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Treatment of Hypertriglyceridemia-Induced Acute Pancreatitis With Plasma Diafiltration
A Pilot Study

To the Editor:

Severe hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is a critical illness associated with high mortality rate and potentially fatal complications,[1,2] whereas triglyceride (TG)-lowering therapy is crucial in early HTG-AP.[1,3] Plasmapheresis and other extracorporeal filtration techniques were widely used for timely and fast reduction of TG levels. However, it is not an ideal procedure because of potential transfusion related complications or complex operation.[4,5]

Plasma diafiltration (PDF), which used high cutoff hemofilter and diluted plasma as replacement fluid, can significantly decrease middle– and high–molecule-weight mediator levels with low substitution flow, achieving approximately the same effect as that of conventional plasmapheresis.[6] However, no previous reports exist on the treatment of HTG-AP with PDF. Therefore, we designed a retrospective study to evaluate the efficacy and safety of PDF application in combination with routine treatments in 5 HTG-AP patients admitted to the intensive care unit (ICU).

MATERIALS AND METHODS

A total number of 5 HTG-AP patients with a mean age of 35.2 (standard deviation, 1.72; range, 32–37) years who received PDF as part of their treatment during their ICU stay between January 2017 and December 2018 were recruited. All patients received standard conventional treatment. Therapeutic PDF was also performed to rapidly reduce the TG levels, which was discontinued when the levels of serum TGs were less than 1000 mg/dL.

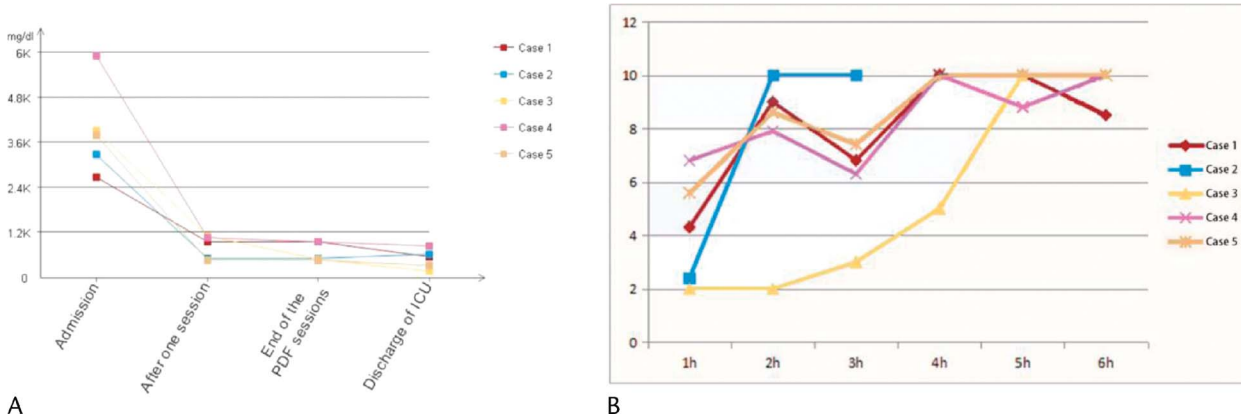
RESULTS

The patients' baseline characteristics are shown in Table 1. The Ranson criteria score values of all patients were greater than 3, indicating severity of pancreatitis. Mechanical ventilation was needed for 1 patient because of acute respiratory distress syndrome for 6 days. Another patient received continuous renal replacement therapy for acute kidney injury. All patients had a known history of hyperlipidemia, whereas 2 of them had alcohol consumption; 2 had hypertension; 1

