Hypokalaemia and enteric peritonitis in CAPD patients

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Abstract

**Background.** Hypokalaemia is a relatively common complication in uraemic patients undergoing continuous ambulatory peritoneal dialysis (CAPD). The hazards of hypokalaemia are multiple and have been correlated with patient morbidity and mortality. Whether it is associated with increased risk of peritonitis remains to be addressed.

**Methods.** We retrospectively analysed our CAPD patients who had complicating peritonitis in a 2-year period. The influence of hypokalaemia on the clinical features of peritonitis was assessed. From September 2003 to August 2005, 140 unselected patients undergoing CAPD treatment and followed up in our hospital were recruited for the study. Hypokalaemia was defined as a serum potassium level <3.5 mmol/l. The impact of hypokalaemia on several clinical parameters, including the nutrition status, dialysis adequacy, occurrence of peritonitis and the etiologic pathogens, was analysed.

**Results.** During the study period, 462 determinations (23.6%) were below quantity <mmol/l. The overall peritonitis rate was 30.6 patient-month per episode (total 64 episodes). The prevalence of peritonitis was significantly higher in patients with hypokalaemia (6.9%) compared to those without hypokalaemia (2.1%, \( P < 0.001 \)). Hypokalaemia was also associated with lower serum albumin (\( P < 0.001 \)), serum phosphate (\( P < 0.001 \)), total serum cholesterol (\( P = 0.049 \)) and normalized protein nitrogen appearance (\( P < 0.001 \)). There was no correlation between serum potassium level and daily PD exchange volume, total Kt/V, urine volume or daily ultrafiltration volume. The peritoneal equilibration test was not significantly different between patients with and without hypokalaemia. When the aetiologic organisms of peritonitis were grouped according to their usual site of colonization, *Enterobacteriaceae* appeared to be much more prevalent than epidermal microorganisms (53.1% versus 18.8%, \( P = 0.004 \)) in the hypokalaemia group. However, this was not the case in patients with normal serum potassium.

**Conclusion.** CAPD patients with hypokalaemia are associated with a higher prevalence of peritonitis and poor nutritional status. *Enterobacteriaceae* were the predominant organisms causing peritonitis in the group with hypokalaemia. This unique and novel finding implies the translocation of these organisms from intestinal mucosa into the peritoneal cavity. A pathogenic mechanism linking malnutrition and hypokalaemia is also proposed.

**Keywords:** CAPD; enteric peritonitis; *Enterobacteriaceae*; hypokalaemia; malnutrition

Introduction

Hypokalaemia is a relatively common feature in end-stage renal disease (ESRD) patients undergoing peritoneal dialysis (PD). The prevalence of hypokalaemia is \(~10–36\%\) in PD patients [1–3]. The consequences of hypokalaemia have as yet not been well defined. In a recent study [4], Szeto et al. found that hypokalaemia was associated with poor nutritional status, severe comorbidity and a decreased patient survival. In another study [5], hypokalaemia was a poor prognostic sign in peritonitis of PD patients. It is frequently associated with malnutrition and may in turn...
compromise the defence mechanism against bacterial infection of the peritoneum in PD patients. Furthermore, hypokalaemia may affect gastrointestinal motility, resulting in bacterial overgrowth and causing peritonitis through transmural migration of enteric organisms. In cirrhotic patients, spontaneous bacterial peritonitis (SBP) is common and the most likely aetiologic organism is gram-negative bacteria. Intestinal bacterial overgrowth and impaired gastrointestinal motility have been documented in such patients [6, 7]. To the best of our knowledge, the association of hypokalaemia with the incidence of peritonitis in PD patients as well as the bacterial species has not been reported before. The aim of this study was to determine the relationship between hypokalaemia and peritonitis in PD patients.

