 (53-70)	60 (53-68)	.028
Sex				.222
Male	29,795 (95.07)	2843 (95.53)	26,952 (95.02)	
Female	1545 (4.93)	133 (4.47)	1412 (4.98)	
Race*				< .0001
White	21,268 (68.31)	2268 (77.86)	19,000 (67.32)	
Black	8041 (25.83)	494 (16.96)	7547 (26.74)	
Other races	1827 (5.87)	151 (5.18)	1676 (5.94)	
Smoking history*				< .0001
Non-smoker	9423 (30.38)	927 (32.48)	8496 (30.17)	
Current smoker	17,580 (56.68)	1472 (51.58)	16,108 (57.20)	
Past smoker	4013 (12.94)	455 (15.94)	3558 (12.63)	
Etiology				< .0001
Gallstones	5396 (17.22)	603 (20.26)	4793 (16.90)	
Non-gallstone	25,944 (82.78)	2373 (79.74)	23,571 (83.10)	
Comorbidities				
History of alcohol	15,918 (50.79)	1302 (43.75)	14,616 (51.53)	< .0001
DM	16,876 (53.85)	1134 (38.10)	15,742 (55.50)	< .0001
Pancreatic cancer	110 (0.35)	20 (0.67)	90 (0.32)	.002
Biliary/ampullary tumors	35 (0.11)	6 (0.20)	29 (0.10)	.1223
Chronic pancreatitis	2615 (8.34)	257 (8.64)	2358 (8.31)	.545
Procedures				
Cholecystectomy	1020 (3.25)	112 (3.76)	908 (3.20)	.10
ERCP	1674 (5.34)	201 (6.75)	1473 (5.19)	.0003
Percutaneous biliary procedures	57 (0.18)	6 (0.20)	51 (0.18)	.791
Open biliary procedures (Common bile duct exploration)	92 (0.29)	12 (0.40)	80 (0.28)	.245

AP = acute pancreatitis; DM = diabetes mellitus; ERCP = endoscopic retrograde cholangiopancreatography; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug.

95% CI, 0.70-0.89; $P = .0002$), cardiovascular failure (OR 0.64; 95% CI, 0.44-0.95; $P = .025$), any organ failure (OR 0.79; 95% CI, 0.71-0.89; $P \leq .0001$), and in-hospital mortality (OR 0.44; 95% CI, 0.36-0.54; $P < .0001$). The rate of respiratory failure, however, lost its statistical significance in this analysis (OR 0.84; 95% CI, 0.69-1.01; $P = .069$) (Table 2). Comparison by duration of NSAIDs exposure was also performed. A total of 5975 and 22,389 patients

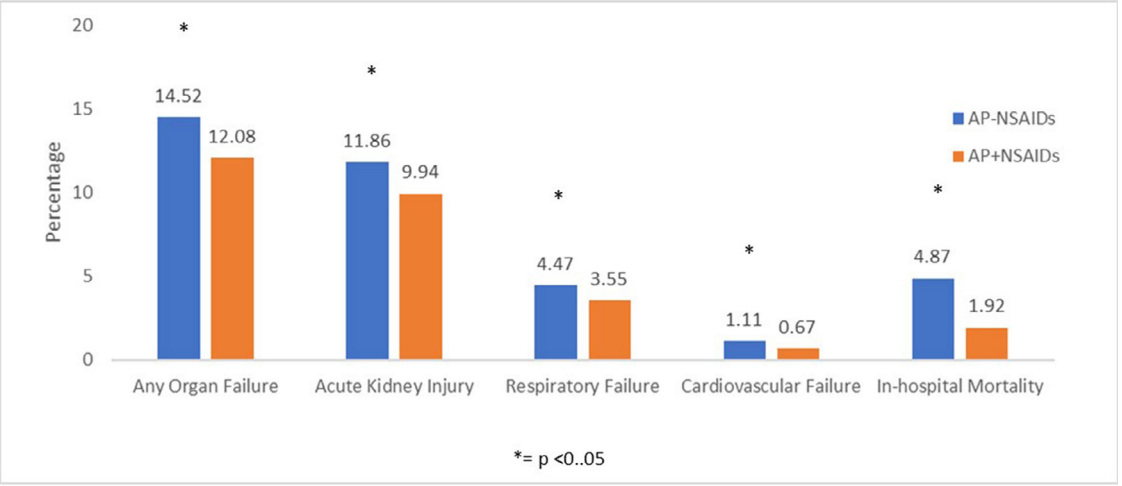

Figure 2 Univariate analysis of primary outcomes. AP = acute pancreatitis; NSAID = nonsteroidal anti-inflammatory drug.

