Refeeding Syndrome as a Possible Cause of Very Early Mortality in Acute Pancreatitis

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Background/Aims: Refeeding syndrome (RFS) is a fatal clinical complication that can occur as a result of fluid and electrolyte shifts during early nutritional rehabilitation for malnourished patients. This study was conducted to determine the clinical implications of RFS in patients with acute pancreatitis (AP). **Methods:** Between 2006 and 2016, AP patients with very early mortality were retrospectively enrolled from three university hospitals. **Results:** Among 3,206 patients with AP, 44 patients died within 3 days after diagnosis. The median age was 52.5 years (range, 27 to 92 years), male-to-female ratio was 3:1, and median duration from admission to death was 33 hours (range, 5 to 72 hours). The etiology of AP was alcohol abuse in 32 patients, gallstones in five patients, and hypertriglyceridemia in two patients. Ranson score, bedside index for severity of AP, and acute physiology and chronic health evaluation-II were valuable for predicting very early mortality (median, [range]; 5 [1 to 8], 3 [0 to 5], and 19 [4 to 45]). RFS was diagnosed in nine patients who died of septic shock (n=5), cardiogenic shock (n=2), or cardiac arrhythmia (n=2). In addition, patients with RFS had significant hypophosphatemia compared to non-RFS patients (2.6 mg/dL [1.3 to 5.1] vs 5.8 mg/dL [0.8 to 15.5]; p=0.001). The early AP-related mortality rate within 3 days was approximately 1.4%, and RFS occurred in 20.5% of these patients following sudden nutritional support. **Conclusions:** The findings of current study emphasize that clinicians should be aware of the possibility of RFS in malnourished AP patients with electrolyte imbalances. **(Gut Liver 2019;13:576-581)**

Key Words: Refeeding syndrome; Acute pancreatitis; Mortality; Prognosis; Nutrition

INTRODUCTION

Acute pancreatitis (AP) is the most common gastrointestinal indication requiring hospitalization. Despite adequate early treatment, it can be life-threatening in one-fifth of patients, and the overall mortality in hospitalized patients with AP is estimated to be approximately 3% to 5%.[1-3] However, the incidence and causal factors for early mortality are not fully understood, even though it is not uncommon for physicians to experience unexpected early mortality while treating pancreatitis.

Malnourished patients with any internal medical disease such as pancreatitis or an eating disorder require nutritional rehabilitation. However, a potential risk associated with nutritional therapy in undernourished patients is refeeding syndrome (RFS), where electrolyte (phosphate, magnesium, and potassium) disturbances can lead to clinical deterioration and possible sudden mortality. Estimates of the prevalence of RFS vary widely from 0.43% to 34%.[4] RFS broadly encompasses clinical complications that can occur as result of fatal fluid and electrolyte shifts in malnourished patients during refeeding by oral, enteral, or parenteral[5] routes and can lead to cardiac arrhythmia, muscle weakness and cramping, seizures, delirium, and death.[6-12] Although the relationship between AP-related early mortality and RFS has not been reported, patients with severe AP, especially those with chronic alcoholism and/or malnourishment, may be at risk of developing RFS.[13] Although routine use of total parenteral nutrition (TPN) is not recommended for early management of pancreatitis, high calorie nutrition rehabilitation is often provided to patients with AP on admission. Therefore, RFS may be responsible for unexpected and unexplained early AP related mortality.

However, the importance of RFS has been overlooked in many clinical fields, and most gastroenterologists pay little attention to the risk of RFS during initial nutritional support. Because RFS may be a possible cause of early AP-related mortality, we aimed to determine the possible causes of very early mortality (within 3 days) in patients with AP.

MATERIALS AND METHODS

1. Patients and methods

This was a retrospective multicenter study involving three university hospitals: Gil Medical Center of Gachon University, Wonju Severance Christian Hospital of Yonsei University Wonju College of Medicine, and Sanggye Paik Hospital of Inje University. Medical records of patients admitted from January 2006 to December 2016 were reviewed and a total of 3,206 patients with suspected AP were identified (Fig. 1). This study was approved by the Institutional Review Boards for Human Research of Gachon Gil University (GAIRB2017-220), Wonju Severance Christian Hospital (CR315005), and Sanggye Paik Hospital (SGPAIK2018-11-017). This study was performed in accordance with the relevant guidelines and regulations of each institution. No consent was required because data were anonymized before analyses.