Subjects and methods

Patients

This was a retrospective study that included 140 unselected patients undergoing continuous ambulatory peritoneal dialysis (CAPD) in our centre from September 2003 to August 2005. The exchange volume, dextrose concentration and calcium concentration were determined and adjusted according to clinical situations. Baseline data, including age, gender, underlying renal disease, duration of dialysis, daily exchange volume and urine amount, were recorded. Comorbidities, including coronary heart disease, congestive heart failure, diabetes mellitus, hypertension, cirrhosis, malignancy, systemic lupus erythaematosus and cerebral vascular disease, were also recorded. The peritoneal equilibration test (PET) was usually performed a month after the initiation of PD therapy and then every 6 months thereafter. If peritonitis occurred, PET was delayed till 1 month after complete treatment of peritonitis. Patients were followed up monthly at the CAPD clinic. The following parameters were checked monthly: albumin, creatinine, potassium, phosphate, sugar and total protein. Fasting cholesterol and triglyceride were checked every 3 months, while daily PD exchange volume, total Kt/V, urine volume, daily ultrafiltration volume and PET were checked every 6 months. If peritonitis occurred, we would choose the data before the episode of peritonitis for analysis. All patients were followed up until August 2005.

Detection of hypokalaemia and peritonitis

The serum potassium level was measured monthly by means of a conventional method. Hypokalaemia is defined as a serum potassium level < 3.5 mmol/l. The diagnosis of peritonitis was based on at least two of the following criteria: abdominal pain or cloudy PD effluent (PDE), leukocytosis in PDE (white cell count at least 100/mm3), or positive gram stain or culture of effluent. Peritonitis was treated according to the proposed guidelines [8]. Relapsing peritonitis was excluded. The impact of hypokalaemia on several clinical parameters, including the nutrition status, dialysis adequacy, occurrence of peritonitis and the aetiologic pathogens, was analysed. The levels of these parameters, which were collected days before the occurrence of peritonitis, were taken as the level at the moment peritonitis occurred.

Statistical analysis

The clinical outcome was assessed by technical survival and the calculation of actuarial patient survival. Technique failure was defined as removal of catheter, death or transfer to long-term haemodialysis. Analyses were censored at death, switch to long-term haemodialysis therapy, kidney transplantation, loss to follow-up and transfer to other dialysis centres. Statistical analysis was performed by using SPSS for Windows software version 10.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.1. All data were expressed as mean ± SD, unless otherwise specified. Data were compared by the chi-square test, Wilcoxon rank-sum test, Yate’s correction of contingency, logistic regression analysis or generalized estimating equations (GEE) with a backward step as appropriate. A P-value of < 0.05 was considered significant. All probabilities were two tailed. Actuarial survival curves were determined according to the Kaplan–Meier life table method and compared with a log rank test.

Results

A total of 140 PD patients were enrolled in the study. Clinical characteristics of study patients are shown in Table 1. Fifty-five patients were male, and the mean age was 47.8 ± 16.0 years (range: 8–82 years). The ratio of male to female was 55/85. The most common underlying renal disease was chronic glomerulonephritis (43.6%) followed by diabetic nephropathy (19.3%). The average duration of dialysis was 37.8 ± 30.9 months. The total duration of the study was 1961 patient-months.

Table 1. Patients’ demographics and baseline clinical data

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>55:85</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.8 ± 16.0</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>37.8 ± 30.9</td>
</tr>
<tr>
<td>BMI (m2/kg)</td>
<td>23.0 ± 3.9</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>61 (43.6)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>27 (19.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Polycystic kidney</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Others/unknown</td>
<td>40 (28.6)</td>
</tr>
<tr>
<td>Major comorbidity</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>12 (6.9)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32 (18.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>108 (62.1)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Systemic lupus erythaematosus</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>Daily exchange volume (l/day)</td>
<td>9.0 ± 2.4</td>
</tr>
<tr>
<td>Urine amount (l/day)</td>
<td>0.63 ± 0.54</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or number of patients (percent).
Hypokalaemia and other parameters

Of the 140 patients, 82 patients (58.6%) had at least one episode of hypokalaemia, while the others (41.4%) had normokalaemia throughout the whole study period. Table 2 depicts the comparison of clinical parameters stratified according to the concentrations status of hypo- or normokalaemia. Hypokalaemia was associated with lower serum albumin (3.69 ± 0.48 versus 3.84 ± 0.39 g/dl; P < 0.001), elevated serum phosphate levels (1.43 ± 0.37 versus 1.68 ± 0.39 mmol/l; P < 0.01), total serum fasting cholesterol levels (5.19 ± 1.24 versus 5.32 ± 1.06 mmol/l; P = 0.049) and serum creatinine (965 ± 283 versus 1018 ± 292 µmol/l, P < 0.001). The PET was not significantly different between the normokalaemia and hypokalaemia groups. Linear regression analysis revealed that the serum potassium level was correlated with the serum total protein level (r = 0.12, P < 0.001), nPNA (r = 0.32, P < 0.01) and serum creatinine level (r = 0.35, P < 0.01). Conversely, the serum potassium level did not correlate with the fastiging serum triglyceride level. There was no correlation between the serum potassium level and daily PD exchange volume, total Kt/V, urine volume or daily ultrafiltration volume.