TABLE 1. Baseline Characteristics and the Treatment of HTG-AP Patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Baseline characteristics					
Sex	Male	Male	Male	Female	Male
Age, y	37	36	35	32	36
Alcohol use	No	No	Yes	No	Yes
T2DM	Yes	No	No	No	No
HP	No	No	Yes	No	No
HTG	Yes	Yes	Yes	Yes	Yes
Ca^{2+}, mmol/L	2.04	1.79	1.72	1.35	2.17
Cholesterol, mmol/L	11.56	12.12	12.66	18.59	14.2
HDL, mmol/L	0.88	0.75	0.77	0.99	0.9
LDL, mmol/L	10.68	11.37	11.24	16.38	7.02
Amylase on admission, μ/L	284	111	491	138	354
APACHE II score	3	5	5	12	7
Ranson score	3	4	5	5	3
Marshall score	3	1	2	3	2
TG on admission, mg/dL	2681.5	3291.3	3932.9	5928.83	3796.22
TG after one session, mg/dL	948.7	516.8	1115.9	1056.57	474.3
TG after PDF, mg/dL	948.7	516.8	493.6	945.07	474.3
TG on discharge from ICU, mg/dL	560.2	613.7	167.3	836.2	324.6
Local complications	None	None	None	None	None
Systematic complications	None	None	None	None	None
Mechanical ventilation	No	No	No	Yes	No
CRRT	No	No	No	Yes	No
LOS in ICU, d	3	3	4	10	2
Total LOS, d	13	21	19	23	12
PDF treatment					
No. PDF sessions	1	1	2	2	1
Duration of apheresis, h	6	3	6 + 6	6 + 6	6
Heparin dosage, U/h	750	500	No	No	No
Blood flow rate, mL/min	180	180	180	180	180
Dialysate flow rate, mL/min	3000	3000	3000	3000	3000
Replacement flow rate, mL/min	600	600	600	600	600
Removal rate for TC after one session, %	57.8	57.9	31.9	49.2	4.8
Removal rate for TG after one session, %	64.6	84.3	71.6	82.2	87.5
Maximal TMP, mm Hg	10	10	10	10	10
Maximal arterial pressure, mm Hg	−110	−160	−90	−100	−85
Maximal venous pressure, mm Hg	80	500	80	120	101

APACHE II indicates Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy; HP, hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LOS, length of stay; T2DM, type 2 diabetes mellitus; TC, total cholesterol.



A B

FIGURE 1. A, Triglyceride levels at various time points during hospitalization. B, Curve of TMP.

experienced type II diabetes mellitus and was administered insulin infusion before PDF. None of the patients with HTG received oral lipid-lowering medicine.

The average TG level before PDF was 3926.2 (range, 2681.5–5928.8) mg/dL. All patients received PDF therapy, which alleviated HTG-AP with a significant decrease in the TG levels. Three patients received 1 PDF session, whereas the other 2 patients were subjected to 2 sessions. After the first session, the average reduction of TG level was 3103.0 (range, 1732.8–3321.9) mg/dL, dropping approximately by 79.06%. At the end of the PDF sessions, the average TG concentration was 675.9 (range, 474.3–945.0) mg/dL, representing an 87.2% reduction. The TG level at ICU discharge was 500.4 (range, 167.3–836.2) mg/dL. Triglyceride concentrations of less than 1000 mg/dL were attained in all patients by the end of the procedure (Fig. 1A).

The mean pre- and post-PDF levels of cholesterol were 13.8 (range, 11.56–18.59) mmol/L and 8.31 (range, 4.88–13.51) mmol/L, respectively, with a decrease of 39.8%. Moreover, the mean amylase and lipase values, determined before and 3 days after PDF, were 275.6 (range, 111.0–491.0) U/L and 58.2 (range, 33.6–86.9), with a decrease of 78.8% U/L, respectively. The transmembrane pressure (TMP) values (Fig. 1B) showed no trend of increase of TMP caused by PDF.

Therapeutic PDF was well tolerated. The occurrence of asymptomatic hypotension in 1 patient was observed. In addition, 1 patient had hypervolemia, which was successfully treated with intravenous furosemide. Hemolysis was not detected in any of the patients. Catheter occlusion occurred in 1 patient. However, PDF was not discontinued in any of these cases.

