ORIGINAL ARTICLE

The Effect of Non-Steroidal Anti-Inflammatory Drugs on Acute Pancreatitis: A Retrospective Study at a London District General Hospital

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ABSTRACT

Context Acute pancreatitis (AP) is a common emergency condition. Despite a complication rate of up to 20%, current management only includes supportive treatment and surgery in specific circumstances. Non-steroidal anti-inflammatory drugs (NSAIDs) are shown to reduce post-endoscopic retrograde cholangiopancreatography pancreatitis. **Objective** To assess the effect of NSAIDs on disease progress and patient outcomes in acute pancreatitis in a large district general hospital. **Methods** A retrospective analysis was performed on 361 consecutive, adult patients with AP from April 2018 to September 2020. Demographic data, biochemical information, pancreatitis severity scores and clinical outcomes were recorded. Patients were divided into two groups based on NSAID usage prior to hospital admission. Results Patients on NSAIDs prior to admission were older (69.4 vs 54.4, p-value<0.0001) and less likely to have ASA grade I (16.1% vs 34.6%, p-value=0.0446). They had a significantly lower Day 5 C-reactive protein (CRP) (89.0 mg/L vs 155.4 mg/L, p-value=0.0226). No patient using NSAIDs prior to admission developed pancreatic necrosis, however, this was not statistically significant (0.0% vs 6.4%, p-value=0.1478). There were no statistically significant differences in other clinical and biochemical outcomes. **Discussions** Routine NSAIDs use appears to reduce CRP level five days after admission and may protect from pancreatic necrosis after AP. Despite being older and in a poorer fitness level, patients on NSAIDs had similar outcomes to those without NSAIDs, suggesting potential benefits on AP. **Conclusion** NSAIDs may have some therapeutic value in AP. More studies are recommended to evaluate this further.

INTRODUCTION

Acute pancreatitis (AP) is an inflammation of the pancreas, typically characterised by abdominal pain and raised serum pancreatic enzymes. In Europe, the incidence of AP varies between 4.6 to 100 per 100 000 population [1]. However, with the increased rates of obesity and gallstones globally, its incidence is expected to rise [2]. Up to 20% of patients with AP develop complications such as organ failure and necrosis [3]. A 2010 meta-analysis of 1478 patients indicates that the mortality of these complications is 30% and 32% respectively [4], suggesting a need for better management options. A retrospective study in Edinburgh shows that an average cost of care for direct admissions and transfers of AP requiring critical care are £16,760, and £34,413 respectively [5]. In the United Kingdom, the annual cost of treating AP is estimated to be £200 million [6]. Several factors are believed to contribute to early acute changes such as activation of proteolytic enzymes, microcirculatory injury, and the uncontrolled release of proinflammatory cytokines [7]. Animal studies demonstrate that cellular infiltration and local inflammation are prevalent in AP with key inflammatory markers including tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and nuclear factor kappa B [8, 9]. Furthermore, clinical studies have shown that levels of cytokines correlate well with the severity of pancreatitis [10, 11].

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of medications that inhibit cyclooxygenase, an enzyme that converts arachidonic acid to prostanoids such as thromboxane and prostaglandins [12]. These compounds are involved in several signalling pathways, especially those activated as part of a proinflammatory

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response. In 1985, a small (n=30) double-blind trial in Denmark showed that those given indomethacin had a significantly lower pain intensity rate at day 7 [13]. However, the study did not look at other clinical outcomes and complications of AP. A meta-analysis of seven randomised-controlled trials (n=1846) shows that rectal NSAIDs reduce the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis by 55% [14]. This prompted the American Society for Gastrointestinal Endoscopy and the European Society of Gastrointestinal Endoscopy to recommend prophylaxis rectal NSAIDs prior to ERCP [15,16]. Additionally, Baxter et al conducted a retrospective study on 324 UK patients with AP in 2018, which demonstrated that those who took NSAIDs prior to admission were less likely to develop necrosis and pseudocyst [17].

These studies highlight a beneficial role of NSAIDs and warrant more research into the use of anti-inflammatory medications in AP. Hence, this study aimed to provide further evidence if routine use of NSAIDs would improve patient's outcomes in AP.

