Rectal Indomethacin Does Not Mitigate the Systemic Inflammatory Response Syndrome in Acute Pancreatitis: A Randomized Trial

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INTRODUCTION: **Experimental data suggest that nonsteroidal antiinflammatory drugs may prevent disease severity and mortality in acute pancreatitis (AP). The aim of this study was to compare the efficacy of rectal indomethacin vs placebo in reducing the systemic inflammatory response syndrome (SIRS) score in a high-risk AP population for clinical progression.**

METHODS: **We conducted a single-center, quadruple-blinded, randomized, placebo-controlled trial. Eligible criteria were subjects with AP and SIRS within 72 hours of presentation and those without organ failure. Subjects were allocated in a 1:1 ratio to indomethacin or placebo using simple randomization. Both interventions were administered rectally every 8 hours for 6 doses and compared using both intention-to-treat and per-protocol analyses.**

RESULTS: **A total of 42 subjects (mean age 52 years, 55% men) were randomized to indomethacin (n = 18) or placebo (n = 24). There was no significant difference between the indomethacin and placebo groups in the change of SIRS score, proportion of subjects with SIRS, and distribution of SIRS scores at 24, 48, and 72 hours from randomization. There were no significant differences in the change of C-reactive protein levels at 48 hours or clinical outcomes between both treatment groups. Indomethacin was as safe as placebo, with 2 adverse events occurring in the placebo and none in the indomethacin arm.**

DISCUSSION: **Rectal indomethacin can be safely administered over 48 hours; however, it is not superior to placebo in reducing the SIRS or clinical progression in a high-risk population with AP (ClinicalTrials.gov: NCT02692391).**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A716

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INTRODUCTION

Acute pancreatitis (AP) is one of the leading causes of gastrointestinal-related emergency department visits and hospital admissions, with an estimated global incidence of 34 per 100,000 population (1). Although most of the subjects with AP have a mild clinical course, 10%–15% progress to severe AP (SAP) with persistent organ failure (OF), and approximately 2% die (2). Progression to SAP increases the risk of mortality (~20%–50%), healthcare utilization, and post-AP long-term complications (e.g., diabetes mellitus and, exocrine insufficiency) (2–5). Despite increasing knowledge of AP pathogenesis, there is still no effective pharmacologic agent to prevent clinical progression, manifesting by worsened disease severity and/or death (6,7). Therefore, randomized controlled trials (RCTs) that test pharmaceutical agents to prevent clinical progression in AP are needed.

The onset of AP is followed by an exaggerated immune response that plays a critical role in the pathogenesis of SAP and may represent a potential therapeutic target for AP. The initial parenchymal injury activates inflammatory cells and transcription factors, which lead to the production of various proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8 (8,9). The proinflammatory

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stimuli induce the production of cyclooxygenase (COX)-2, a rate-limiting enzyme that converts arachidonic acid to prostaglandins, leukotrienes, and thromboxanes (10). These inflammatory mediators are released into the systemic circulation, contributing to the development of systemic inflammatory response syndrome (SIRS), multiorgan failure, and even death (11,12).

Nonsteroidal antiinflammatory drugs (NSAIDs) are potent inhibitors of COX enzymes, which prevent prostaglandin biosynthesis and could reduce the inflammatory response of AP (13). Nonselective NSAIDs are routinely used to prevent postendoscopic retrograde cholangiopancreatography pancreatitis, given their efficacy, safety, availability, and affordability (14,15). Experimental studies and a recent RCT have suggested that selective COX-2 inhibitors are effective in reducing the risk of persistent OF in subjects with predicted SAP (16,17). However, there are limited data on the role of nonselective NSAIDs for preventing clinical progression in subjects with established AP. Early studies in animal models showed that the administration of indomethacin or diclofenac after AP induction decreased disease severity and mortality (18–22). In humans, 2 RCTs have evaluated the analgesic effect and safety profile of nonselective NSAIDs on subjects with AP (23,24). However, to our knowledge, no RCTs have evaluated the efficacy of nonselective NSAIDs in preventing the clinical progression of AP.

SIRS precedes OF in AP and compares favorably with other clinical scores in predicting persistent OF, primarily because of its strong negative predictive value (25,26). In this trial, we studied subjects with AP who had SIRS at the time of enrollment because they represent a high-risk patient population for clinical progression (2). Furthermore, we used the SIRS score as a surrogate end point for disease progression, as has been applied in other recent RCTs of AP (27,28). We hypothesized that rectal indomethacin was more effective than placebo in reducing SIRS at 48 hours in subjects with AP and high risk of clinical progression.

METHODS

Study design

This single-center, parallel-group, quadruple-blinded, randomized, placebo-controlled trial was conducted at the University of Pittsburgh Medical Center, Pittsburgh, PA, USA. Before initiation, the study was approved by the institutional review board of the University of Pittsburgh and was registered in ClinicalTrials.gov (NCT02692391). Informed consent was obtained from all subjects. An internal data and safety monitoring board provided regulatory oversight. The study was performed according to the original protocol without deviations. All the authors had access to the study data and approved the final manuscript.

Study population

Adult subjects (18 years or older) admitted with AP were assessed for eligibility. AP was defined based on at least 2 of the following criteria: characteristic abdominal pain; serum amylase and/or lipase >3× upper limit of normal; or findings of AP on cross-sectional images (29). Subjects with SIRS within 72 hours of initial presentation to the emergency department were eligible for randomization. SIRS was defined by the presence of 2 or more abnormal parameters tabulated in Supplementary Table 1 (http://links.lww.com/CTG/A716) (30). Exclusion criteria included SIRS onset after 72 hours of initial hospital presentation, established cardiovascular failure (systolic blood pressure ≤90 mm Hg), respiratory failure (partial pressure of oxygen <60 mm Hg), renal failure (creatinine >1.5 mg/dL), active peptic ulcer disease, pregnancy, active use of NSAIDs within 1 week of presentation, and allergy to NSAIDs. Subjects were identified by daily electronic notifications of lipase levels sent to the study team. In addition, care teams in the emergency department, inpatient units, and pancreatobiliary consult service were educated to directly contact the study team for potential subjects.