Patients diagnosed with AP were required to satisfy two of the following three criteria: abdominal pain characteristic of AP, serum amylase and/or lipase ≥3 times the upper limit of normal, and computed tomography (CT) findings of AP.[14] In this study, very early mortality was defined as death within 3 days after diagnosis of AP, because RFS can develop rapidly within 3 days after beginning nutritional rehabilitation.[15-18] The severity of AP was evaluated using Ranson criteria, bedside index for severity of AP (BISAP), CT severity index (CTSI), acute physiology and chronic health evaluation-II (APACHE-II), sequential organ failure assessment (SOFA), Harmless AP, and simplified acute physiology score (SAPS) II.
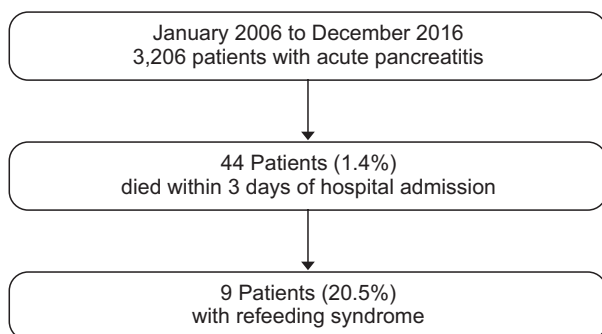
2. Definitions of refeeding syndrome

Although there is no universal agreement on the definition of RFS, it has been defined as severe fluid and electrolyte shifts in malnourished patients during oral, enteral, or parenteral refeeding. If one of the following criteria was met: body mass index <16 kg/m^2, unintentional weight loss >15% in the preceding 3 to 6 months, very little or no nutritional intake for more than 10 days, or low levels of serum potassium phosphate or magnesium prior to feeding, the patient was determined to be at risk of RFS.[19] The patient was also considered at risk of RFS if two of the following criteria were met: body mass index <18.5 kg/m^2, unintentional weight loss >10% in the preceding 3 to 6 months, minimal or no significant nutritional intake for >5 days, and/or medical history of alcohol or drug abuse.[19] RFS was confirmed using the three diagnostic criteria of severely low-serum electrolyte levels of phosphate, magnesium, or potassium; fluid balance abnormalities such as cardiac failure, pleural effusion, hypotension and acute kidney injury; and organ dysfunction.[20,21]

3. Statistical analyses

Standard descriptive statistics were used to evaluate data from the participants. The Mann-Whitney test and Fisher exact test were used to compare data between patients with RFS and without RFS. A p-value <0.05 was considered statistically significant.

RESULTS

1. Characteristics of AP patients with very early mortality

In this study, 44 (1.4%) of 3,206 patients with AP died within 3 days after diagnosis. Their median age was 52.5 years (range, 27 to 92 years), and very early mortality affected more male than female patients. The most common etiology of AP was alcohol abuse, while other causes were gallstones, malignancy, hypertriglyceridemia, pancreas divisum, and idiopathic. In terms of immediate cause of death, septic shock was the most common cause of very early mortality in AP, followed by cardiogenic shock, cardiac arrhythmia, alcoholic ketoacidosis, and respiratory failure. Median duration of admission to death was 33 hours (range, 5 to 72 hours). Among various scoring systems, Ranson score, BISAP, and APACHE-II were confirmed to be valuable at predicting very early mortality in AP patients (median [range]; 5 [1 to 8], 3 [0 to 5], 19 [4 to 45]); however, CTSI was not helpful for predicting very early mortality in AP patients (median, 2; range, 0 to 10) (Table 1).

2. Characteristics of AP patients with RFS

Of 44 AP patients with very early mortality, nine (20.5%) were diagnosed with RFS because of a positive history of alcohol abuse, inadequate nutritional intake for more than 5 days, or low serum levels of phosphate (n=5), magnesium (n=1), and

Fig. 1. The study design evaluating early mortality of patients with acute pancreatitis and refeeding syndrome.

