

Is Prior Aspirin Use Associated with Reduced Severity in Patients with Acute Pancreatitis?

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Abstract Clinical severity of Acute Pancreatitis (AP) following the use of Aspirin is inconclusive in previous studies. This study investigated predicting the severity of AP using Ranson criteria at admission and at 48 hours and, the length of hospital stay by prior aspirin use. Medical records of first-presentation AP patients during the five years between 2010 and 2015 were examined in the Goulburn Valley Base Hospital, Victoria, Australia. Uses of aspirin at admission with some co-morbidity, Ranson criteria at admission and at 48 hours, duration of hospital stay including other information were collected. A total of 245 AP medical records were reviewed, of them, 178 used and 67 did not use aspirin prior attending to the hospital. In simple regression analysis, Ranson score was 60% higher at admission ($P < 0.001$) and 64% higher at 48 hours ($P < 0.01$) among aspirin users compared to non-aspirin users. These findings remained statistically significant after adjusting for other potential indicators. Aspirin use was also found associated with a longer hospital stay both in the unadjusted and adjusted analysis ($P < 0.01$). Further studies using revised Atlanta classification instead of Ranson scoring for the diagnosis of AP severity in aspirin users are critical for clinical guidance.

Keywords Aspirin, Acute Pancreatitis, Ranson Score

1. Introduction

Acute pancreatitis (AP) is a common cause of hospital admission [1]. Current management is aimed at symptomatic relief of the inflammatory cascade [2, 3]. Pancreatic acinar cell injury causes the release of pro-inflammatory markers, which in turn sets off a cascade of systemic inflammation [4]. The broad spectrum of clinical disease is due to the balance of pro and anti-inflammatory responses, which ranges from self-limiting pancreatic inflammation to systemic inflammatory response syndrome (SIRS) and multi-organ

failure [4].

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin act by inhibiting the COX (cyclooxygenase) 1 and 2 enzymes that mediate systemic inflammation [5]. Aspirin, a NSAID, has a broad spectrum of clinical indications due to its analgesic, antipyretic, anti-inflammatory, and antiplatelet effects. The variety of therapeutic uses seen with aspirin is believed to stem from mechanisms distinct from its COX inhibitory effect, which are beginning to be understood [5, 6]. Traditionally used for primary and secondary prophylaxis against cardiovascular events, there is current interest in its protective role against colorectal cancer [7].

Although controversial, NSAIDs are most frequently used in mild AP or in combination with stronger multimodal analgesics in more severe AP, where it is effective in reducing pain scores [8]. A large RCT of a novel anti-inflammatory agent (lexipafant) in severe AP was disappointing, as it did not produce a significant reduction in complications [9]. However, in laboratory-induced AP in rats, it was demonstrated that long-term aspirin pre-treatment reduced the level of serum inflammatory markers and histological severity of inflammation of pancreatic cells [5]. Another previous study in rats found that indomethacin (a NSAID) administration shortly before and after the onset of AP reduced the severity [10]. In vitro, indomethacin showed effective inhibition of the inflammatory enzyme phospholipase-A2 from AP patients serum [11]. Subsequent clinical studies showed that rectal indomethacin administration in AP patients reduced pain and severity [12]. More recently, rectally administered NSAIDs have been widely reported to reduce the incidence of post-ERCP pancreatitis [8, 13]. Taken together, these data suggest that prior exposure to anti-inflammatory medication may be therapeutic by reducing the severity of AP. In contrast, one case-control study demonstrated an association between AP and NSAID use, with the risk being dependent on the type of drug; highest with diclofenac and lowest with COX-2 selective inhibitors [14]. To our knowledge, no clinical

studies have been published to date assessing the association between the use of the NSAID, aspirin and AP severity and prognosis. In this study we calculated Ranson score to predict the severity of acute pancreatitis and compared how prior use of aspirin influenced AP presentation.

2. Aims

We primarily determined the association between prior histories of aspirin use and predict the severity of AP. We also determined the length of hospital stay of these patients.

3. Methods

We conducted a retrospective study of cases of acute pancreatitis (AP) presenting to a rural hospital in Victoria, Australia. The study was approved by the Human Research Ethics Committee, Goulburn Valley Health, Victoria, Australia.