Randomization and masking

Subjects were randomly assigned in a 1:1 allocation ratio to either rectal indomethacin or placebo control group. Simple nonblock randomization was used. The randomization sequence was generated using computer-based random numbers and was only available to the central University of Pittsburgh Medical Center pharmacy for allocation concealment. A 24-hour pharmacist was assigned to implement the randomization sequence immediately after the study coordinator communicated a patient's enrollment. Study subjects, investigators, outcome evaluators, and care providers were blinded to treatment assignment.

Study interventions

Subjects randomized to the intervention arm received a loading dose of two 50-mg indomethacin suppositories, which was rectally administered by the registered nurse assigned to the subjects care team. This was followed by five 50-mg maintenance doses rectally administered at intervals of 8 hours for a total of 6 doses. The rectal route was selected based on previous data demonstrating more rapid and complete availability of indomethacin when compared with oral administration (31). Subjects in the placebo arm received glycerin suppositories at similar intervals, identical in number, shape, size, color, and packaging to the intervention arm. Subjects in both groups received intravenous pantoprazole for gastrointestinal prophylaxis, as-needed opioids for analgesia, and standard-of-care treatment of AP at the direction of the treating physician (7,32).

Data collection

SIRS score (0–4) was calculated on randomization and at 24, 48, and 72 hours from the time of initial intervention. The levels of C-reactive protein (CRP) were measured at the time of randomization and at 48 hours from the initial intervention. Other clinical outcomes and treatment strategies were evaluated daily during hospitalization. OF was defined as a score of ≥2 for cardiovascular, respiratory, or renal systems using the Modified Marshall Scoring System (33). Persistent OF was defined as OF that lasted for ≥48 hours. Severity of AP was categorized as mild, moderately severe, and severe according to the Revised Atlanta Classification (34). Daily recorded data were used for *post hoc* calculation of the pancreatitis activity scoring system (PASS) (35). Abdominal computed tomography was obtained at the discretion of care providers and was interpreted by blinded abdominal radiologists. Adverse events (AEs) were monitored daily during the admission. Major AEs were reported to the institutional review board and data and safety monitoring board, including gastrointestinal bleeding, perforated viscus, acute kidney injury (increase in serum creatinine ≥0.3 mg/dL within 48 hour), allergic reaction, myocardial infarction, and death.

Study outcomes

The predefined primary end point was the change in the SIRS score from randomization to 48 hours after the initial

intervention. Secondary end points were classified as surrogate, clinical, and safety outcomes. Surrogate outcomes included change in SIRS score at 24 and 72 hours and change in CRP levels at 48 hours. Reported clinical outcomes were as follows: (i) AP severity, (ii) progression to OF, (iii) pancreatic necrosis, (iv) length of hospital and ICU stay, (v) PASS score at 24/48/72 hours, and (vi) mortality.

Statistical analysis

The sample size calculation was based on our prospective observational data on the incidence of SIRS among hospitalized subjects with AP and on the assumption that a mean SIRS score reduction of 0.5 with a SD of 0.64 was clinically meaningful (25,32). We estimated that a sample size of 42 subjects was needed to detect a difference of 0.5 in the SIRS change (baseline to 48 hour) between the indomethacin and placebo arms, with a power of 80% and a one-sided alpha of 0.05.

Descriptive statistics are reported as absolute values (percentage), mean ± SD, and median (interquartile range [IQR]), as appropriate. For the analysis of the primary end point, we used a two-sided Wilcoxon rank-sum test to analyze the difference in the change of SIRS scores at 48 hour between the treatment groups. Missing data of the primary outcome were handled using the last observation carried forward imputation method. Comparisons of baseline characteristics and secondary end points were evaluated using the χ^2 or Fisher's exact tests for categorical data and *t* test or Wilcoxon rank-sum test for continuous data, as appropriate. Kaplan-Meier methodology was used to estimate the overall OF risk in each treatment group, and the log-rank test was used to test the difference between treatments. Subjects were followed up until the date of OF or censoring. All analyses were performed according to the intention-to-treat principle. Per-protocol analysis was also performed. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Study participants

Between August 2013 and July 2019, a total of 418 subjects were screened, of which 42 were randomized to indomethacin (n = 18) and placebo (n = 24) groups (Figure 1). Baseline characteristics were equally distributed between treatment groups (Table 1). At the time of randomization, the mean age was 51.5 ± 19.5 years, 54.8% subjects were men, 83.3% were White, 40.5% had gallstone etiology, and 30.9% had previous AP. The median duration of symptoms before hospital presentation was 12 hour (IQR: 3.8, 20.0). We observed no significant difference in the amount of fluids administered in the first 6 hour (1,750 mL vs1,600 mL, $P = 0.66$) or first 24 hour (4,400 mL vs4,000 mL, $P = 0.99$).

Subjects were randomized at a median of 31 hour (IQR: 22, 47.2) from hospital presentation and received the assigned therapy 2.5 hour (IQR: 1.3, 4.5) from randomization. Compliance with the full treatment regimen was similar for subjects assigned to indomethacin (67%) or placebo (75%) treatment ($P = 0.55$; Figure 1).

