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Original Article

Prior statin use and the outcomes in patients with first-attack acute pancreatitis: A retrospective cohort study

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ABSTRACT

Background: We investigated whether prior stain use before admission for a first-attack AP would reduce the severity and mortality rate of a first-attack of AP with a dose–response relationship.
Methods: We conducted a retrospective cohort study from a tertiary medical center's database in Taiwan. We evaluated the dose–response relationship between statin use and the first-attack of AP by defining the daily dose (DDD). The cumulative DDD (cDDD) was calculated as the sum of the dispensed DDD of any specific statin. The outcome measures in our study included the hospital mortality rate, duration of hospitalization, Ranson's score, computed tomography severity index (CTSI), and C-reactive protein (CRP) level.
Results: In our study, we enrolled 31 patients in statin group and 63 matched patients in control group. In the univariate analysis there was no significant difference between them with regard to the outcomes except the CTSI and serum calcium concentration. According to multivariate analysis the serum calcium concentration was significantly higher in the statin group, and the CTSI was lower in the statin group. In subgroup analysis we divided the statin group into two groups according to the cDDDs (<365 days and >365 days) and the results showed no significance in the demographic data, overall mortality rate, hospitalization days, CRP level, Ranson's score, or CTSI.
Conclusion: Our study rejected the hypothesis that statins have beneficial effects on the clinical outcomes of patients with a first-attack of AP. However we demonstrated that statins have a positive effect on the CTSI.

1. Introduction

Pancreatic inflammatory disease has a diverse spectrum of clinical presentations, prognoses, and etiologies. It can be classified as acute pancreatitis (AP) or chronic pancreatitis based on the disease onset, and it can also be classified as interstitial pancreatitis or necrotizing pancreatitis according to disease severity. In a nationwide, population-based cohort study in Taiwan between 2000 and 2009, the annual incidence of the first episode of AP was estimated at 36.9 per 100,000 persons, and the annual hospital all-cause mortality rate decreased as time passed from 4.3% (2000–2001) to 3.3% (2008–2009) [1]. Although the annual prevalence of AP in severe cases significantly increased from 21.0% (2000–2001) to 22.3% (2008–2009), the annual hospital mortality rate of severe cases decreased from 18.5% (2000–2001) to 13.3% (2008–2009).

A review article from 2012 indicated that there was no effective pharmacological treatment for reducing the severity and mortality rate of AP [2]. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor or statins are prescribed frequently for lowering lipoprotein cholesterol levels. A systematic review of observational studies and various case reports in 2006 indicated that statins may induce AP [3]. The review revealed that AP can develop from high and low doses of statins, even at less than the defined daily dose equivalent of simvastatin (20 mg daily), and it can occur at any time, especially after the statin has been prescribed for several months. In another review of selected cases of statin-associated AP, most cases had self-limiting AP that resolved quickly after the discontinuation of causative statins, or AP developed after rechallenge with the possible causative statins in 9 of 20 cases [4]. However the rechallenge of causative agents may be unethical and risky for patients' health. The role of statins for AP is still under investigation.

Recently, a meta-analysis regarding lipid-modifying therapy and the risk of AP revealed that statin therapy was beneficial for lowering the incidence of AP in patients with normal or mildly elevated triglyceride (TG) levels [5]. There was no relevant information to discuss the relationship between the therapeutic effects of statins on patients

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with AP and the etiology of AP from the subgroup analysis. Another prospective cohort study from 2013 also showed that prior statin treatment may reduce the pancreatitis-related mortality in AP [6]. It did not mention the dose–response relationship between statin use and the risk of AP. Therefore, it is unknown whether the protective benefit of statins exists with a dose–response correlation and whether a different etiology of AP would significantly benefit from the use of statins.

We investigated whether prior stain use before admission for a first-attack AP would reduce the severity and mortality rate of a first-attack of AP with a dose–response relationship.

2. Materials and methods

2.1. Subjects and data collection

We collected the study patients' information retrospectively from a tertiary medical center's database in Taiwan from January 1, 2009 to December 31, 2013. The inclusion criteria were as follows: age ≥ 18 years; admission to our emergency department, hospital ward, or intensive care unit with a first-attack of AP (ICD-9-CM code 577.0); and prior statin use. The exclusion criteria were as follows: 1) admission to our emergency department, hospital ward, or intensive care unit with a first-attack of AP (ICD-9-CM code 577.0) before January 1, 2009; 2) irregular statin use prior to admission; and 3) incomplete basic demographic data for calculating Ranson's score or no available image for outcome measurements. The study was approved by the institutional review board of the Taichung Veterans General Hospital in Taichung, Taiwan.