Methods

Clinical data were obtained retrospectively via an electronic patient record (EPR). Between April 2018 to September 2020, adult patients from Northwick Park Hospital, London North West University Healthcare Trust, UK, were identified using the codes for 'acute pancreatitis', 'alcohol-induced acute pancreatitis', 'biliary acute pancreatitis' or 'idiopathic acute pancreatitis'. Acute-on-chronic pancreatitis was excluded as the disease course tends to be milder than AP and may confound the result. After excluding patients who were inaccurately coded, 361 patients were included in the study. Demographic data including the American Society of Anesthesiologists (ASA) physical status were recorded. Pancreatitis severity were documented using the Glasgow-Imrie criteria and Atlanta classification [18]. Biochemical outcomes such as c-reactive protein (CRP), white cell counts (WCC), and lactate dehydrogenase (LDH) were recorded up to five days from admission. The following clinical outcomes were recorded: length of stay, High Dependency Unit (HDU) and Intensive Therapy Unit (ITU) stay, presence of necrosis on computerised tomography scan, need for surgery, and mortality.

Drug history on EPR and electronic Summary Care Record (SCR) via the National Health Service's Spine portal were used to determine NSAIDs usage prior to admission. In this study, no distinctions were made between each type of NSAIDs (e.g., acetylsalicylic acid, ibuprofen and mefenamic acid). Patients were classified into two groups, NSAID or non-NSAID, accordingly. The use of aspirin as a cardio protective agent was included.

Statistics

Two-tailed student's t test, chi-squared test with Fisher's exact correction were used to compare the differences between the two groups when appropriate. Multiple logistic regression was performed to adjust for confounders. Model included Atlanta classification. Day 3 (D3) CRP >150 mg/L and D5 CRP >150 mg/L as dependent variables. Calculations were made using GraphPad Prism version 9.0 (GraphPad Software, San Diego, California, USA).

RESULTS

There was a total of 361 patients admitted with AP during the study period, 31 patients in the NSAID and 330 patients in the non-NSAID group. Patients in the NSAIDs group tended to be older (69.4 vs. 54.4, p-value<0.0001) and less likely to have ASA grade I (16.1% vs. 34.6%, p-value=0.0446). Patients in the NSAID group had a higher point on the Glasgow-Imrie score (48.2% vs. 20.3%, p-value=0.0011) and more severe Atlanta classification (12.9% vs. 3.9%, p-value=0.0479). There was a comparable proportion of males (48.4% vs. 60.3%, p-value=0.2511) (Table 1).

No patient in the NSAID group developed necrosis. However, this was not statistically significant when compared to necrosis rate in the non-NSAIDs group (0.0% vs. 6.4%, p-value =0.1478). Similarly, there were no statistically significant differences in median length of hospital stay (7 days vs. 4 days, p-value=0.0843), HDU or ITU stay (3.2% vs. 6.4%, p-value=0.7078), the need for surgery (6.5% vs. 8.8%, p-value >0.9999) and death (3.2% vs. 3.3%, p-value>0.9999). Biochemically, patients in the NSAID group had a statistically lower CRP level on Day 5 (89.0 mg/L vs. 155.4 mg/L, p-value =0.0226) and albumin on Day 1 (40.5 g/L vs. 42.9 g/L, p-value=0.0322). They also had lower CRP level on Day 3, however, this was not statistically significant (110.9 mg/L vs. 148.6 mg/L, p-value=0.1658). There were no statistically significant differences in other biochemical outcomes.

A binary logistic regression analysis was conducted to investigate if age, sex, ASA grade and NSAIDs usage would predict Atlanta severity (severe v non-severe). The model showed that age, sex and NSAIDs usage were not statistically significant as independent variables (p-value>0.05). However, ASA grade was found to be a statistically significant predictor with an adjusted odds ratio of 4.465 (95% confidence interval (CI) 2.147-10.17, p-value=0.0001) (Table 2).