Primary end point

The change of SIRS scores at 48 hour from randomization was similar for subjects receiving indomethacin (−1.0 ± 1.24) vs placebo (−0.96 ± 0.81) ($P = 0.87$) (Table 2 and Figure 2).

Secondary end points

Surrogate outcomes. There was no significant difference in the change of SIRS score from randomization to 24 hour ($P = 0.16$) and to 72 hour ($P = 0.72$) between the treatment arms. SIRS was present in a similar proportion of subjects at 24 hour (indomethacin 88.9% vs placebo 70.8%, $P = 0.26$), 48 hour (61.1% vs 62.5%, $P = 1.00$), and 72 hour (44.4% vs 50%, $P = 0.72$). The distribution of SIRS scores (0–4) was not significantly different across treatment groups at 24 hour ($P = 0.34$), 48 hour ($P = 0.24$), and 72 hour ($P = 0.90$). We observed no significant differences between treatment groups in the mean CRP levels at 48 hour

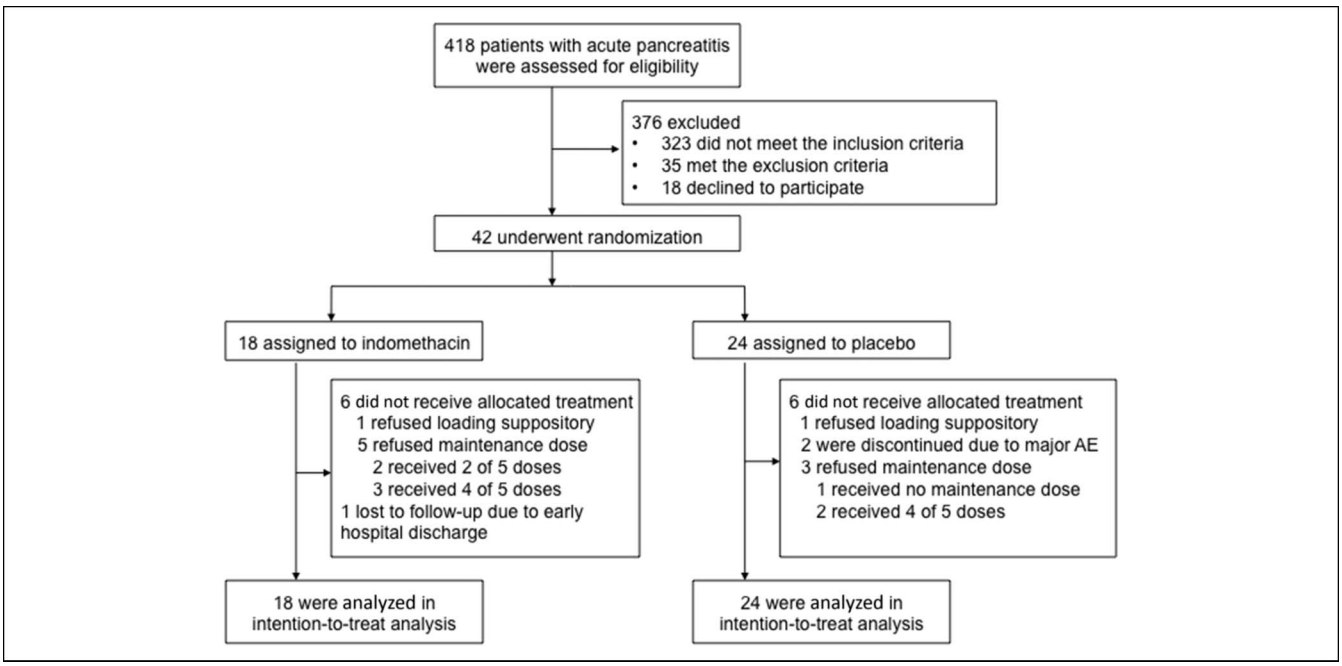

Figure 1. Study flow chart.

Table 1. Baseline characteristics according to randomization

Characteristics	Total (n = 42)	Indomethacin (n = 18)	Placebo (n = 24)	*P* value
Age, mean ± SD	51.5 ± 19.5	51.8 ± 16.7	51.22 ± 21.7	0.93[a]
Male sex, n (%)	23 (54.8)	7 (38.9)	16 (66.7)	0.07[b]
BMI (kg/m^2), mean ± SD	30.9 ± 8.4	32.7 ± 7.5	29.5 ± 8.9	0.22[a]
White race, n (%)	35 (83.3)	15 (83.3)	20 (83.3)	1.00[c]
Transferred, n (%)	23 (54.8)	11 (61.1)	12 (50.0)	0.47[b]
Preexisting diabetes, n (%)	10 (23.8)	4 (22.2)	6 (25.0)	1.00[c]
Etiology of AP				0.63[c]
Gallstones	17 (40.5)	7 (38.9)	10 (41.7)	
Alcoholic	7 (16.7)	5 (27.8)	2 (8.3)	
Idiopathic	5 (11.9)	2 (11.1)	3 (12.5)	
Hypertriglyceridemia induced	7 (16.7)	2 (11.1)	5 (20.8)	
Post-ERCP	1 (2.4)	0 (0)	1 (4.2)	
Other	5 (11.9)	2 (11.1)	3 (12.5)	
History of AP episode, n (%)	13 (31.0)	6 (33.3)	7 (29.2)	0.77[b]
Fluid volume administered in the first 6 hr, median mL (IQR)	1,600 (1,000, 2000)	1,750 (1,000, 2000)	1,600 (1,000, 2,100)	0.66[d]
Fluid volume administered in the first 24h, median mL (IQR)	4,000 (3,000, 5,200)	4,400 (2,300, 5,200)	4,000 (3,000, 5,800)	0.99[d]
SIRS score at randomization, n (%)				1.00[c]
2	19 (45.2)	8 (44.4)	11 (45.8)	
3	20 (47.6)	9 (50.0)	11 (45.8)	
4	3 (7.1)	1 (5.6)	2 (8.3)	
Serum CRP level at randomization, mean ± SD	24.1 ± 10.1	24.5 ± 11.0	23.8 ± 9.6	0.70[d]
PASS at randomization, median (IQR)	196 (165, 240)	203 (163, 240)	196 (165, 242)	0.99[d]
Hours from pain onset to admission, median (IQR)	12.0 (3.8, 20.0)	11.8 (3.5, 19.8)	12.5 (3.9, 24.0)	0.69[d]
Hours from admission to randomization, median (IQR)	31.0 (22.0, 47.2)	29.7 (22.1, 60.1)	34.1 (21.1, 45.6)	0.61[d]
Hours from randomization to treatment, median (IQR)	2.5 (1.3, 4.5)	2.7 (2.1, 5.0)	1.9 (1.0, 3.6)	0.16[d]

