Implications of refeeding syndrome in postoperative total parenteral nutrition

Angelos Assiotisa and Haussam Eleninb

*aKing George Hospital, Ilford, Essex, UK; bGeneral Surgery, Sheffield Teaching Hospitals, Northern General Teaching Hospital, Sheffield, UK

Corresponding address: Angelos Assiotisa, General Surgery, BHR Hospitals NHS Trust, Ilford, Essex, IG3 8YB, UK.
Email: aassiotis9@hotmail.com

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Abstract

Refeeding syndrome is a serious complication of enteral or parenteral feeding of malnourished patients. The learning point from this case report is to raise awareness that total parenteral nutrition is not a simple undertaking. Diagnosing refeeding syndrome requires a high index of suspicion and close collaboration with hospital pharmacists and nutritionists.

Keyword

Refeeding syndrome; hypophosphataemia; total parenteral nutrition.

Clinical case history

An 88-year-old female patient was admitted via Accident and Emergency with the presenting complaints of dysphagia and anorexia for 2 weeks, weakness and loss of 12 kg of body weight within the past 2 months. On admission, her weight was 66 kg and her height was 1.65 m. Her body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) was 24.2 kg/m². Clinical examination revealed general malnourishment and she was weak, with obvious ascites. There were no other clinical findings of relevant significance.

On admission her electrolytes and full blood count were normal but her albumin level was 27 g/l. Specific investigations included an oesophagogastroscopy, the results of which were unremarkable, a flexible sigmoidoscopy demonstrating an area of external compression of the sigmoid colon and a computed tomography (CT) scan demonstrating ascites, liver metastases and an extraluminal mass compressing the sigmoid colon. A magnetic resonance imaging (MRI) scan of her pelvis demonstrated a mass originating or infiltrating the uterus and both ovaries, enlarged lymph nodes, an incomplete external obstruction of the sigmoid colon and peritoneal deposits.

Subsequently, she developed nausea and vomiting. Her abdomen became generally tender and was distended and tympanic with no passage of flatus or stools. Consequently, a decision was made to proceed to urgent laparotomy with a view to fashioning a defunctioning loop ileostomy. Peripheral total parenteral nutrition (TPN) was introduced as she was not able to tolerate food in the first 2 days postoperatively. TPN was started on a Friday and an entry making the surgical team aware of the potential for refeeding syndrome was written in the patient’s notes. Her estimated energy demands were 1450 kcal/day and she was given a feed at a rate that...
administered 15.5 kcal/kg per day and 60 mmol/l sodium, 64 mmol/l potassium, 4.8 mmol/l magnesium, 4.8 mmol/l calcium and 14.4 mmol/l phosphate per day. As the patient already had ascites, the initial rate of infusion for the TPN was 40 ml/h, administering a total of 960 ml of fluid per day. The rest of the patient’s fluid requirements (calculated to be 1800 ml per day) would be carefully replaced through a peripheral line. Further to the TPN, a water-soluble preparation of vitamins B and C was prescribed intravenously.

Bloods at the initiation of the feed demonstrated sodium of 139 mmol/l, potassium of 3.6 mmol/l, phosphate of 1.26 mmol/l and magnesium of 0.80 mmol/l. Repeat blood tests on day 1 demonstrated a significant hyponatraemia of 129 mmol/l. The rest of her electrolytes were normal. On day 2 after the onset of TPN, she rapidly developed oedema associated with significant weakness in her limbs and constant nausea. On day 3, a quite substantial and remarkable dip in the concentration of phosphate and magnesium was noted, with the concentrations dropping to 0.43 mmol/l and 0.40 mmol/l respectively, whereas sodium increased to 132 mmol/l and potassium remained within the normal range. The patient became very confused and an electrocardiogram demonstrated new ventricular ectopics on a background of sinus rhythm.

The diagnosis of refeeding syndrome was made, with immediate sequential and appropriate actions to stop the feed and start careful intravenous replacement of magnesium at a rate of 80 mmol over 8h and phosphate at 25 mmol over 10h, through a central venous line and under constant cardiac monitoring. Blood tests on day 4 demonstrated an improvement in the value of phosphate and normalization of the value of magnesium, the concentrations increasing to 0.78 mmol/l and 1.00 mmol/l, respectively. Sodium increased to 135 mmol/l, although potassium had fallen to 3.1 mmol/l, at which point 40 mmol of potassium were given over 8h. On day 5, her clinical and biochemical parameters improved dramatically. It was therefore decided to restart TPN at a slower rate, which delivered 5 kcal/kg, and to repeat blood tests daily in order to guide further treatment and nutrition (Table 1).

**Clinical evidence**

Today, most TPN solutions are prescribed as a total nutrition admixture (TNA or 3-in-1 solution) with lipid emulsion incorporated into the final solution. TPN is made up on an individual requirement basis in the pharmacy from concentrated stock solutions, which in turn can limit the range of individual solute concentrations achievable and can lead to requirements of greater volumes of solutions to be delivered than might seem apparent initially. Furthermore, there is a risk that calcium and phosphate will form an insoluble precipitate. This risk can be reduced by keeping the calcium and phosphate solubility product less than 150 and by avoiding the addition of calcium and phosphate in close sequence during preparation of the mixture.

Commonly recognized complications of TPN include liver disease and metabolic derangement. Refeeding syndrome was first recognized during the World War II, when returning prisoners of the Japanese who had been starved rapidly developed neurological and cardiovascular abnormalities after the institution of a normal diet\[1\]. Due to the lack of a universally agreed definition of refeeding syndrome, its exact epidemiology is not known.

