Refeeding hypophosphataemia in a Malaysian intensive care unit: incidence, risk factors and outcomes

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ABSTRACT

Introduction: Refeeding syndrome is characterised by acute electrolyte derangement following the start of nutrition. Hypophosphataemia is the predominant feature of the electrolyte derangement, hence commonly used for its definition. We aim to assess the incidence of refeeding hypophosphataemia, and its associated risk factors, and outcome in our local ICU. **Materials and Methods:** This was a single centre, prospective observational study at the ICU of Hospital Tengku Ampuan Afzan Kuantan, involving adult admission longer than 48 hours. Chronic renal failure patients and those receiving dialysis were excluded. Refeeding hypophosphataemia (RH) was considered if plasma phosphate was less than 0.65 mmol/l. **Results:** Fifty-four patients were screened. After exclusion, 29 were recruited, of which, 13 (44.8%) patients had RH. Of this, 66% occurred with duration of fasting of less than two days. These patients had higher NUTRIC score (3.9 ± 2.1 versus 2.4 ± 1.9, p=0.05). There was a trend of lower albumin, magnesium, calcium and potassium concentration, however these were not statistically significant. All patients with hypomagnesaemia (less than 0.5 mmol/l) had RH (p=0.01). There were no differences in mortality, length of hospital or ICU stay and duration of mechanical ventilation. **Conclusion:** Refeeding hypophosphataemia is common, occurring in 45% of ICU admission regardless of their fasting status. Higher NUTRIC score and hypomagnesaemia were the risk factors, however we showed no differences in outcome. Future larger studies could evaluate the association between its risk factors and outcome in our local population.

Keywords: Refeeding syndrome, refeeding hypophosphataemia, nutritional status, electrolytes, incidence, risk factors

INTRODUCTION

Refeeding syndrome is characterised by acute electrolyte derangement including hypophosphataemia, hypomagnesaemia, hypokalaemia or hypocalcaemia, following the start of nutrition. [1, 2] Institution of carbohydrate or glucose after period of starvation stimulates insulin release and cellular anabolism, which en-

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hance intracellular ion transport. [3] Redistribution of phosphates, magnesium, potassium and calcium into cells, and depletion of ATP occurs during initiation of nutritional support via enteral or parenteral route. [2] Lack of ATP may result in hypoxia at the tissue level, which may result in cardiovascular and respiratory dysfunction. Increase insulin secretion may also increase renal sodium reabsorption and water retention. Complications associated with this syndrome include heart failure, respiratory failure, paraesthesia, seizure and death.

There is no standardised definition; most studies defined it based on serum phosphate level since it is the predominant features of electrolyte derangement. [2, 4] Marik *et al.* defined it based on a drop in serum phosphate of more than 0.16 mmol/l to 0.65 mmol/l, and has termed is as refeeding hypophosphataemia (RH) [4] However since the pathophysiology of this syndrome involves other electrolytes, other studies defined it based on the presence of other electrolyte abnormalities including potassium, and magnesium. [5] In addition to the electrolyte abnormalities, it was also being defined based on the presence of organ dysfunction. [6] Its incidence varies according to definition used, and on population studied. [4, 5, 7, 8]

Several risk factors related to physiology of starvation had been associated with the development of this syndrome, [9, 10] which includes chronic malnutrition, [7, 11] chronic alcoholism, [12] prolonged fasting, anorexia nervosa, [12] serum prealbumin level, [4] low baseline serum magnesium, [6] oncology and postoperative patients. [13] Heyland *et al.* [14] described the NUTrition in critically ill patients (NUTRIC) score from 597 ICU patients for risk stratification of patients at risk of malnourishment. Identification of patients at risk may assist in prevention measures by instituting hypocaloric nutritional treatment. However, not all patients at risk had RH, and hypocaloric nutrition could lead to undernutrition and impaired healing. [10]

We aim to assess the incidence and outcome of RH in a prospective observational study of ICU patients in Hospital Tengku Ampuan Afzan, Kuantan. We also aim to evaluate the association between its development and the associated risk factors.