AP, acute pancreatitis; BMI, body mass index; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; IQR, interquartile range; PASS, pancreatitis activity scoring system; SIRS, systemic inflammatory response syndrome.
[a]*t* test.
[b]χ^2 test.
[c]Fisher exact test.
[d]Wilcoxon rank-sum test.

($P = 0.70$) and in the change of CRP levels at 48 hour from baseline ($P = 0.48$) (Table 2).

Clinical outcomes. The development of moderately severe (indomethacin 50% vs placebo 54.2%) and severe (16.7% vs 12.5%) AP was similar between the treatments arms ($P = 1.00$) (Table 3). There was no significant difference in the risk of developing OF after treatment administration (16.7% vs 25%, $P = 0.71$). Figure 3 shows Kaplan-Meier estimates of OF-free survival in subjects assigned to indomethacin and placebo. A log-rank test demonstrated that both interventions had a similar effect on the OF risk ($P = 0.73$). There was no significant difference in the risk of pancreatic necrosis (55.6% vs 50%, $P = 0.72$), infected pancreatic necrosis (0% vs 4.2%, $P = 1.00$), length of hospital stay (9 vs 8 days, $P = 0.84$), ICU admission (61.1% vs 33.3%, $P = 0.07$), length of ICU stay (5 days for both groups, $P = 0.37$), and mortality (0% vs 4.2%, $P = 1.00$). The median PASS score at 24 hour (170 vs185, $P = 1.00$), 48 hour (128 vs116, $P = 0.73$), and 72 hour (125 vs145, $P = 0.42$) from the time of randomization was not significantly different between the treatment groups. The change of PASS score from baseline to 24 hour ($P = 0.59$), 48 hour ($P = 0.85$), and 72 hour ($P = 0.32$) was also similar for both arms.

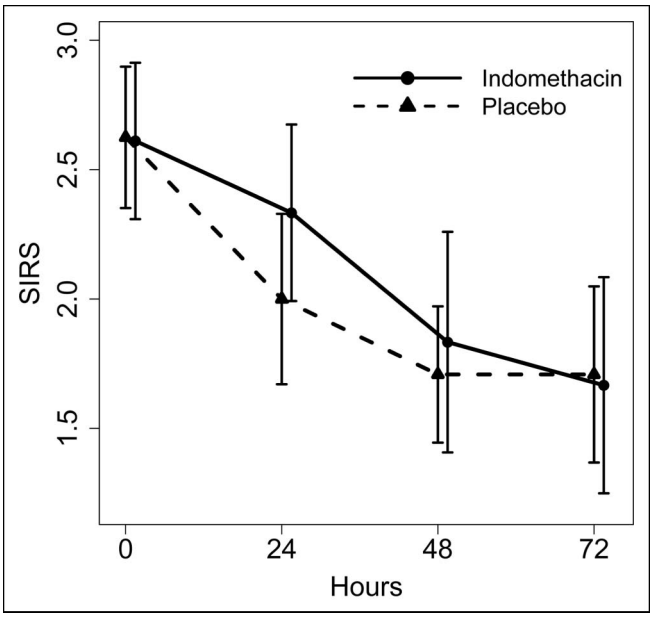

Figure 2. Trajectory of SIRS scores at baseline and at 24, 48, and 72 hours after randomization. SIRS, systemic inflammatory response syndrome. Data points are the mean SIRS score for each time. The vertical bars represent the 95% confidence interval at each time point. Missing SIRS data imputed using last observation carried forward.

Safety outcomes. There was no difference in major AEs between the 2 treatment groups (Table 4). There were 2 major AEs that were potentially attributed to the assigned treatment and triggered discontinuation of the study drug. Both AEs occurred in the placebo arm: 1 acute kidney injury and 1 gastrointestinal bleeding. There were no perforations, allergic reactions, or myocardial infarctions in either group.

Per-protocol analysis

Additional per-protocol analyses did not affect the results of the primary or secondary end points (see Supplementary Table 2, http://links.lww.com/CTG/A716).

DISCUSSION

Novel interventions are needed to reduce the progression of AP to local/systemic complications and death. Multiple drugs have been studied and found to be ineffective in altering the natural history of AP. Until new pharmacologic agents are developed and evaluated in humans, known drugs with suitable mechanisms of action should be tested on AP. Inflammatory cytokines play a critical role in AP, and the inhibition of COX-2 and TNF-α pathways has shown potential benefits in preventing SAP (17,36). The administration of nonselective NSAIDs has suggested a reduction of AP severity and mortality in some animal models (37). If effective, NSAIDs would be a relatively safe, widely available, and inexpensive therapeutic option that could ameliorate clinical progression in AP.