A separate regression analysis was conducted with the same independent variables using D5 CRP >150 mg/L as a dependent variable. Similarly, age, sex and NSAIDs usage were not statistically significant as independent variables (p-value>0.05) although NSAIDs usage was negatively associated with D3 CRP >150 mg/L (adjusted odds ratio 0.4380, 95% CI 0.1234-1.208, p-value=0.1463). ASA grade was statistically significant as an independent variable with an adjusted odds ratio of 1.263 (95% CI 1.024-2.139, p-value = 0.0364) (Table 3).

Table 1 Demographic and outcome data. ASA = American Society of Anesthesiologists; CRP = C-reactive protein; HDU = high dependency unit; ITU = intensive care unit; NSAIDs = non-steroidal anti-inflammatory drugs; WCC = white cell count, LDH = lactate dehydrogenase.

Demographic	NSAIDs (n=31)	Non-NSAID (n=330)	P value
%Male	15/31 (48.4%)	199/330 (60.3%)	0.2511
Age (mean)	69.4 (3.1)	54.4 (1.1)	**<0.0001**
ASA Grade			
I	5 (16.1%)	114 (34.5%)	**0.0447**
II	15 (48.4%)	144 (43.6%)	0.7059
III - IV	11 (35.5%)	72 (21.8%)	0.1152
Pancreatitis Severity			
Glasgow-Imrie Criteria			
0-1 point	16 (51.6%)	263 (79.7%)	**0.0011**
2-3 points	15 (48.2%)	67 (20.3%)	
Atlanta Classification			
Mild - Moderate	27 (87.1%)	317 (96.1%)	**0.0479**
Severe	4 (12.9%)	13 (3.9%)	
Clinical Outcome			
Length of Stay/day (median)	7 (4-10)	4 (2-7)	0.0843
HDU or ITU admission rate (%)	1/31 (3.2%)	21/330 (6.4%)	0.7078
Necrosis (%)	0/31 (0.0%)	21/330 (6.4%)	0.1478
Surgery (%)	2/31 (6.5%)	29/330 (8.8%)	>0.9999
Death (%)	1/31 (3.2%)	11/330 (3.3%)	>0.9999
Biochemical Outcome			
D1 WCC (x10^9/L)	12.4 (1.0)	12.1 (0.3)	0.7416
D1 CRP (mg/L)	51.4 (13.2)	50.8 (5.0)	0.9746
D3 CRP (mg/L)	110.9 (20.2)	148.6 (8.6)	0.1658
D5 CRP (mg/L)	89.0 (21.7)	155.4 (9.8)	**0.0226**
D1 Creatinine (µmol/L)	108.6 (11.3)	86.8 (3.6)	0.0763
D3 Creatinine (µmol/L)	99.6 (11.4)	76.8 (4.6)	0.115
D1 Albumin (g/L)	40.5 (0.9)	42.9 (0.3)	**0.0322**
D3 Albumin (g/L)	35.3 (1.1)	35.2 (0.4)	0.9774
D1 Calcium (mmol/L)	2.4 (0.03)	2.4 (0.01)	0.7022
D1 LDH (U/L)	260.8 (23.3)	305.3 (12.8)	0.3140
D1 Glucose (mmol/L)	12.2 (2.8)	9.0 (0.6)	0.1976

Table 2: Multiple logistic regression with Atlanta severity as dependent variable. CI: confidence interval; CRP = C-reactive protein; NSAIDs = non-steroidal anti-inflammatory drugs; M: male; ASA = American Society of Anesthesiologists.

Variable	Adjusted odds ratio	95% CI	P-value
NSAIDs Usage	2.969	0.7267 to 10.34	0.1006
Age	0.9992	0.9709 to 1.029	0.9565
Sex[M]	0.7195	0.2235 to 2.128	0.5607
ASA Grade	4.465	2.147 to 10.17	**0.0001**

Table 3: Multiple logistic regression with **D5 CRP >150 mg/L as dependent variable**. CI: confidence interval; CRP = C-reactive protein; NSAIDs = non-steroidal anti-inflammatory drugs; M: male; ASA = American Society of Anesthesiologists.