MATERIALS AND METHODS

This prospective observational study was conducted in a single centre of the Intensive Care Unit (ICU) of Hospital Tengku Ampuan Afzan, Kuantan, Malaysia in 3-week period. The study was registered under the Malaysian National Medical Research Register (NMRR-14 - 803-19813,https://www.nmrr.gov.my). Ethical approval was obtained from the Medical Ethics and Research Committee (MREC Number P14-909) and the International Islamic University Ethics Committee (IREC Number 277). As only routinely available clinical information was collected, the need for informed consent was waived. The inclusion criteria for this study were patients older than 18 years old and duration of ICU stay of at least 48 hours. All patients admitted to the ICU within the study period were considered for inclusion screening. Patients with diabetic ketoacidosis, and end stage renal failure on dialysis were excluded from the study. In this study, RH was considered in patients with drop of serum phosphate less than 0.65 mmol/l within 7 days of ICU admission. [4]

The number of fasting days was recorded for each patient. Patient's clinical records and ICU charts were reviewed for baseline and daily serum albumin, phosphate, magnesium, potassium and calcium levels. Demographic profiles, including age, gender, race, height, weight, admission diagnosis, past medical history, length of ICU and hospital stay, duration of mechanical ventilation, concurrent medications, electrolyte supplementations and death status were extracted from the ICU charts and clinical records. Baseline serum albumin, and total lymphocyte count were recorded. The baseline Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) were used to assess severity of illness in each patients.

Risk factors were defined for each patient based on the NUTRIC score [14] that includes; age, APACHE II, SOFA, comorbidities, and days from hospital to ICU admission. Other risk factors that were considered in this study such as body mass index (BMI), duration of fasting, low baseline levels of albumin, phosphate, magnesium, or potassium prior to recruitment.

Measurements: Plasma phosphate, magnesium, calcium, potassium and albumin analysed using the Olympus AU2700™ chemistry-immunoanalyser *(Olympus, Philadelphia, USA).* Weight was calculated from the formula utilising the knee height × mid-arm circumference (MAC), as follow: 1.01 + MAC (cm) × 2.81 – 66.04 in female, and knee height × 1.10 + MAC (cm) × 3.07 – 75.81 in male. [15] Knee height was measured while patient lying supine, both the knee and ankle are held at a 90-degree angle. MAC was measured by taking the circumference of the arm between tip of shoulder and tip of bent elbow.

Statistical Analysis: Statistical analyses were performed using PASW® version 18.0 (IBM, Somers, New York, USA). Results were presented as mean ± standard deviation (SD) for normally distributed variables (parametric) or median (inter-quartile range or IQR) for non-normally distributed variables (non-parametric). For continuous variables, differences in two variables were analysed using independent-t test for parametric data, or Mann-Whitney U test for non-parametric data. For categorical variables, differences in proportions were analysed using Chi-Square test.

RESULTS

Fifty-four consecutive patients were screened between the 3rd to 29th of July 2014. Twenty-five patients were excluded; six with renal failure, eighteen with ICU stay of less than 48 hours and one with age less than 18 years old. Of the 29 patients analysed, 13 (44.8%) patients had RH, defined as fall in plasma phosphate less than 0.65 mmol/l. Of these, two had severe hypophosphataemia (≤0.32 umol/l), and 11 with moderate hypophosphatemia (>0.32 and ≤0.65mmol/l). The flow of the study inclusion is depicted in Figure 1.

Utilising a definition of refeeding syndrome by O'Connor *et al*., [5] 21 (72%) had either: serum phosphate of <0.7 mmol/l, potassium of <3.5 mmol/l, or magnesium of <0.5 mmol/l. Whereas, only 1 patients (3.4%) had severely deranged electrolytes (potassium <2.5 mmol/l, phosphate < 0.32 mmol/l, or magnesium < 0.5 mmol/l), and 16 patients (55%) had cardiovascular and respiratory organ failure on ICU admission. [6]

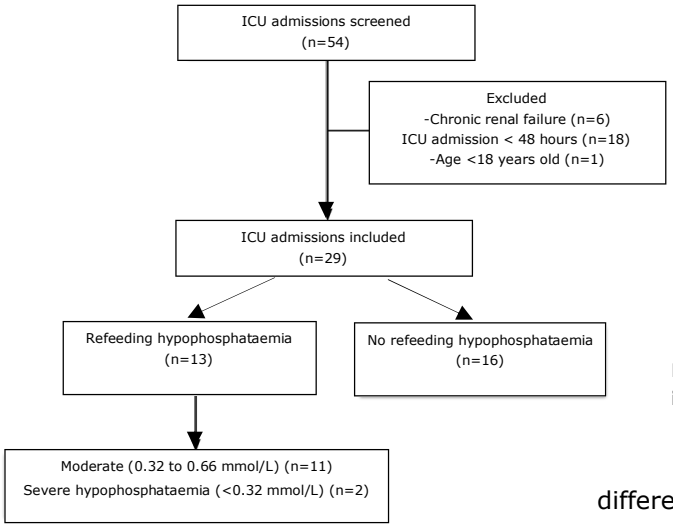


Fig. 1: Flow chart of inclusion of patients into the study.