We report the results of an RCT comparing the efficacy of rectal indomethacin vs placebo in a population of subjects with AP at high risk for clinical progression. To our knowledge, this is the first RCT evaluating the efficacy of nonselective NSAIDs in preventing the clinical progression in AP. We found that rectal indomethacin was not superior to placebo in reducing the SIRS score or the serum CRP levels, which are surrogate markers for AP progression to local/systemic complications and death. The inefficacy of rectal indomethacin in our study was further supported by the lack of observed differences between the treatment groups in clinical outcomes such as new-onset OF, pancreatic necrosis, SAP, and mortality. Our results are consistent with some animal studies suggesting that the administration of indomethacin after induction of AP is not beneficial in reducing TNF-alpha levels, histologic changes, hemodynamic abnormalities, or mortality (38,39). The lack of benefits with NSAIDs could be explained because SAP is determined by a multiplicity of other factors unaffected by the inhibition of prostaglandins.

Previous RCTs evaluating the role of nonselective NSAIDs in AP have focused on analgesic properties (23,24). A pilot RCT comparing rectal indomethacin with placebo on 30 subjects with AP showed a beneficial effect of indomethacin on pain experience and opiate requirements; however, the study did not report on outcomes of clinical progression (23). A more recent RCT in 50

Table 2. Overall SIRS and CRP end points

Characteristics	Indomethacin (n = 18)	Placebo (n = 24)	*P* value
Change in SIRS score (48 hr − baseline), mean ± SD	−1.0 ± 1.24	−0.96 ± 0.81	0.87[a]
Change in SIRS score from baseline, mean ± SD			
At 24 hr	−0.39 ± 1.04	−0.75 ± 0.99	0.16[a]
At 72 hr	−1.28 ± 1.27	−1.13 ± 1.03	0.72[a]
SIRS, n (%)			
At 24 hr	16 (88.9)	17 (70.8)	0.26[b]
At 48 hr	11 (61.1)	15(62.5)	1.00[b]
At 72 hr	8 (44.4)	12 (50.0)	0.72[b]
SIRS score at 24 hr, n (%)			0.37[b]
0–1	2 (11.1)	7 (29.2)	
2	8 (44.4)	10 (41.6)	
3	8 (44.4)	7 (29.2)	
4	0 (0)	0 (0)	
SIRS score at 48 hr, n (%)			0.72[b]
0–1	7 (38.9)	9 (37.5)	
2	8 (44.4)	13 (54.2)	
3	2 (11.1)	2 (8.3)	
4	1 (5.6)	0 (0)	
SIRS score at 72 hr, n (%)			0.92[b]
0–1	10 (55.6)	12 (50)	
2	4 (22.2)	7 (29.2)	
3	4 (22.2)	5 (20.8)	
4	0 (0)	0 (0)	
Change in serum CRP level (48 hr − baseline), mean ± SD (mg/dL)	−2.08 ± 12.55	−1.43 ± 8.73	0.48[a]
Serum CRP level at 48 hr, mean ± SD (mg/L)	23.16 ± 8.22	22.30 ± 9.61	0.70[a]

CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome.
[a]Wilcoxon rank-sum test.
[b]Fisher exact test.

Table 3. Clinical outcomes

Characteristics	Indomethacin (n = 18)	Placebo (n = 24)	*P* value
Severity, n (%)			1.00[a]
Mild	6 (33.3)	8 (33.3)	
Moderately severe	9 (50)	13 (54.2)	
Severe	3 (16.7)	3 (12.5)	
New-onset organ failure, n (%)	3 (16.7)	6 (25.0)	0.71[a]
Overall pancreatic necrosis, n (%)	10 (55.6)	12 (50.0)	0.72[b]
Infected necrosis, n (%)	0 (0)	1 (4.2)	1.00[a]
PASS score, (median, IQR)			
At 24 hr	170 (135, 222)	185 (123, 235)	1.00[c]
At 48 hr	128 (93, 150)	116 (85, 153)	0.73[c]
At 72 hr	125 (70, 180)	145 (115, 180)	0.42[c]
Change in PASS score from baseline (median, IQR)			
At 24 hr	−23 (−73, 0)	−17 (−58, 8)	0.59[c]
At 48 hr	−91 (−117, −27)	−82 (−101, −55)	0.85[c]
At 72 hr	−66 (−123, −27)	−53 (−83, −20)	0.32[c]
Length of hospital stay, d (median, IQR)	9 (5,17)	8 (6,14)	0.84[c]
ICU Admission, n (%)	11 (61.1)	8 (33.3)	0.07[b]
Length of ICU stay, d (median, IQR)	5 (3,10)	5 (2,6)	0.37[c]
Mortality	0 (0)	1 (4.2)	1.00[a]

ICU, intensive care unit; IQR, interquartile range; PASS, pancreatitis activity scoring system.
[a]Fisher exact test.
[b]χ^2 test.
[c]Wilcoxon rank-sum test.