Table 1. Clinical Features of Patients with Acute Pancreatitis Related to Very Early Mortality (within 3 Days of Diagnosis)*

Clinical characteristic	Value (n=44)
Age, yr	52.5 (27–92)
Sex, female:male	1:3
BMI, kg/m²	23.4 (17.6–28.4)
Etiology	
Alcohol abuse	32 (72.7)
Gallstones	5 (11.4)
Hypertriglyceridemia	2 (4.5)
Malignancy	1 (2.3)
Pancreas divisum	1 (2.3)
Idiopathic origin	3 (6.8)
Immediate cause of death	
Septic shock	24 (54.5)
Cardiogenic shock	9 (20.5)
Cardiac arrhythmia	5 (11.4)
Alcoholic ketoacidosis	4 (9.1)
Respiratory failure	2 (4.5)
Duration from admission to death, hr	33 (5–72)
Scoring systems and laboratory findings	
Ranson score	5 (1–8)
BISAP	3 (0–5)
CT severity index	2 (0–10)
APACHE-II	19 (4–45)
SOFA	7 (0–16)
Harmless AP	1 (0–3)
SAPS II	45 (23–93)
Hematocrit, %	40.85 (27.8–54.3)
Phosphate, mg/dL	5.0 (0.8–15.5)
Potassium, mEq/L	4.2 (2.6–6.6)
Sodium, mEq/L	131.5 (109.0–149.0)
Albumin, g/dL	3.5 (1.7–5.0)

Data are presented as median (range) or number (%).
BMI, body mass index; BISAP, bedside index for severity of acute pancreatitis; CT, computed tomography; APACHE-II, acute physiology and chronic health evaluation-II; SOFA, sequential organic failure assessment; AP, acute pancreatitis; SAPS II, simplified acute physiology score II.
*Reference range (serum), conventional units; hematocrit, males 42% to 52%, females 37% to 47%; phosphate, 2.7–4.5 mg/dL; potassium, 3.5–5.1 mEq/L; sodium, 136–145 mEq/L; albumin, 3.5–5.2 g/dL.

potassium (n=2) before initial nutritional rehabilitation. Also, all patients expired suddenly after rapid parenteral nutritional support, and most showed electrolyte imbalance and/or abnormal fluid distribution such as pleural effusion (n=6). Immediate causes of death in RFS were septic shock (n=5, 55.6%), cardiogenic shock (n=2, 22.2%), and cardiac arrhythmia (n=2, 22.2%), which coincided with nutritional support of total parental nutrition of more than 10 kcal/kg/day. This nutritional rehabilitation

Table 2. Detailed Clinical Characteristics Related to Early Mortality in Patients with Acute Pancreatitis with Refeeding Syndrome*

Case	Age, yr	Sex	Alcohol abuse	BMI, kg/m²	Nutritional support on the 1st day, kcal/day	Phosphate, mg/dL†	Magnesium, mg/dL†	Potassium, mEq/L†	Creatinine, mg/dL	Albumin, g/dL†	Pleural effusion	Causes of death	Duration from admission to death, hr	Diagnostic criteria of RFS‡
1	47	M	+	19.2	1,200	2.5		3.9	0.4	3.8	–	Septic shock	11	1,2,3
2	41	M	+	24.9	1,400	1.8 → 1.3	1.9 → 1.8	6.5 → 6.5	3.0	3.5 → 3.0	+	Septic shock	20	1,2,3
3	52	M	+	28.4	1,000	1.5		4.5 → 5.0	0.7	3.6 → 3.3	+	Cardiac arrhythmia	36	1,2,3
4	27	M	+	20.0	1,000	2.9		3.4	0.7	3.5	+	Cardiac arrhythmia	48	1,2,3
5	46	M	+	24.9	1,200	5.0 → 3.2	1.4 → 1.6	4.5 → 4.9	3.5	3.0 → 1.9	+	Cardiogenic shock	72	1,2,3
6	47	M	+	22.6	1,400	5.1 → 0.9	2.1 → 2.2	4.9 → 3.2	3.13	3.3 → 2.2	+	Septic shock	70	1,2,3
7	80	M	+	23.4	2,300	3.8 → 2.5	2.3 → 2.3	3.6 → 4.5	0.88	4.2 → 2.1	–	Septic shock	25	1,2,3
8	39	M	+	25.7	2,200	1.3 → 1.3		3.4 → 6.9	1.2	5.0	–	Cardiogenic shock	41	1,2,3
9	89	F	–	20.5	1,200	2.6	1.7	4.2 → 4.1	0.9	3.1	+	Septic shock	61	1,2,3