DISCUSSION

To our knowledge, this study is the first to evaluate the effect and safety of PDF treatment in HTG-AP. The most important findings of our research are as follows: (1) PDF can rapidly reduce serum TG in a short period of time, which is key to the successful management of HTG-AP. We achieved 87.2% in TG reduction with 1 to 2 sessions of treatment of our patients, which is faster than in previous reports on double filtration plasmapheresis (from 60% to 70%) or PE (84.5%)[6] and (2) no treatment-related complication occurred.

One possible reason for this is that the optimal pore size of the EC-30W plasma separator used for PDF because the efficiency of the procedure on TG is closely related to the pore size. Besides, the EC-30W plasma separator (Asahi Kasei, Tokyo, Japan) has a smaller pore size than that of the conventional plasma separation membrane (0.01 vs 0.2–0.4 μm). Hence, coagulation factors are preserved because this membrane has a sieving coefficient of 0 for fibrinogen and immunoglobulin M (IgM). Therefore, a tradeoff between removing TG could be realized while maintaining constant of the coagulation factors and IgM. In PDF, lipoprotein can be selected and discharged into the waste liquid by ultrafiltration. Moreover, dialysis is added to this type of selective plasma filtration. In that case, the latter has a higher potential to avoid blockage of the membrane filter compared with simple selective plasma filtration.

In conclusion, our study suggested that PDF could lower the TG level rapidly and dramatically compared with PE. Moreover, PDF therapy is less plasma consuming and avoids heavy leakage of important components such as coagulation factors and IgM. However, because of the small number of the participants in our research, a further prospective study with large sample size is required to evaluate the impact of PDF therapy on HTG-AP.

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Predictive Value of Acute Pancreatitis Diagnosis Code in Diabetic Patients Is Similar to Nondiabetic Patients

To the Editor:

Acute pancreatitis (AP) is among the most common gastrointestinal causes of inpatient admissions in the United States.[1] Patients with diabetes mellitus (DM) exhibit a 3-fold increased risk of AP compared with the general population.[2,3] Clinical practice guidelines recommend that the diagnosis of AP be made if at least 2 of 3 typical features are present—upper abdominal pain, elevation of serum pancreatic enzymes at least 3 times the reference value, and imaging findings consistent with AP.[4] However, serum pancreatic enzymes are often elevated in diabetic patients in the absence of AP.[5] Conversely, pancreatic enzymes may be minimally elevated in hypertriglyceridemia-induced pancreatitis, which is more common among patients with DM.[6]

Administrative data sets in large populations are increasingly utilized to evaluate associations, severity, and outcomes in many conditions,[7,8] including AP. The validity of administrative codes for AP in patients with diabetes has been understudied and may be limited by the aforementioned variations in pancreatic enzymes in diabetic patients. The aim of this study was to evaluate the predictive value of the diagnosis code for AP based on the presence of preexisting DM.

We performed a retrospective analysis of all 579 patients hospitalized at the University of Pittsburgh Medical Center Presbyterian Medical Center between June 2009 and August 2014 with a first-time, primary inpatient discharge diagnosis code of AP International Classification of Diseases 9, Clinical Modification 577.0). Demographic and clinical information was abstracted from the electronic health record. The diagnosis of AP was confirmed if 2 or more of the following criteria were present—a mention of upper abdominal pain in clinical notes, serum amylase, and/or lipase elevation of 3 or more times the upper limit of normal, and imaging findings consistent with pancreatitis from imaging reports. Diabetes was confirmed in patients with a documented clinical history of DM, use of oral or injectable hyperglycemic agents, or hemoglobin A1c of 6.5% or greater.