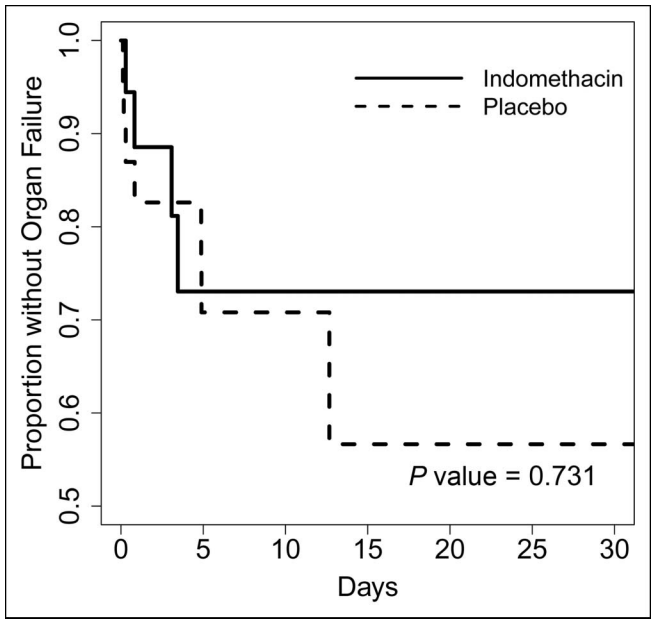

Figure 3. Kaplan-Meier curve depicting the organ failure–free survival in the indomethacin and placebo arms.

subjects with AP demonstrated that pentazocine (a kappa-opioid agonist) was superior to intravenous diclofenac on pain relief (24). In line with our study, Mahapatra et al. did not find advantages of nonselective NSAIDs on SIRS reduction, fluid collections, length of stay, and mortality, although the primary aim of the study was not to assess the prevention of disease progression (24). Moreover, our research question went beyond the analgesic effect of NSAIDs in AP and evaluated the trajectory of the PASS score, a validated AP activity index that incorporates pain experience (40,41).

The use of selective COX-2 inhibitors for prevention of AP clinical progression was found to be effective in experimental animal studies (16,42,43). A recent single-center RCT from China showed that a 10-day regimen of COX-2 inhibitors (intravenous parecoxib for 3 days, followed by oral celecoxib for 7 days) was superior to placebo in reducing progression to persistent OF (39% vs69%) among 190 subjects with predicted SAP (APACHE II score ≥8) (17). There are several biological and methodological reasons that can explain the differences between this recent RCT and our study. It is possible that the beneficial effect of COX-2 inhibition of nonselective NSAIDs is counteracted by altered pancreatic and renal arterial flow not present with selective COX-2 inhibitors (44,45). In addition, the inefficacy of indomethacin in our study may be explained by differences in prediction of SAP, route/duration of intervention, primary outcome definition, and sample size. Another difference that may explain the inconsistencies in results is that drug adherence was reported to be 99% in the study from China, whereas 71% of subjects adhered to the full regimen in our study. However, most COX-2 inhibitors are not commercially available in the United States given their risk for cardiovascular events, and a 10-day drug inpatient regimen would be impractical (46). Future studies that assess the effect of COX-2 inhibition in other diverse populations are needed.

Our study showed that a 2-day course of indomethacin was as safe as placebo in subjects with AP. Limited preclinical data suggested that NSAIDs could increase histologic changes of severity and mortality (44,45). However, 2 RCTs and a systematic review indicate comparable AEs between AP subjects treated with NSAIDs and control subjects, which is in alignment with our findings (23,24,37). Moreover, the safety of a single dose or short course of NSAIDs has also been reported in systematic reviews of RCTs with subjects receiving NSAIDs for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis and for various other indications (47,48).

Table 4. Adverse events

Characteristics	Indomethacin (n = 18)	Placebo (n = 24)	*P* value
Acute kidney injury, n (%)	0	1 (4.2)	1.00[a]
Gastrointestinal bleeding, n (%)	0	1 (4.2)	1.00[a]
Perforation, n (%)	0	0	n/a
Allergic reaction, n (%)	0	0	n/a
Myocardial infarction, n (%)	0	0	n/a

[a]Fisher exact test.

Our results should be interpreted with caution and not considered conclusive in determining the effect of NSAIDs in the prevention of AP clinical progression. First, this was a pilot study, which was not powered to detect a difference on major clinical outcomes, so a type 2 error is possible. Second, we included only subjects with AP and SIRS, given the higher risk of this subset of subjects for clinical progression. However, indomethacin might not alter the natural history of AP after SIRS is already established. Third, the median time to first treatment was 45.5 hour from the onset of symptoms and 33.5 hour from hospital presentation. In part, this can be explained because development of SIRS was a prerequisite for eligibility in this RCT, and this may have delayed the administration of nonselective NSAIDs out of a beneficial time window. The appropriate therapeutic window for prevention of SAP is unknown. However, a large multicenter study of >1,500 subjects with AP recently demonstrated that the median time from presentation to onset of persistent OF was 31 hours, which suggests that disease-modifying drugs would be most effective if administered within 12–24 hours from hospital presentation (2). It is unclear whether nonselective NSAIDs might be effective when administered within this narrower time frame. Fourth, the selected route of rectal drug administration in our study was proven to be inconvenient for subjects with AP (49). This likely resulted in low adherence to the 6-dose suppository regimen, which was not considered in the original sample size calculation and may have affected the study power. It is unknown whether using a different administration route, frequency, duration, or type of NSAID would have resulted in different results. Nonetheless, based on the results of our study, even if nonselective NSAIDs carry any benefit on AP clinical outcomes, such an effect is likely to be small.

This pilot RCT has a few additional limitations. This was an explanatory trial, conducted with the goal of assessing the efficacy of rectal indomethacin in subjects with AP under rigorous conditions. As such, the study was conducted at a single tertiary care center in a well-defined population of subjects with AP with established SIRS, which hampers the generalizability of our results to subjects before SIRS develops or when SIRS is absent. There was a relative imbalance in the planned 1:1 treatment allocation ratio, which can occur when using a simple randomization scheme in small study populations. This is a valid randomization approach that reduces confounding by indication and still resulted in similar baseline characteristics between both treatment arms.