Table 1 compares the demographic, clinical characteristics and outcome between patients with and without RH. There were no differences in the demographic data or clinical characteristics. Two patients died, with no differences in mortality. There were also no differences in length of ICU or hospital stay, or duration of mechanical ventilation.

The risk factors for RH are shown in Table 2. Patients with RH had higher NUTRIC score compared to those without (3.7 ± 2.1 versus 2.2 ± 1.9, p=0.05, Figure 2). Eight

Table 1: Demographic, Clinical Profiles and Outcomes of patients.

Variables	All patients (n=29)	RH (n=13)	No RH (n=16)	p-value
Age (SD) years	46 ± 17	48 ± 17	45 ± 17	0.56
Ethnicity				
Malay	20 (69.0)	7 (53.8)	13 (81.2)	
Chinese	2 (6.9)	2 (15.4)	0 (0)	0.06
Indian	1 (3.4)	1 (7.7)	0 (0)	
Orang Asli	3 (10.3)	3 (23.1)	0 (0)	
Foreigner	2 (6.9)	0 (0)	2 (12.5)	
Sex (Male)	16 (55.2)	5 (38.5)	11 (68.8)	0.10
Weight (kg)	72 ± 22	65 ± 14	78 ± 26	0.15
Height (cm)	159 ± 11	157 ± 10	162 ± 11	0.21
Body Mass Index (BMI) kg/m^2	28.4 ± 9.0	26.2 ± 4.7	29.6 ± 10.6	0.35
Diagnostic class				0.60
Surgical	17 (58.6)	8 (61.5)	9 (56.2)	
Medical	12 (41.4)	5 (38.5)	7 (43.8)	
APACHE II Score	18.1 ± 6.9	20.5 ± 6.9	16.1 ± 6.4	0.09
SOFA Score	5.3 ± 3.8	6.7 ± 4.3	4.2 ± 2.9	0.08
Mortality	2 (6.9)	1 (7.7)	1 (6.2)	0.88
Length of ICU stay (days)	4.6 (1.9 - 8.0)	3.7 (1.9 – 5.9)	5.7 (2.2 – 18.7)	0.15
Length of hospital stay (days)	17.9 ± 10.7	13.4 (6.4 – 26.0)	18.9 (9.5 – 26.2)	0.50
Mechanical ventilation	25 (86.2)	11 (84.6)	14 (87.5)	0.82
Duration of Mechanical Ventilation (days)	4.1 (1.8-8.3)	4.0 (1.0 – 4.3)	3.6 (1.5 - 14.4)	0.74

Data expressed as mean ± SD, n (%), or median (lower quartile – upper quartile). APACHE II Score: Acute Physiological and Chronic Health Evaluation II Score. SOFA Score: Sequential Organ Failure Score. Comparison of variables between the two groups was analysed using the independent t test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. Categorical variables were compared with Chi-Square test. RH: Refeeding Hypophosphataemia

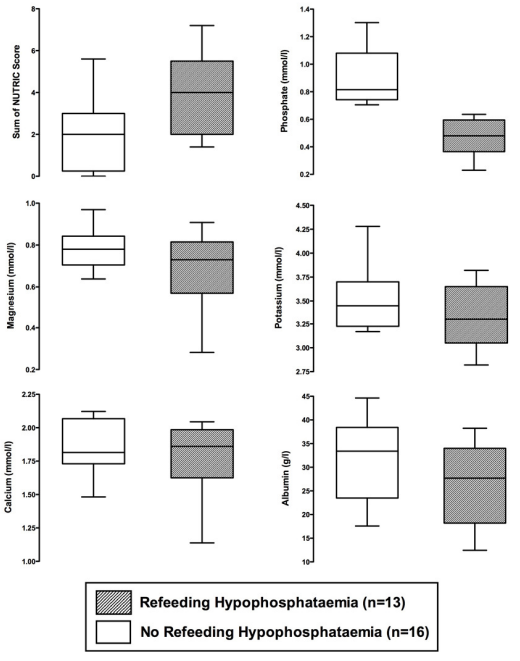
Table 2: Risk factors for refeeding hypophosphataemia.