The mean age of patients was 53.7 (standard deviation [SD], 18.3 years). Patients were predominantly White (68.4%) and male (55.6%). Preexisting DM was noted in 170 (29.4%) patients, 164 of whom had a DM-related diagnosis code. There were no differences between diabetic and nondiabetic patients with respect to age, sex, ethnicity, history of tobacco use, and history of prior cholecystectomy. Diagnostic criteria for AP were met in 459 of 579 patients (positive predictive value [PPV] = 0.79), and did not vary significantly with DM status (PPV = 0.76 in diabetics vs PPV = 0.81 in non-diabetics; $P = 0.19$). About one fourth of patients identified by billing codes as having sentinel-episode AP had documentation of prior acute and/or chronic pancreatitis.

Diabetic patients with AP were older than nondiabetic patients (age, 56.6 years [SD, 17.1 years] vs 52.8 years [SD, 18.7 years]; $P = 0.046$), but were otherwise similar with respect to sex, ethnicity, history of smoking. There were significant differences in the etiology of AP based on preexisting diabetic status, with gallstone pancreatitis as the most common etiology in both groups, but hypertriglyceridemia was more prevalent in patients with DM, and alcohol was more prevalent in nondiabetics (Table 1).

Among 120 patients who did not meet the diagnostic criteria for AP, 85 (70.8%) fulfilled 1 criterion (31 [25.8%] typical pain, 24 [20.0%] enzyme elevation, 30 [25.0%] abnormal imaging), whereas 35 (29.2%) did not fulfill any of the 3 criteria. There was no difference in the distribution of these criteria based on DM status.

Our study confirmed findings of prior studies that approximately 4 of 5 patients, who receive first-time primary inpatient discharge diagnosis code of AP, meet guideline-recommended criteria for diagnosis. Ours is the first study to demonstrate that this predictive value is similar in patients with and without prevalent DM. We hypothesized that elevated serum pancreatic enzymes would be observed more frequently in diabetic patients, leading to increased rates of false AP diagnosis in this subset. Although pancreatic enzymes can be elevated in non-AP abdominal pain in diabetics, they are rarely above 3 times the upper limit of the normal required to meet diagnostic criteria, which may explain this finding.[9]

Our study is limited by the use of the electronic health record as the criterion standard for diagnosis, which likely resulted in an underestimation of diagnosis-code accuracy. As a referral center, the lack of comprehensive patient medical records introduces the potential for further error. Finally, lacking a control group of patients without AP, we are unable to identify other test characteristics, such as sensitivity,

TABLE 1. Demographics, Select Risk Factors, and Etiology in Patients Who Met Diagnostic Criteria for AP

	Total (N = 459)	Diabetics (n = 129; 28.1%)	Nondiabetics (n = 330; 71.9%)	P*
Age, mean (SD), y	53.9 (18.3)	56.6 (17.1)	52.8 (18.7)	**0.046**
Sex, male, n (%)	256 (55.8)	75 (58.1)	181 (54.8)	0.52
Ethnicity, White, n (%)	309 (67.3)	80 (62.0)	229 (69.4)	0.13
Tobacco use ever, n (%)	223 (48.6)	68 (52.7)	155 (47.0)	0.27
History of cholecystectomy, n (%)	91 (19.8)	29 (22.5)	62 (18.8)	0.37
First episode of AP, n (%)	344 (74.9)	91 (70.5)	253 (76.7)	0.17
Etiology, n (%)				**<0.001**
Biliary	149 (32.5)	49 (38.0)	100 (30.3)	
Alcohol	102 (22.2)	15 (11.6)	87 (26.4)	
Hypertriglyceridemia	23 (5.0)	16 (12.4)	7 (2.1)	
Idiopathic	114 (24.8)	31 (24.0)	85 (25.8)	
Other	71 (15.5)	18 (14.0)	51 (15.5)	

Bolded *P* values identify characteristics which were significantly different ($P \leq 0.05$) between diabetic and nondiabetic cohorts.

**P* value compares diabetic and nondiabetic patients.