Identification of cases of acute pancreatitis was based on the revised Atlanta Classification (2012), fulfilling at least two of the following three criteria: i. abdominal pain i.e. acute onset, epigastric pain, pain radiating to back; ii. serum lipase or amylase at least 3 times upper than normal limit; or iii. characteristic findings of pancreatitis on contrast-enhanced CT or MRI or trans-abdominal ultrasound study. Ranson score were calculated at admission and at 48 hours for these patients to predict the severity of AP by their prior aspirin using status.

Ranson score represents the cumulative score from Table 1 and each criterion in the table scores 1 point [15]. Aspirin use was determined by its documentation in the patients' current medication list or as a regular medication in the admission medication chart.

Table 1. Ranson scoring

Admission	Within 48 hours
Age > 55	Haematocrit drop >10%
WCC >16 mmol/L	BUN rise >1.79 mmol/L
Serum glucose >11.1 mmol/L	Serum calcium <2 mmol/L
LDH>350 mmol/L	PO2 <60mmHg
ALT > 250 mmol/L	Base deficit >4 mmol/L
	Fluid sequestration > 6L

We conducted the search of hospital records by using the keywords "acute pancreatitis" between January 1, 2010, and January 1, 2015. In the case of multiple records of AP for a patient, the earliest diagnosis by date was selected. Exclusions to the search were "chronic pancreatitis",

"acute-on-chronic pancreatitis", and dubious cases in which amylase/lipase was not sufficiently elevated to meet the Atlanta definition or episodes where an unclear diagnosis existed.

Information of cases and pathology results corresponding to the first admission for the following data were recorded in a spreadsheet: aspirin use, hypertension, diabetes mellitus, ischaemic heart disease, Ranson score at admission and at 48 hours, length of hospital stay, ICU admission, mortality, and C-reactive protein level (CRP).

Statistical Analysis

Data were entered into an MS Excel spreadsheet and transferred to STATA version 11.0 (STATA Corporation, Texas, USA) for analysis. Summary statistics were calculated and presented as mean, standard deviation, proportion, and if required as median. We performed univariate linear regression analysis for the primary outcome as Ranson Score at admission and at 48 hours of admission by prior use of aspirin. The length of hospital stay was considered as the secondary outcome and similar analyses were performed to that of the primary outcome. Multivariate linear regression modeling was performed using the backward stepwise method to identify the indicators for final modeling. P value of <0.05 was considered as significant for both adjusted and unadjusted analysis.

4. Results

A total of 245 records of AP cases were identified between January 2010 and January 2015, of them 33.5% (n=82) were due to gallstone. At the time of admission, 72.6% (178) cases were not taking aspirin while the remaining 27.4% (67) reported using aspirin. Non-aspirin users were significantly younger than aspirin users (P<0.001), as expected. This eventually influenced the increase of Ranson score in the older participants (Figure 1). Approximately 60% of the aspirin users were female and contrary to that, the proportion of female was much lower (47%) among non-aspirin users. Prevalence of diabetes mellitus and hypertension was significantly higher among aspirin users. The average length of hospital stay for AP patients was significantly higher (6.9 days vs 4.7 days) in the aspirin using group compared to the non-aspirin using group (P<0.01). Records for C-reactive protein levels were found for a total of 234 AP patients (mean 45.1mg/L ±81.3 mg/L; median 12mg/L, min 0.1mg/L, and max 450 mg/L). The demographic and clinical characteristics of the study population are shown in Table 2.