The demographic, clinical, laboratory, and radiological data were reviewed. The definitions of AP were according to the revised Atlanta classification by the International Consensus of 2012 [7]. The diagnosis of AP required two of three of the following criteria: (1) acute onset of abdominal pain refined to the epigastria area with radiation to the back; (2) serum lipase or amylase activity at least three times greater than the upper limit of the normal range; and (3) typical presentation of AP on radiological imaging such as computed tomography with contrast enhancement or magnetic resonance imaging. Once patients were enrolled, we evaluated the severity and etiology of AP and matched the intervention group to the control group by age and sex using one-to-two matching. The statins used in Taiwan included simvastatin, atorvastatin, pravastatin, and rosuvastatin. We evaluated the dose–response relationship between statin use and the first-attack of AP by defining the daily dose (DDD). The DDD was recommended by the World Health Organization as a unit of assumed average maintenance dose per day of a drug consumed for its main indication in adults. The DDD for each kind of statin were defined as follows: simvastatin, 30 mg; atorvastatin, 20 mg; pravastatin, 30 mg; and rosuvastatin, 10 mg. We compared the different kinds of statins based on the same standard: (total amount of the drug) ÷ (the amount of drug in a DDD) = the number of DDDs [8]. The cumulative DDD (cDDD) was calculated as the sum of the dispensed DDD of any specific statin, which indicated the exposure duration of stains earlier before the admission of patients with a diagnosis of acute-attack of AP. To analyze the dose–response relationship, we categorized the cDDD of the statins into two groups: <365 days and >365 days.

2.2. Outcome measures

In our study, the outcome measures were the hospital mortality rate, duration of hospitalization, Ranson's score, computed tomography severity index (CTSI), and C-reactive protein (CRP) level. Regarding the cut-off value for evaluating the severity of AP, we defined severe pancreatitis when Ranson's score was ≥3 and the CTSI was ≥3 [12–14]. In one study, treatment of AP was possible in patients with a low CTSI (0–2) and high CTSI (7–10), but it was questionable for patients with an intermediate CTSI (3–6) [13]. Therefore, we decided to include patients with an intermediate and high CTSI to evaluate the role of statin.

2.3. Statistical analysis

We performed univariate analysis to determine the association between the treatment groups and the demographic parameters for patients who had a first-attack of AP. Quantitative variables such as calcium (mg/dL), triglycerides (mg/dL), CRP (mg/dL), and hospitalization days were described with the median and interquartile range. The Wilcoxon rank sum test was used to compare the distributions of each covariate between the statin and control groups. Categorical variables such as diabetes mellitus and hypertension were described with frequencies and percentages. Pearson's chi-square test was performed to assess the relationship between the groups and the variables. Multivariate logistic regression was also used, and the regression coefficients were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for each independent variable in the model. The receiver operating characteristic (ROC) curves of the CTSI were generated to assess the diagnostic accuracy of each model. The area under (AUC) the ROC curve was considered as a measure of discriminative ability. All the tests were two-sided, and a P-value < .05 was considered statistically significant. Statistical analyses were performed using the statistical software R, version 3.0.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

3. Results

In our study, we enrolled 763 patients with AP from the database within 5 years. Among them, 45 patients had prior statin use, and we excluded 13 because of irregular statin use (8), inaccurate diagnosis of AP (3), and incomplete data or imaging (2). We chose 1:2 matching by sex and age to determine the target numbers for the groups (statin group, 32 and control, 64). Among 96 cases screened, we excluded 2 in each group that had an extended hospital stay related to another disease complication. The final numbers of cases in the analysis were 31 in the statin group and 63 in the control. Demographic data and the outcome of the groups are summarized in Table 1.

According to the univariate analysis, the statin group had a higher serum calcium concentration than the control (P < .05). There was no difference between the statin and control groups with regard to the overall mortality rate, hospitalization days, CRP level, and Ranson's score. However, the CTSI was lower in the statin group than in the control (P < .05).

According to multivariate analysis, which used four variables from Table 1 (i.e., diabetes mellitus, the calcium concentration, Ranson's score, and the CTSI score), the serum calcium concentration was significantly higher in the statin group than in the control (OR, 1.95; 95% CI: 1.08–3.84), and the CTSI (OR, 0.20; 95% CI: 0.05–0.64) was lower in the statin group than in the control (Table 2). There were more patients

Table 1
The demographic data of patients with first-attack acute pancreatitis: control group (n = 63) compared with statin group (n = 31).

Variables	Control group (n = 63)	Statin group (n = 31)	P-value
Diabetes mellitus	28 (44)	20 (65)	0.06[1]
Hypertension	15 (24)	10 (32)	0.38[1]
Gallstone-related AP	36 (57)	15 (48)	0.42[1]
Ca (mg/dL); median (IQR)	8.30 (7.85–8.80)	8.80 (8.30–9.05)	0.01[2]
Triglycerides (mg/dL); median (IQR)	93.0 (73.5–132.0)	121.0 (81.0–156.0)	0.16[2]
CRP (mg/dL); median (IQR)	4.68 (1.35–10.05)	2.65 (1.30–5.69)	0.14[2]
Ranson's score ≥ 3	30 (48)	16 (52)	0.71[1]
CTSI score ≥ 3	27 (43)	5 (16)	0.01[1]
Hospitalization days; median (IQR)	11.0 (7.0–18.5)	10.0 (8.0–14.5)	0.96[2]
Hospital mortality	7 (11)	1 (3)	0.19[1]

Values are presented as number (%), unless otherwise specified.
IQR, interquartile range; CRP, C-reactive protein; CTSI, computed tomography severity index.
Tests used: [1]Pearson test; [2]Wilcoxon test.