BMI, body mass index; RFS, refeeding syndrome; M, male; F, female.
*Reference range (serum), conventional units; hematocrit, males 42% to 52%, females 37% to 47%; phosphate, 2.7–4.5 mg/dL; magnesium, 1.6–2.6 mg/dL; creatinine, male 0.7–1.3 mg/dL, female 0.6–1.1 mg/dL; albumin, 3.5–5.2 g/dL; †Admission → follow-up; ‡Diagnostic criteria for RFS; (1) electrolyte derangements (hypophosphatemia, hypokalemia, hypomagnesemia), (2) fluid balance abnormalities (cardiac failure, pleural effusion, hypotension, acute kidney injury), and (3) organ failure.

aggravated the clinical manifestations of the nine patients and was likely the immediate cause of death within 3 days (Table 2).

The nine RFS AP patients were compared with the 35 non-RFS AP patients with very early mortality. Only phosphate level was significantly different between the two groups (2.6 mg/dL vs 5.8 mg/dL, p=0.001). There were no significant differences in age, sex, duration from admission to death, etiology of AP, immediate cause of death, severity of AP, BMI, or levels of hematocrit, potassium, sodium, and albumin between the two groups (Table 3).

DISCUSSION

This study reviewed the medical records of 44 patients with AP with very early mortality (death within 3 days after diagnosis of AP). The history of alcohol abuse and malnutrition in these patients supports the hypothesis that RFS is associated with early AP-related mortality as 20% of these patients had RFS. Considering the fatal consequences of RFS, early detection and prevention are critical, particular in patients at high risk for RFS, namely elderly patients as well as those with cancer, chronic alcoholism, anorexia nervosa, uncontrolled diabetes mellitus, or malabsorption syndromes such as inflammatory bowel disease or chronic pancreatitis.[4,21,22]

Table 3. Comparison of Clinical Characteristics Related to Very Early Mortality in Patients with Acute Pancreatitis with or without Refeeding Syndrome*

Clinical characteristic	With RFS (n=9)	Without RFS (n=35)	p-value
Age, yr	47 (27–89)	60 (28–92)	0.125
Sex, female:male	1:8	10:25	0.286
BMI, kg/m^2	23.4 (19.3–28.4)	23.4 (17.6–28.4)	0.756
Etiology			0.697
Alcohol abuse	8 (88.9)	24 (68.6)	
Gallstones	0	5 (14.3)	
Others	1 (11.1)	6 (17.4)	
Immediate cause of death			0.956
Septic shock	5 (55.6)	19 (54.3)	
Cardiogenic shock	2 (22.2)	7 (20.0)	
Cardiac arrhythmia	2 (22.2)	3 (8.6)	
Alcoholic ketoacidosis	0	4 (11.4)	
Respiratory failure	0	2 (5.7)	
Duration of admission to death, hr	48 (11–72)	31 (5–2)	0.148
Scoring systems and laboratory findings			
Ranson score	6 (5–8)	5 (1–7)	0.120
BISAP	2.5 (0–4)	3 (1–5)	0.475
CT severity index	3 (0–8)	2 (0–10)	0.626
APACHE-II	19 (4–45)	19.5 (10–45)	0.506
SOFA	7 (3–12)	7.5 (0–16)	0.576
Harmless AP	1 (1–3)	1 (0–3)	0.479
SAPS II	34 (33–35)	50 (23–93)	0.286
Hematocrit, %	40.7 (29.6–49.2)	41.3 (27.8–54.3)	0.731
Phosphate, mg/dL	2.6 (1.3–5.1)	5.8 (0.8–15.5)	0.001
Potassium, mEq/L	4.2 (3.4–6.5)	4.3 (2.6–6.6)	0.607
Sodium, mEq/L	138 (109–142)	131 (111–149)	0.864
Albumin, g/dL	3.5 (3.0–5.0)	3.5 (1.7–5.0)	0.864

Data are presented as median (range) or number (%).
RFS, refeeding syndrome; BMI, body mass index; BISAP, bedside index for severity of acute pancreatitis; CT, computed tomography; APACHE-II, acute physiology and chronic health evaluation-II; SOFA, sequential organic failure assessment; AP, acute pancreatitis; SAPS II, simplified acute physiology score II.
*Reference ranges (serum), conventional units; hematocrit, male 42% to 52%, female 37% to 47%; phosphate, 2.7–4.5 mg/dL; potassium, 3.5-5.1 mEq/L; sodium, 136–145 mEq/L; albumin, 3.5–5.2 g/dL.