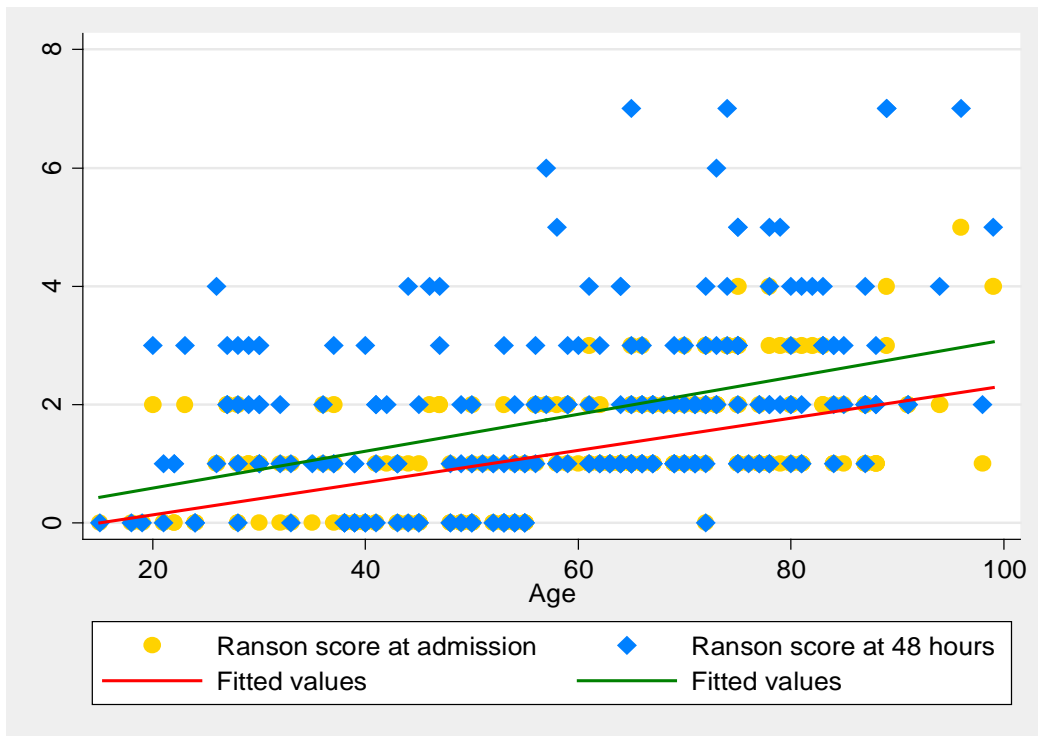


Figure 1. Ranson Score by Age at admission and at 48 hours

Table 2. Clinical characteristics of the study population (N=245)

Indicators	Overall (N=245)	Non aspirin users (n=178)	Aspirin users (n=67)	P (Aspirin Vs Non-aspirin group)
Age, Mean ± SD (min, max)	58.5±19.2 (15, 99)	52.7 ±18.4 (15, 98)	73.9 ±11.5 (45, 99)	<0.001
Gender				
Male, n(%)	122 (49.8)	95 (53.4)	27 (40.3)	0.07
Female, n(%)	123 (50.2)	83 (46.6)	40 (59.7)	
Ranson Score, Mean ± SD				
At admission	1.19 ± 0.99	1.02 ± 0.94	1.62 ± 0.98	<0.001
At 48 hours	1.79 ± 1.50	1.62 ± 1.46	2.25 ± 1.53	0.02
Mortality				
No, n(%)	237 (96.7)	170 (95.5)	67 (100)	-
Yes, n(%)	6 (2.5)	6 (3.4)	0 (0)	
Unknown, n(%)	2 (0.8)	2 (1.1)	0 (0)	
ICU admission				
No, n(%)	206 (84.1)	151 (84.8)	55 (82.1)	0.6
Yes, n(%)	39 (15.1)	27 (15.2)	12 (17.9)	
Length of hospital stay, Mean ± SD (min, max)	5.3 ± 5.7 (0, 45)	4.7±4.7 (0, 45)	6.9±7.5 (1, 39)	0.009
Diabetes Mellitus				
No, n(%)	200 (81.6)	152 (85.4)	48 (71.6)	0.01
Yes, n(%)	45 (18.4)	26 (14.6)	19 (28.4)	
Hypertension				
No, n(%)	137 (55.9)	123 (69.1)	14 (20.9)	<0.001
Yes, n(%)	108 (44.1)	55 (30.9)	53 (79.1)	
*C Reactive Protein (mg/L), Median (min, max)	*12 (0.1, 450)	†10 (0.1, 450)	‡17 (0.4, 373)	0.6