This study has several strengths, including a rigorous design with proper randomization, allocation concealment, quadruple blinding, and selection of a previously used surrogate end point (27,28). Furthermore, the study explored several clinical end points, including severity using Revised Atlanta Classification and trajectory of AP using PASS. Our study demonstrated the feasibility of performing an RCT in this patient population to address an unmet clinical need and provided several insights for future RCTs. Investigators need to consider that enrollment of subjects with AP with SIRS and without OF can be intense and time sensitive even in a high-volume center, requiring great commitment and prolonged effort from the study team. In addition, future trials should consider alternative administration routes other than rectal, based on our experience that indomethacin suppositories were inconvenient and affected treatment adherence. These studies need to be powered for meaningful clinical outcomes and should administer the assigned treatment within 12–24 hours from hospital presentation. Such a study would require hundreds of subjects, and therefore, future multicenter RCTs will be needed to determine the role of nonselective and selective NSAIDs in AP.

In this RCT, rectal indomethacin given over 48 hour in subjects with AP and SIRS was safe but not superior to placebo in reducing the SIRS score or preventing clinical progression of AP. Future investigations should focus on the efficacy of NSAIDs when administered earlier in the disease course (within 12–24 hours from presentation) before SIRS onset.

CONFLICTS OF INTEREST

Guarantor of the article: Georgios I. Papachristou, MD, PhD.

Specific author contributions: R.M. and G.P.: study concept and design. P.P. and I.P.: generation and collection of data. A.H.: data analysis. J.D.M. and G.I.P.: drafting of the manuscript. J.D.M., R.M., P.P., J.P., I.P., P.A.H., D.L.C., E.d.-M., P.G., D.Y., D.C.W., P.J.L., A.H., and G.I.P.: data interpretation, critical revision of the manuscript for important intellectual content, and final approval of the manuscript.

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Data transparancy statement: Deidentified participant data and analytic code will not be publicly available but can be requested by researchers to the principal investigator (Georgios. I. Papachristou). The study protocol can be found at Clinicaltrials.gov (NCT02692391).

Study Highlights

WHAT IS KNOWN

- ✓ There is no effective pharmacologic agent that prevents progression of acute pancreatitis (AP) to local/systemic complications and death.
- ✓ Animal studies have suggested that nonsteroidal antiinflammatory drugs (NSAIDs) can prevent disease progression and death in AP.
- ✓ The effect of NSAIDs on preventing clinical progression in subjects with AP remains unknown.

WHAT IS NEW HERE

- ✓ Rectal indomethacin was ineffective in preventing clinical progression among subjects with AP at high risk for clinical progression.
- ✓ A short course of NSAIDs in subjects with AP seemed to be safe.