Table 2 Multivariate Analysis of Primary Outcomes

Outcomes	Odds Ratio (95% CI)	*P* Value
Acute kidney injury	0.79 (0.70-0.89)	.0002
Acute respiratory failure	0.94 (0.69-1.01)	.069
Cardiovascular failure	0.64 (0.44-0.95)	.025
Any organ failure	0.79 (0.71-0.89)	< .0001
In-hospital death	0.44 (0.36-0.54)	< .0001

CI = confidence interval.

used NSAIDs for <1 year and >1 year, respectively. The rates of all outcomes were equally significantly lower in both exposure duration groups, with the exception again of respiratory failure. The rate of this particular outcome was lower in the <1 year group but lost its statistical significance in the >1 year group (Table 3).

DISCUSSION

Despite extensive research, a drug capable of improving clinical outcomes in acute pancreatitis has not been identified. Multiple agents with diverse mechanisms of action such as antisecretory agents, protease inhibitors, antioxidants, and anti-inflammatory agents have failed to demonstrate palpable benefits.[10-23] However, recent evidence suggests that NSAIDs may have a role beyond their well-established prophylactic effect in post-ERCP pancreatitis.[24-26]

Animal models have demonstrated that NSAIDs are effective at reducing the expression of pro-inflammatory cytokines and the degree of histological damage to the gland in acute pancreatitis.[5,6,8,10,11] Perhaps the study with the highest clinical application potential was that by Cosen-Binker et al.[5] In this study, the authors evaluated rats that received ibuprofen, flurbiprofen, or aspirin (ASA) at different intervals prior to and after induction of acute pancreatitis. Flurbiprofen and ibuprofen administered 1 hour pre-induction and up to 4 hours post-induction significantly reduced the expression of C-reactive protein, interleukin (Il)-6, IL-10, and heat shock protein (HSP72). The degree of histological damage to the pancreas was also reduced.

Table 3 Multivariate Analysis of Primary Outcomes by NSAIDs Exposure Duration

Outcome	Odds Ratio (95% CI)	*P* Value
Acute kidney injury		
No NSAIDs use	Reference	
<1 year	0.71 (0.61-0.83)	< .001
>1 year of NSAIDs use	0.82 (0.72-0.93)	.001
Acute respiratory failure		.069
No NSAIDs use	Reference	
<1 year	0.77 (0.61-0.97)	.029
>1 year of NSAIDs use	0.86 (0.71-1.05)	.146
Cardiovascular failure		
No NSAIDs use	Reference	
<1 year	0.57 (0.34-0.94)	.027
>1 year of NSAIDs use	0.67 (0.45-0.99)	.046
Any organ failure		
No NSAIDs use	Reference	
<1 year	0.72 (0.63-0.82)	< .001
>1 year of NSAIDs use	0.82 (0.73-0.92)	< .001
In-hospital death		
No NSAIDs use	Reference	
<1 year	0.43 (0.32-0.56)	< .001
>1 year of NSAIDs use	0.49 (0.36-0.55)	< .001

CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drug.

These anti-inflammatory effects seen in animals were reproduced in humans for the first time in a recent trial. Huang et al[9] demonstrated that the expression of tumor necrosis factor α and IL-6 at days 4 and 8 post admission were significantly lower in patients with acute pancreatitis treated with standard of care plus cyclooxygenase-2 inhibitors than in those with standard of care alone.[9] Unfortunately, the authors were not able to find any differences in clinical outcomes and hence, the clinical relevance of these finding remains unknown.

The effect of NSAIDs on clinical outcomes of acute pancreatitis has been scarcely studied, perhaps out of concern due to a few case reports in which NSAIDs have been proposed as a cause of acute pancreatitis.[27-30] However, no convincing conclusions have been drawn from them. In fact, indomethacin, an NSAID that has been targeted in some of these reports, has convincingly proven to be effective in preventing post-ERCP pancreatitis in well-designed studies.[24,25]

Two underpowered interventional studies have evaluated the role of NSAIDs on pain control in acute pancreatitis. Ebbehøj et al[31] reported that the number of days in pain and the number of opiate injections were significantly lower in patients treated with rectal indomethacin when compared with placebo. Similarly, Peiró et al[32] randomized patients to metamizole or morphine and established that pain control within 24 hours of admission was better in the metamizole arm. In a retrospective study by Baxter et al,[33] a significantly lower incidence of pancreatic necrosis and pseudocyst formation was documented in patients with prior NSAIDs use compared with those without it. Interestingly, the authors of this study also reported a lower concentration of C-reactive protein in the NSAIDs group, correlating with the results recently reported by Huang et al.[9]

Due to the available evidence to date, this study was carried out in an attempt to establish if prior exposure to NSAIDs is associated with improved immediate clinical outcomes in acute pancreatitis. In order to avoid the low-power shortcoming of the above-mentioned studies, a large national patient database was analyzed. The decision to adopt a retrospective design was made given the challenges of performing controlled clinical trials in acute pancreatitis. Using this methodology, the findings demonstrated a statistically significant association between prior NSAIDs use and a lower rate of organ failure and in-hospital morality. These findings confirmed our hypothesis that the effect of NSAIDs in attenuating the inflammatory response in

humans with acute pancreatitis translates into improved immediate clinical outcomes.