*n=234, †n=171, ‡n=63

Table 3. Ranson score by aspirin use (N=245)

Time of Ranson scoring	Ranson Score				P (Aspirin Vs Non-aspirin group)
	Mean	Standard deviation	Minimum	Maximum	
At admission					
-Non aspirin users (n=178)	1.02	0.94	0	4	<0.001
-Aspirin users (n=67)	1.62	0.98	0	5	
At 48 hours					
-Non aspirin users (n=178)	1.62	1.46	0	0	0.02
-Aspirin users (n=67)	2.25	1.53	7	7	

Table 4. Multiple linear regression analysis for Ranson score at admission and at 48 hours by aspirin use (N=234)

Indicators	Ranson Score					
	At admission			At 48 hours		
	Coefficient	95% Confidence Interval	P Value	Coefficient	95% Confidence Interval	P Value
Prior use of aspirin	0.57	0.29 - 0.85	<0.001	0.63	0.20 - 1.05	<0.01
Gender (female)	-0.33	-0.57 - -0.08	<0.01	-0.44	-0.82 - -0.07	<0.05
Diabetes mellitus	0.28	-0.03 - 0.59	0.08	0.35	-0.13 - 0.83	0.15
C reactive protein	0.002	0.0009 - 0.004	<0.01	0.004	0.002 - 0.006	<0.001
Constant	1.04	0.85 - 1.24	<0.001	1.71	1.42 - 1.99	<0.001

Table 5. Multiple linear regression analysis for length of hospital stay by aspirin use (N=245)

Indicators	Length of hospital stay		
	Coefficient	95% Confidence Interval	P Value
Prior use of aspirin	2.27	0.67 - 3.87	<0.01
Gender (female)	-0.29	-1.70 - 1.13	0.69
Diabetes mellitus	0.73	-1.09 - 2.56	0.43
C reactive protein	0.01	0.003 - 0.02	<0.01
Constant	4.15	3.02 - 5.27	<0.001

In Table 3, we provide the summary statistics of Ranson score at admission and at 48 hours between patients who used aspirin and patients who did not use aspirin prior to their hospital admission. Using simple linear regression analysis, we found the Ranson score was significantly higher at admission (Coefficient 0.60, 95% CI 0.33-0.87) and at 48 hours (Coefficient 0.64, 95% CI 0.22-1.05) among prior aspirin users.

Table 4 and 5 represents multivariable analyses for primary and secondary outcomes. Patient's age and hypertensive status were highly correlated with Ranson score ($r=0.53$ and 0.35 , respectively) while CRP level had little or no correlation ($r=0.17$). Therefore, age and hypertension were taken out from the model for possible co-linearity. We observed that prior aspirin use was significantly associated with higher Ranson score both at admission (Coefficient 0.57, 95% CI 0.29 - 0.85) and at 48 hours (Coefficient 0.63, 95% CI 0.20 - 1.05) after adjusting for gender, diabetes mellitus and C-reactive protein level. We also found a doubled hospital staying period for AP patients those who used aspirin previously before presenting to the hospital (Coefficient 2.27, 95% CI: 0.67 - 3.87).

5. Discussion

The study demonstrated that aspirin use was significantly associated with higher Ranson score both at admission and at 48 hours of admission. Aspirin users were significantly older than the non-aspirin group. We also found that the proportion of diabetic was double and the proportion of hypertensive was more than 2.5 times in the aspirin than in the non-aspirin using group.

Despite limited availability of data, there is laboratory evidence for aspirin attenuating the inflammatory response in AP. In a previous study, long-term aspirin pretreatment was shown to associate with a dose-dependent reduction in the severity of cerulein-induced AP in rats [5]. In human subjects, a meta-analysis supports the use of rectal NSAID on reducing the incidence of post-ERCP pancreatitis [16]. NSAIDs including aspirin may prevent mechanical and chemically-triggered inflammation through its inhibition of prostaglandins, lipoxygenase, and neutrophil-endothelial interactions. However, it is uncertain if the findings can be generalised to other causes of pancreatitis as the therapeutic benefit may depend on the patient risk, the procedure, and

the route of administration [16].