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REFERENCES

1. Xiao AY, Tan ML, Wu LM, et al. Global incidence and mortality of pancreatic diseases: A systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol 2016;1:45–55.
2. Machicado JD, Gougol A, Tan X, et al. Mortality in acute pancreatitis with persistent organ failure is determined by the number, type, and sequence of organ systems affected. United Eur Gastroenterol J 2021;9:139–49.
3. Zhi M, Zhu X, Lugea A, et al. Incidence of new onset diabetes mellitus secondary to acute pancreatitis: A systematic review and meta-analysis. Front Physiol 2019;10:637.
4. Huang W, de la Iglesia-García D, Baston-Rey I, et al. Exocrine pancreatic insufficiency following acute pancreatitis: Systematic review and meta-analysis. Dig Dis Sci 2019;64:1985–2005.
5. Sternby H, Bolado F, Canaval-Zuleta HJ, et al. Determinants of severity in acute pancreatitis: A nation-wide multicenter prospective cohort study. Ann Surg 2019;270:348–55.
6. Machicado JD, Papachristou GI. Pharmacologic management and prevention of acute pancreatitis. Curr Opin Gastroenterol 2019;35:460–7.
7. Vege SS, DiMagno MJ, Forsmark CE, et al. Initial medical treatment of acute. Gastroenterology 2018;154:1103–39.
8. Kylänpää L, Rakonczay Z, Jr., O'Reilly DA. The clinical course of acute pancreatitis and the inflammatory mediators that drive it. Int J Inflam 2012;2012:360685.
9. Mayer J, Rau B, Gansauge F, et al. Inflammatory mediators in human acute pancreatitis: Clinical and pathophysiological implications. Gut 2000;47:546–52.
10. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011;31:986–1000.
11. Garg PK, Singh VP. Organ failure due to systemic injury in acute pancreatitis. Gastroenterology 2019;156:2008–23.
12. Malmstrøm ML, Hansen MB, Andersen AM, et al. Cytokines and organ failure in acute pancreatitis: Inflammatory response in acute pancreatitis. Pancreas 2012;41:271–7.
13. Pezzilli R, Morselli-Labate AM, Corinaldesi R. NSAIDs and acute pancreatitis: A systematic review. Pharmaceuticals 2010;3:558–71.
14. Yang C, Zhao Y, Li W, et al. Rectal nonsteroidal anti-inflammatory drugs administration is effective for the prevention of post-ERCP pancreatitis: An updated meta-analysis of randomized controlled trials. Pancreatology 2017;17:681–8.
15. Smith ZL, Elmunzer BJ, Cooper GS, et al. Real-world practice patterns in the era of rectal indomethacin for prophylaxis against post-ERCP pancreatitis in a high-risk cohort. Am J Gastroenterol 2020;115:934–40.
16. Song AM, Bhagat L, Singh VP, et al. Inhibition of cyclooxygenase-2 ameliorates the severity of pancreatitis and associated lung injury. Am J Physiol Gastrointest Liver Physiol 2002;283:G1166–74.
17. Huang Z, Ma X, Jia X, et al. Prevention of severe acute pancreatitis with cyclooxygenase-2 inhibitors: A randomized controlled clinical trial. Am J Gastroenterol 2020;115:473–80.
18. Lankisch PG, Koop H, Winckler K, et al. Indomethacin treatment of acute experimental pancreatitis in the rat. Scand J Gastroenterol 1978;13:629–33.
19. Wildenhain PM, Melhem MF, Birsic WI, et al. Acute hemorrhagic pancreatitis in mice: Improved survival after indomethacin administration. Digestion 1989;44:41–51.
20. Lu G, Pan Y, Kayoumu A, et al. Indomethacin inhabits the NLRP3 inflammasome pathway and protects severe acute pancreatitis in mice. Biochem Biophys Res Commun 2017;493:827–32.
21. Bhatia M, Sidhapuriwala JN, Sparatore A, et al. Treatment with H2S-releasing diclofenac protects mice against acute pancreatitis-associated lung injury. Shock 2008;29:84–8.
22. Ozer Cakir O, Esen H, Toker A, et al. Effects of diclofenac sodium and octreotide on treatment of caerulein-induced acute pancreatitis in mice. Int J Clin Exp Med 2015;8:17551–64.
23. Ebbehøj N, Friis J, Svendsen LB, et al. Indomethacin treatment of acute pancreatitis. A controlled double-blind trial. Scand J Gastroenterol 1985; 20:798–800.
24. Mahapatra SJ, Jain S, Bopanna S, et al. Pentazocine, a kappa-opioid agonist, is better than diclofenac for analgesia in acute pancreatitis: A randomized controlled trial. Am J Gastroenterol 2019;114:813–21.
25. Mounzer R, Langmead CJ, Wu BU, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. Gastroenterology 2012;142:1476–6.
26. Di MY, Liu H, Yang ZY, et al. Prediction models of mortality in acute pancreatitis in adults: A systematic review. Ann Intern Med 2016;165: 482–90.
27. Wu BU, Hwang JQ, Gardner TH, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol 2011;9:710–17.e1.
28. Buxbaum JL, Quezada M, Da B, et al. Early aggressive hydration hastens clinical improvement in mild acute pancreatitis. Am J Gastroenterol 2017; 112:797–803.
29. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: Management of acute pancreatitis. Am J Gastroenterol 2013; 108:1400–16.
30. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
31. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414–22.
32. Koutroumpakis E, Slivka A, Furlan A, et al. Management and outcomes of acute pancreatitis patients over the last decade: A US tertiary-center experience. Pancreatology 2017;17:32–40.
33. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638–52.
34. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: Revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
35. Wu BU, Batech M, Quezada M, et al. Dynamic measurement of disease activity in acute pancreatitis: The pancreatitis activity scoring system. Am J Gastroenterol 2017;112:1144–52.
36. Vege SS, Atwal T, Bi Y, et al. Pentoxifylline treatment in severe acute pancreatitis: A pilot, double-blind, placebo-controlled, randomized trial. Gastroenterology 2015;149:318–20.e3.
37. Wu D, Bai X, Lee P, et al. A systematic review of NSAIDs treatment for acute pancreatitis in animal studies and clinical trials. Clin Res Hepatol Gastroenterol 2020;44S:100002.
38. Matheus AS, Coelho AM, Sampietre S, et al. Effect of inhibition of prostaglandin E2 production on pancreatic infection in experimental acute pancreatitis. HPB (Oxford) 2007;9:392–7.
39. Kiviniemi H, Rämö OJ, Ståhlberg M, et al. Indomethacin in canine acute hemorrhagic pancreatitis. Res Exp Med 1988;188:35–40.
40. Meng W, Yuan J, Zhang C, et al. Parenteral analgesics for pain relief in acute pancreatitis: A systematic review. Pancreatology 2013;13:201–6.
41. Paragomi P, Tuft M, Pothoulakis I, et al. Dynamic changes in the pancreatitis activity scoring system during hospital course in a multicenter, prospective cohort. J Gastroenterol Hepatol 2021;36:2416–23.
42. Ethridge RT, Chung DH, Slogoff M, et al. Cyclooxygenase-2 gene disruption attenuates the severity of acute pancreatitis and pancreatitis-associated lung injury. Gastroenterology 2002;123:1311–22.
43. Alhan E, Kalyoncu NI, Ercin C, et al. Effects of the celecoxib on the acute necrotizing pancreatitis in rats. Inflammation 2004;28:303–9.
44. Coelle EF, Adham N, Elashoff J, et al. Effects of prostaglandin and indomethacin on diet-induced acute pancreatitis in mice. Gastroenterology 1983;85:1307–12.
45. Studley JG, Lee JB, Schenk WG Jr. Pathophysiology of acute pancreatitis: Evaluation of the effects and mode of action of indomethacin in experimental pancreatitis in dogs. J Surg Res 1982;32:563–8.
46. Singh H, Gougol A, Mounzer R, et al. Which patients with mild acute pancreatitis require prolonged hospitalization? Clin Transl Gastroenterol 2017;8:e129.
47. Aminoshariae A, Kulild JC, Donaldson M. Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects: An updated systematic review. J Am Dent Assoc 2016;147:98–110.
48. Hou YC, Hu Q, Huang J, et al. Efficacy and safety of rectal nonsteroidal anti-inflammatory drugs for prophylaxis against post-ERCP pancreatitis: A systematic review and meta-analysis. Sci Rep 2017;7:46650.
49. Hall EW, Heneine W, Sanchez T, et al. Preexposure prophylaxis modality preferences among men who have sex with men and use social media in the United States. J Med Internet Res 2016;18:e111.