The exact mechanism by which NSAIDs exert this beneficial effect is not completely understood at this time. As a medication class, NSAIDs are best known to inhibit cyclooxygenases that produce prostaglandins and thromboxanes. However, attributing this beneficial effect solely to this mechanistic explanation may be an underestimation of their full therapeutic capabilities. Studies on ASA show that its anti-inflammatory effects go well beyond cyclooxygenase inhibition, including inhibition of the pivotal nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[34] and induction of certain types of eicosanoids, such as 15-epi-lipoxins. These lipoxins promote resolution of inflammation by counter-regulating proinflammatory mediators such as tumor necrosis factor α, IL-1β, IL-6, and IL-4.[35-38] Whether these anti-inflammatory effects are class related or characteristic of ASA alone remains unknown. Although ASA was not one of the NSAIDs included in the present study, >15 different NSAIDs were analyzed in it, suggesting that the beneficial effect observed is a class effect. Similar findings have been reported in the post-ERCP pancreatitis prevention literature, where different NSAIDs have proven effective.[24-26] However, research on specific NSAIDs is needed to establish if there are differences in their efficacy.

The specific exposure time necessary for NSAIDs to exert the benefits observed in this study remains similarly uncertain. Given its retrospective design, the prior NSAIDs exposure time was arbitrarily divided into <1 and >1 year. Nevertheless, the results showed that patients in both groups experienced benefits. This suggests that NSAIDs have both immediate and cumulative effects that result in lower rates of organ failure and mortality. Because the study by Huang et al[9] was underpowered to establish differences in these outcomes, the only remaining available background to justify these possible immediate effects comes from the post-ERCP pancreatitis prevention literature. When administered within 1 hour of the procedure, NSAIDs are effective at preventing acute pancreatitis;[24-26] confirming that they exert immediate anti-inflammatory effects that prevent it. Similar immediate effects were seen in the present study. Patients exposed to NSAIDs as early as 1 day prior to acute pancreatitis onset were less likely to develop organ failure or to die in the hospital. This may be related to an immediate inhibition in the synthesis of NF-κB and proinflammatory cytokines; but future research will be required to further clarify this effect. On the other hand, the explanation for the cumulative effect of NSAIDs seen in this study may be more complex. This cumulative effect may be related to a persistent anti-inflammatory state derived from long-term modification or regulation of inflammation pathways similar to the ones accounting for decreased risk of different cancers.[39]

The results of the present study are both exciting and thought provoking. Although these findings will need to be verified with further research, the potential clinical implications of its verification could be groundbreaking. If NSAIDS are proven to be effective therapeutic agents for acute pancreatitis, their addition to the current standard-of-care treatment would represent the single most important break-through in the management of this condition in over 50 years.

The present study has several important strengths. First, its large sample size allowed it to prove the working hypothesis with statistically significant results and excellent power. Second, it suggests the hypothesis is true regardless of the etiology of acute pancreatitis, risk factors, and duration of NSAIDs exposure. Third, it included a variety of NSAIDs, suggesting that this effect is class related and not specific to certain agents in it. Fourth, the 2-year washout period applied to the cohort minimized inclusion of patients with recurrent acute pancreatitis that may have biased the results.

Its main limitations are those inherent to its retrospective design. By relying on ICD-9 codes and prescription databases in a VA system, timing of NSAIDs consumption prior to admission, compliance in the AP+NSAIDs group and use of over-the-counter NSAIDs among the entire patient population could not be accounted for. Also, the NSAIDs use prevalence documented in the study may have been influenced by clinical and socioeconomic factors specific to patients in the VA system, thereby limiting generalization of its results. Despite its limitations, this study contributes provocative new information to the acute pancreatitis treatment literature.

In conclusion, to the best of our knowledge this is the first study linking a drug to lower rates of organ failure and in-hospital mortality in patients with acute pancreatitis. The present results should serve as background for future interventional studies exploring the therapeutic potential of NSAIDs in this disease. Such studies should focus on aspects such as therapeutic window, dosage, side effects, and effect on long-term outcomes such as rates of walled-off necrosis and pseudocyst formation. If proven effective in clinical trials, NSAIDs could substantially change the current treatment paradigms of acute pancreatitis in a simple and inexpensive manner.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.amjmed.2021.10.020.

APPENDIX: LIST OF NSAIDS EVALUATED IN THIS STUDY

ibuprofen
flurbiprofen
diclofenac
celecoxib
sulindac
oxaprozin
naproxen
etodolac
piroxicam
fenoprofen
indomethacin
ketoprofen
meclofenamate
mefenamic acid
meloxicam
nabumetone
ketorolac
tolmetin