The Ranson score was the most widely utilised scoring system for predicting the severity of AP. A higher score indicates a higher risk of morbidity and mortality. Our findings suggest that prior aspirin use is associated with more severe AP. Also, aspirin use was found associated with longer hospital stay both in uni and multivariable analysis, controlled for a few associated factors.

Hypertension [17], cardiovascular disease [17, 18], and diabetes [19, 20] have been independently associated with the incidence of AP. Indeed, a higher number of the comorbid disease has been shown to associate with poorer outcomes in AP, including the length of hospitalisation and mortality [21]. There is some evidence that salicylate use confers worse outcomes in AP which is in line with our findings. Two case reports suggest that aspirin in high dose, and its use over a long period of time, may trigger AP. The former describes AP associated with aspirin overdose [22]. The latter describes a case of AP believed to be triggered by aspirin and simvastatin [23]. The patient had high cardiovascular morbidity and had been taking aspirin for 6 years. A case-controlled study reported celecoxib use associated with increased relative risk of AP [24], although, there is a lack of data on aspirin and AP.

CRP is an inflammatory marker that has been described as a marker of AP severity [25-27]. Various studies have used different cut-off points to differentiate mild and severe AP [26, 28]. Unfortunately, it is neither disease-specific nor the absolute values are accurate at predicting necrosis or organ failure [28]. We did not find any significant association between aspirin use and CRP, measured at the time of admission. Previous studies demonstrated that CRP level peaks after 48 hours of admission [27, 28], and therefore measurement at the time of admission may have yielded a different result.

This study had several limitations including generalisability. Firstly, being a retrospective study, there were some missing points for Ranson criteria (32% at admission) which led to the incomplete calculation of Ranson score. We commonly encountered a lack of testing of arterial blood gas (ABG) and incomplete recording of fluid balance. In practical terms, it was likely that patients with mild pancreatitis did not routinely undergo invasive testing with ABG nor rigorous fluid status assessment when they were clinically stable on admission. Secondly, as alluded in Akyazi's study, it could not be determined if there is a relationship between the dosage and duration of aspirin use and the severity of AP. We also did not have aspirin dose data that were used prior to hospital presentation. In this study, we observed that the Ranson score was increased with the increase of age and the aged population is more likely to use aspirin for several causes. None but one patient over 50 years of age used aspirin prior attending to the hospital. Although AP can cause at any age irrespective of gender, the most common causes in developed countries include common bile duct obstruction by stones and alcohol abuse.

Since our study was retrospective in nature therefore we were not able to look at all these potential factors from the record of AP patients such as alcohol abuse and aspirin or other NSAID use among younger age-group. Moreover, the higher prevalence of aspirin use in middle age or elderly population and an increasing Ranson score with the increase of age should be carefully examined for concluding the severity of AP by aspirin use.

Ideally, a randomised placebo-controlled prospective study could be designed comparing aspirin in various doses in age and morbidity matched patients, with the primary outcome being AP incidence, and secondary outcome its severity. Besides Ranson criteria is less useful after the introduction of revised Atlanta classification although, it helps to predict the severity of AP. Finally, the efficacy of aspirin may depend on the aetiology and route of administration since one RCT did not find that oral diclofenac prevented post-ERCP pancreatitis [29]. Although the present study did not account for the various types of AP owing to the difficulty in determining the aetiology in most cases, it is assumed that AP shares a common underlying pathophysiological mechanism.

6. Conclusions

The study suggests that aspirin did not confer a benefit to patients presenting with AP in this population. Conversely, pre-existing use of aspirin may, in fact, be detrimental to prognosis. Perhaps the lack of prospective clinical studies examining aspirin on outcomes in AP is posing difficulty in predicting the severity of the disease in patients presenting with abdominal pain. Besides, self-use of these drugs in the community is very common, and prospective studies on their effects in various diseases would lead to better understanding of their benefits and adverse effects, specifically for AP patients. Despite several influencing factors, Ranson Scoring is a useful tool for the prediction of the severity of AP. Future prospective studies for predicting the AP severity using Ranson scoring against revised Atlanta classification would be invaluable for better clinical guidance.

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