It is important to gain an understanding of the pathogenic mechanisms involved in refeeding to examine how this may result in early mortality in patients with AP. Introduction of energy can cause RFS because of the change from the catabolic state of starvation to anabolic metabolism during nutritional rehabilitation. Initial nutrition support with TPN can elicit congestive heart failure and pulmonary edema because of hyperinsulinemia and decreased renal excretion of sodium and water.[21,22] A physiological shift from fat to carbohydrate metabolism will result in electrolyte imbalance, which is responsible for cellular uptake of phosphate, magnesium, and potassium ions. Phosphate is the major intracellular divalent anion and is an important intracellular buffer as well as a major structural component of nucleic acids, nucleoproteins, and phospholipids. It plays an important role in maintenance of the structural integrity of the cell membrane, activation of many enzymes and second messengers, and energy storage in the form of adenosine triphosphate.[21] Severe hypophosphatemia is an early warning sign of RFS, and serum phosphate level should be closely monitored in patients at high risk of RFS.[23] However, other electrolyte imbalances such as hypokalemia, hypocalcemia, and hypomagnesemia can also develop.[24-27]

Some patients with AP also have typical characteristics of alcohol abuse and little or no nutritional intake for more than 5 days, which are both risk factors for RFS according to criteria established by the guidelines of the National Institute for Health and Clinical Excellence (NICE).[19] However, most gastroenterologists have paid little attention to RFS. Starvation for a period as short as 48 hours and poor nutrition status can predispose a person to RFS.[28] In our study, the nine patients with RFS had little or no nutritional intake for more than 5 days. Among them, eight patients were chronic alcoholics. Hypophosphatemia is known as a major feature of RFS after reintroduction of nutrition. In our study, five of the nine RFS patients had hypophosphatemia before TPN and the other three patients developed hypophosphatemia after administration of TPN. Unfortunately, one patient did not have a follow-up phosphate level measurement due to sudden death, but hypokalemia was observed in this patient. Potassium is also depleted in undernutrition, but serum concentrations remain normal.[21] In our study, hyperkalemia or an increase in potassium levels were seen in five patients. Dehydration and acute kidney injury may have induced these phenomena. In addition, six AP patients with RFS developed fluid overload such as pleural effusion. Thus, electrolyte imbalance and abnormal fluid distribution might have contributed to the early deaths of nine patients with RFS because their conditions were definitely aggravated after nutritional rehabilitation.

Therefore, in patients with severe AP, especially chronic alcoholics, serum electrolytes such as sodium, potassium, magnesium and phosphorus should be checked before starting nutritional support.[29] High calorie nutrition rehabilitation using TPN or enteral feeding should not be started in patients with severe fluid and electrolytes imbalances. For patients at high risk of RFS, energy replacement should be started slowly at a maximum rate of 10 kcal/kg/day and be increased over 4 to 7 days.[5,21] Complete normalization of electrolytes before feeding is not necessary, but correction should be started from the beginning and maintained alongside feeding.[29]

There are several limitations that warrant careful interpretation of our findings. First, this was a retrospective small population study. Second, many patients with AP died due to sudden death before their phosphate level was rechecked. Therefore, it is likely that the incidence of hypophosphatemia after refeeding was underestimated. Third, we only included patients with early AP-related mortalities within 3 days. Patients with all AP-related mortality should be included in future studies to determine if there is a causal relationship between RFS and early mortality in AP patients. Finally, although there is some consensus regarding risk factors and timely occurrence of RFS, the definition of RFS is heterogeneous. Therefore, further prospective well-designed studies using an established definition of RFS are warranted to evaluate the association between RFS and prognosis of AP.

In conclusion, clinicians should consider AP patients to be at risk of RFS when these patients present with little or no nutritional intake for more than 5 days, a history of alcohol abuse, old age, or a low level of phosphate before refeeding. When treating such patients, energy replacement should be started at no more than 10 kcal/kg/day and slowly increased over 4 to 7 days. It is also necessary to supplement thiamine, vitamin B, potassium, phosphate, calcium, and magnesium levels.[21] Careful monitoring and multidiscipline nutritional team management may help to reduce the morbidity and mortality of RFS in patients with AP.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

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