Variable	Adjusted odds ratio	95% CI	P-value
NSAIDs Usage	0.4380	0.1234 to 1.208	0.1463
Age	1.011	0.9951 to 1.027	0.1827
Sex[M]	0.8109	0.4581 to 1.413	0.4642
ASA Grade	1.480	1.024 to 2.139	**0.0364**

DISCUSSION

In this study, the majority of NSAIDs used were aspirin as a secondary prevention of acute coronary syndrome while some used NSAIDs as analgesia for rheumatoid arthritis or chronic pain. Patients with AP who routinely used NSAIDs prior to their admission were generally older and had a poorer level of fitness. This could explain why they were more likely to develop severe pancreatitis according to the Glasgow-Imrie criteria and Atlanta classification. However, despite the difference in severity, there were no cases of necrosis among patients who regularly took NSAIDs and there were no statistically significant differences between the clinical outcomes in both groups. Furthermore,

patients on NSAIDs had a significantly lower CRP five days after presentation.

Our results agree with Baxter et al who demonstrated that patients who routinely took NSAIDs were less likely to develop necrosis in AP [17]. One plausible explanation is that inflammation plays a significant role in necrosis formation. It is postulated that in the early stages of AP, uncontrolled local inflammation may disrupt the pancreatic microcirculation, resulting in vasoconstriction, shunting, inadequate perfusion, and coagulation [19]. This process may be exacerbated by ischaemia–reperfusion injury and subsequently lead to necrosis. Since NSAIDs are a potent inhibitor of cyclooxygenase, which plays a central role in proinflammatory response, they may provide some benefits in treating AP.

The finding that D5 CRP was significantly lower in the NSAID group could provide further evidence for this explanation. CRP is part of a non-specific acute phase response to inflammation, infection and tissue damage that can be readily measured in a blood test [20]. CRP value correlates with pancreatitis severity [21]. A value of >150 mg/L 48 hours post admission is as sensitive as a computed tomography severity index for severe pancreatitis and is recommended by the British Society of Gastroenterology as part of the assessment of AP and the Atlanta classification [18 ,22, 23].

A 2020 systematic review on NSAIDs and AP in animal studies and clinical trials has shown that NSAIDs significantly reduce serum pancreatic enzymes level and improve histopathological damage in animals [24]. In clinical studies, apart from reducing pain, patients who received NSAIDs (celecoxib plus octreotide and lornoxicam) have significantly lower proinflammatory cytokines such as IL-6 and TNF-α [25, 26] Interestingly, CRP was not used as an endpoint in these studies.

Furthermore, one randomised trial has shown that patients on lornoxicam developed fewer complications and had lower mortality than those who were randomised to standard therapy alone [25]. Nonetheless, the study was relatively small with only 88 participants receiving lornoxicam, and it is not clear if the study was blinded appropriately.

Drug-induced AP is rare. There are case studies that suggested probable scenarios of ibuprofen-induced AP [27, 28]. However, in these cases, patients received a large dose of ibuprofen (20.4 and 51.0 mg/kg). In contrast, a meta-analysis involving 1846 patients demonstrated that therapeutic dose of rectal NSAIDs reduce the incidence of post-ERCP pancreatitis [14], suggesting that NSAIDs have a beneficial role in AP. Our study further supports the need for more and larger trials to investigate the role of NSAIDs in AP in the future. This study is not without limitations. Firstly, as a retrospective study, data were obtained from an electronic system, which might not contain every relevant risk factor and variable. Secondly, our NSAID cohort was relatively small compared to the non-NSAID group, which may account for why the difference in certain variables was not statistically significant. Furthermore, the wide 95% confidence interval in odd ratios might suggest that the study was underpowered. Finally, there were confounding factors such as age and ASA grades that were different at baseline.

CONCLUSION

Patients on regular NSAIDs prior to AP had a poorer baseline. However, they were no worsening differences in the clinical outcomes. Although, this study did not clearly demonstrate significant beneficial effects of NSAIDs in AP, we would recommend further studies, particularly larger trials in a randomised, controlled setting to explore the effects of NSAIDs further in AP.

Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

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