### Table 1. Electrolytic values during admission, at initiation of TPN and up to day 4 of TPN

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>On admission</th>
<th>Day 0 (first day of TPN)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4 (after magnesium and phosphate infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>138</td>
<td>139</td>
<td>129</td>
<td>130</td>
<td>130</td>
<td>134</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.4</td>
<td>3.6</td>
<td>3.2</td>
<td>3.2</td>
<td>3.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Urea</td>
<td>6.4</td>
<td>7.3</td>
<td>7.8</td>
<td>6.5</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>69</td>
<td>67</td>
<td>71</td>
<td>56</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Adjusted Ca</td>
<td>2.42</td>
<td>2.47</td>
<td>2.27</td>
<td>2.20</td>
<td>2.16</td>
<td>2.29</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.16</td>
<td>1.26</td>
<td>0.96</td>
<td>0.90</td>
<td>0.43</td>
<td>1.05</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.64</td>
<td>0.80</td>
<td>0.86</td>
<td>0.87</td>
<td>0.40</td>
<td>1.04</td>
</tr>
</tbody>
</table>
A definition of this syndrome, as suggested by Crook et al. in 2001\[2\], is the condition in which there are ‘severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding, whether orally, enterally, or parenterally’. It is thought that the syndrome is caused both by a rapid institution of feeding\[3\], resulting in rapid hormonal changes, and by a regime that is rich in carbohydrates and amino acids and which induces the rapid depletion of substrates that are used in glucose metabolism\[4\].

The identification of patients who are at high risk of developing this abnormality before initiating a refeeding regimen is equally, if not more, crucial than the management of the syndrome itself. Patients at particularly high risk of developing this serious and potentially life-threatening complication include patients with cancer, chronic alcoholism, postoperative patients who receive TPN, diabetics, patients who have been taking diuretics and antacids for a long time, elderly patients, and patients who have established chronic malnutrition. In the care of such patients, it is highly advisable to secure the early involvement of dieticians and to test the baseline levels of electrolytes and micronutrients. Although the previous trend was to withhold the introduction of diet until pre-existing electrolytic disorders were corrected, newer National Institute of Health and Clinical Excellence (NICE) guidelines advise that such an approach is unnecessary and that we should aim for the concurrent correction of abnormalities and the initiation of nutrition\[3\].

The syndrome’s cardinal features include the rapid development of hypophosphataemia, hypomagnesaemia, hypokalaemia, hyponatraemia, fluid shifts (especially water retention) and changes in glucose, fat and protein metabolism\[4\].

Starvation for more than a few days reduces the overall stores of phosphorus, magnesium and potassium and induces a reduction in the secretion of insulin. Energy is mainly produced through lipolysis rather than gluconeogenesis. The underlying cause for the manifestations of the syndrome is the rapid hormonal change that occurs after the re-institution of a diet, enteral or parenteral. The absorbed carbohydrate rapidly increases the levels of glucose, leading to increased insulin and decreased glucagon secretion and a net anabolic state. This state requires phosphate, magnesium, potassium and cofactors such as thiamine and induces the intracellular shift of these ions, thereby rapidly decreasing their serum concentrations\[4\]. Specifically, potassium and thiamine are necessary for the intramembranous transport of glucose molecules and phosphate and magnesium are essential in the formation of adenosine triphosphate\[4\]. Insulin also acts upon renal tubules causing an antinatriuretic effect and extracellular space expansion through water retention. Hypophosphataemia itself is a recognized cause of reduction in the excretion of water and sodium from the kidneys, which in turn causes congestive cardiac failure\[4\].

Symptoms secondary to the electrolytic disorders mentioned include ataxia, paralysis, coma, cardiac dysrhythmias\[5\], nausea, anaemia, respiratory and cardiac failure, acute tubular necrosis secondary to rhabdomyolysis, constipation, ileus and varying degrees of confusion leading even to delirium.

The treatment of a recognized case of refeeding syndrome should include vitamin replacement, including thiamine and other members of the vitamin B complex. If electrolytes are found to be low then they should be replaced and the rates that NICE suggest are 2–4 mmol/kg per day for potassium, 0.3–0.6 mmol/kg per day for phosphate and 0.2 mmol/kg per day for magnesium. According to the same guidelines, the rate of refeeding depends on the degree of malnutrition. Patients at moderate risk of developing this syndrome should not receive more than 50% of their energy requirements initially, and if no electrolytic disorders are detected, the rate of feeding can be increased. However, in the high-risk group of patients, the rate of feeding should initially be even lower (10 kcal/kg per day) and in the treatment of an established case of refeeding syndrome, the food intake can be stopped for 12–24 h and restarted at lower rates. Volume should also be replaced with great care to avoid overloading patients. Electrolyte levels should be checked daily for the first week and every 2–3 days in the second week.

**Teaching points**

- Initiating a feeding regimen in patients with a high risk of refeeding syndrome should never be done hastily and without careful planning and advice from a dietician.
Refeeding syndrome is not as rare as medical professionals tend to believe as many cases go unnoticed. A high index of suspicion will lead to the early recognition of this problem, which is of great significance in the success of its management. Current management dictates correcting the missing electrolytes by administering them enterally or parenterally. Careful monitoring of electrolytes on a daily basis is required.

References