Spectrum of organisms and hypokalaemia

The overall peritonitis rate was 30.6 patient-month per episode. The organisms identified during peritonitis are shown in Table 3. There were five patients with repeat peritonitis. However, there was no patient with multibacterial peritonitis. Twenty-three episodes were caused by gram-positive organisms (35.9%), while 26 episodes (40.6%) were caused by gram-negative organisms. Fungus was identified in one patient (1.6%), while the others showed no growth (14 episodes, 21.9%). When the aetiological organisms were grouped according to their usual site of colonization, Enterobacteriaceae accounted for 22 episodes (34.4%) and epidermal flora accounted for 20 episodes (31.3%) of all peritonitis. The prevalence of peritonitis was significantly higher in patients with hypokalaemia (6.9%) compared to those without hypokalaemia (2.1%, P < 0.001, Figure 1). There was no correlation between peritonitis and age, BMI, gender, with or without DM as well as comorbidity. More specifically, when considering isolated bacte-
Hypokalaemia is a relatively common complication among patients undergoing CAPD. In our study, the prevalence of hypokalaemia was 23.6% in 1961 determinations of the serum potassium level among 140 patients during approximately a 2-year follow-up period. Hypokalaemia appears to be associated with poor nutrition and coexisting comorbid conditions. It was found to be an independent risk factor for patient mortality in a recent study on Chinese patients [4]. The aetiology of hypokalaemia is multifactorial and may include an intracellular shift, loss via dialysate, poor nutrition and other factors. A previous study suggested that hypokalaemia is a surrogate marker of malnutrition or severe comorbid illness, both related to the poor dietary intake [4]. In our study, hypokalaemia was related to lower level of serum albumin, phosphate, creatinine, cholesterol and nPNA (Table 2), all of which imply a poor nutritional status. This finding was very similar to that reported by Szeto et al. [4]. Previous studies also showed that malnutrition was a strong predictor of peritonitis and patient survival [9–12]. There were no obvious differences in lipid control between the two groups in our study. It may be due to the patients with dyslipidaemia being treated with statin or fibrate. The mechanisms underlying this association are multiple. Poor nutritional status can provoke both humoral and cellular immunological alterations, such as the decrease in serum complement levels, total IgG level as well as β2 integrin expression in circulating polymorphonuclear neutrophils (PMNs) and inhibition of PMN exudation into inflamed sites, which determine a higher susceptibility to infections [13–15]. Hypoalbuminaemia has been reported to be related to decreased serum complement levels [15], which may result in a higher susceptibility to infection.

Whether hypokalaemia is an independent risk factor for peritonitis has not been reported yet. In Szeto's study [4], CAPD patients with hypokalaemia had more than double the peritonitis rate of patients without hypokalaemia (14.8 versus 6.1%), although the rate did not reach a statistically significant difference [4]. One study indicated that the potassium level reflects lean body mass, and changes in total body potassium per month correlated negatively with episodes of peritonitis per month [12]. In the present study, we found that CAPD patients with hypokalaemia were associated with a higher incidence of peritonitis (Figure 1). In GEE analysis, both hypokalaemia and hypoalbuminaemia were independent risk factors for the development of peritonitis (Table 4). To the best of our knowledge, this is the first report that addresses the association of hypokalaemia and the occurrence of peritonitis. We speculate that previous studies emphasized the importance of serum albumin and other surrogate markers of nutrition, but neglected the importance of hypokalaemia in the pathogenesis of peritonitis in PD patients. Although hypokalaemia and malnutrition are closely linked, an independent effect of both parameters on actuarial survival has been reported before [4].

In general, the peritonitis rate in CAPD patients has been decreasing [16]. However, the decrease is due to a marked decline in gram-positive peritonitis as a result of more advanced devices used for PD, while the rate of gram-negative peritonitis has showed a little change [16]. Gram-negative organisms now account for 20–53% of all PD-related
peritonitis [17–19] and have become a focus of concern because of their association with a significantly worse prognosis, including more patient mortality, requirement of hospitalization and catheter removal [14]. Among all gram-negative organisms, those from the family Enterobacteriaceae are the most common [17–19]. The prevalence of Enterobacteriaceae peritonitis in CAPD patients was reported to be 12.0% in a previous study [17] compared to 34.4% in the present series. Enterobacteriaceae peritonitis has been associated with recent antibiotic therapy, constipation, colitis or transmural migration, but the aetiology is often unclear [17,18,20]. Although diabetes mellitus has been related to the occurrence of gram-negative peritonitis in CAPD patients [10,14,17], we did not find the same result in our study. In our study, patients with hypokalaemia were more prone to have acquired gram-negative bacteria, especially those of the Enterobacteriaceae family (Figure 2). The exact mechanism(s) underlying this novel and unique finding is not clear. Peritonitis caused by Enterobacteriaceae is usually not associated with catheter exit-site or tunnel infections [4]. Because these bacteria most often colonize in the intestines, it is reasonable to postulate that translocation of the bacteria into the peritoneal cavity may occur, resulting in peritonitis. In a previous study [17], nearly half of CAPD patients who had acquired Enterobacteriaceae peritonitis presented with diarrhoea, nausea or vomiting, implying a possibility of bacterial translocation resulting in peritonitis. On the other hand, constipation was a risk factor for the development of endogenous peritonitis [21]. The possible mechanisms promoting bacterial translocation are disruption of the ecologic equilibrium to allow intestinal bacterial overgrowth, deficiencies in host immune defences and increased permeability of the intestinal mucosal barrier [22]. Studies of SBP have revealed that bacterial overgrowth within the intestinal lumen is a major factor in bacterial translocation [6,13]. Disturbed intestinal motility, which commonly presents in cirrhotic patients, may lead to intestinal bacterial overgrowth [6,7,13]. Low serum albumin may cause swelling of intestinal mucosa, which in turn facilitates bacterial translocation. Hypoalbuminaemia and malnutrition both increase intestinal permeability as a consequence of the altered barrier of intestinal mucosa [13,22–24]. Besides, it is known that malnutrition aids the spread of translocated bacteria and diminishes translocated bacteria clearance [13]. Hypokalaemia has been associated with disturbed motility of the small intestine. PD patients who are hypokalaemic may also have the same dysmotility, thus being susceptible to bacterial translocation. Besides, hypokalaemia-related ileus, both obstructive or adynamic, may cause intestinal wall ischaemia and lead to an increase in intra-abdominal pressure [25]. The final result is enhanced bacterial translocation and the development of peritonitis. Increased intestinal permeability occurs in association with colonic-type bacteria, in particular the Enterobacteriaceae [23]. In summary, hypokalaemia is a cause of reduced intestinal mobility and as a sign of malnutrition that is responsible for altered immunologic defences and altered mucosa and media of the bowel loops. Therefore,
hypokalaemia may contribute to *Enterobacteriaceae* peritonitis in CAPD patients. We propose the possible mechanisms underlying the association of hypokalaemia, malnutrition and enteric bacterial peritonitis, as shown in Figure 3. We have designed a further study to confirm our theory. More intensive detection of bowel dysmotility for CAPD patients with hypokalaemia may decrease the prevalence of peritonitis. The scintigraphic measurement of colon transit time, a sensitive marker for detection of constipation, can be suggested for patients with hypokalaemia to prevent bowel dysmotility-related peritonitis [26].

In conclusion, CAPD patients with hypokalaemia may have a higher incidence of malnutrition and peritonitis, especially those derived from *Enterobacteriaceae*. *Enterobacteriaceae* peritonitis is associated with significant relapse, recurrence and mortality as well as remarkable treatment failure unless two antibiotics are used [17]. CAPD patients with hypokalaemia should undergo a thorough check of nutritional status. Intensive treatment, including supplemental diet or intraperitoneal potassium chloride [2], dietary advice to increase fresh fruit and vegetable intake, probiotics and multivitamin oral support [27], may be started as soon as possible in order to minimize the risk of peritonitis complications in CAPD patients.

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**Conflict of interest statement.** None declared.

**References**