Variables	All patients (n=29)	RH (n=13)	No RH (n=16)	p-value
NUTRIC SCORE	2.9 ± 2.1	3.9 ± 2.1	2.4 ± 1.9	0.05
High NUTRIC score (5-9)	8 (27.6)	5 (38.5)	3 (18.8)	0.24
Duration of fasting				
<2 days	19 (65.5)	9 (69.2)	10 (62.5)	0.56
2-5 days	7 (24.1)	2 (15.4)	5 (31.2)	
5-10 days	1 (3.4)	1 (7.7)	0 (0)	
≥ 10 days	2 (6.9)	1 (7.7)	1 (6.2)	
Phoshate (mmol/l)	0.71 ± 0.30	0.47 ± 0.14	0.91 ± 0.24	<0.0001
Magnesium (mmol/l)	0.74 ± 0.17	0.68 ± 0.21	0.79 ± 0.12	0.08
Hypomagnesemia (<0.5 mmol/l)	3 (10)	3 (23.1)	0 (0)	0.01
Potassium (mmol/l)	3.5 ± 0.40	3.3 ± 0.34	3.6 ± .42	0.11
Calcium (mmol/l)	1.81 ± 0.27	1.75 ± 0.31	1.86 ± 0.23	0.32
Albumin (g/l)	29.8 ± 9.2	26.9 ± 9.0	32.0 ± 9.0	0.14
Lymphocyte count	1.2 (0.7 - 2.5)	1.2 (0.6 - 2.9)	1.2 (0.7 – 2.3)	0.89
Inotropic/Vasoconstrictor	7 (24.0)	5 (38.5)	2 (12.5)	0.11

patients had high NUTRIC score of more than 5, of which five of them had RH (p=0.23). There was a trend of lower albumin, magnesium, calcium and potassium concentration, however these were not statistically significant (Table 2, and Figure 2). All patients with hypomagnesaemia (less than 0.5 mmol/l) had RH (p=0.01). More patients with RH needed vasopressor/inotropic support (38.5% versus 12.0%), however this was again not statistically significant. There were no differences in duration of fasting, or lymphocyte count.

Table 3 showed the association between phosphate supplementation and the occurrence of RH. Nineteen patients (65.5%) were given phosphate supplementation. There was no difference in proportion of patients who received phosphate supplementation (p= 0.71), however, those with RH received a higher amount of phosphate (40 ± 22 versus 23 ± 11, p=0.05).

Of the 29 recruited patients, 18 received enteral feeding (Table 4). Feeding was



Figs. 2: (A) Sum of NUTRIC Score, and minimum concentration of (B) Phosphate, (C) Magnesium, (D) Potassium, (E) Calcium, and (F) Albumin between patients with and without Refeeding Hypophosphataemia. Independent t test, p= (A) 0.05, (B) <0.0001, (C) 0.08, (D) 0.11, (E) 0.32, and (F) 0.14.

Table 3: Association between phosphate supplementation and refeeding hypophosphataemia.

	All Patients (n=29)	RH (n=13)	No RH (n=16)	p-value
Need of Phosphate Supplementation	19 (65.5)	9 (69.2)	10 (62.5)	0.71
	n=18	n=9	n=10	p-value
Total Phosphate Needed (mmol/l)	31 ± 19	40 ± 22	23 ± 11	0.05

started at a median time of 14 (9 – 23) hours after ICU admission. The time required to achieve full calories in these patients was 32.6 ± 8.6 hours. There were no differences in the time to start feeding, and the time required to achieve full calories between patients with and without RH. Repeated analysis on these 18 patients showed similar findings (data not shown).

DISCUSSION

In this prospective observational study, we showed that refeeding hypophosphataemia occurs in 45% of ICU admission during the study period regardless of their fasting status. Higher NUTRIC score and hypomagnesaemia were associated with this syndrome. However, there were no differences in mortality, duration of ICU or hospital stay.

To date, there is no standardised guideline in defining refeeding syndrome. Most studies defined it based on serum phosphate concentration since phosphate is the major intracellular anions. [2, 4] However, since the pathophysiology of this syndrome involve other electrolytes, other studies define it based on the presence of other electrolyte abnormalities. O'Connor *et al.* (2009) [5] defined it as "a collection of electrolyte disturbances, including one or more of the following: hypophosphataemia (<0.7 mmol/l), hypokalaemia (<3.5 mmol/l), hypomagnaesemia (<0.5 mmol/l) occurring 2–4 days post dietetic intervention i.e. oral nutrition support, enteral or parenteral nutrition". In addition to the biochemical abnormalities, it is also being defined based on the presence of organ dysfunction. Rio *et al*.[6] defined it using 3 facet diagnosis i.e (i) Severely low electrolyte concentrations (potassium <2.5 mmol/l, phosphate < 0.32 mmol/l, or magnesium < 0.5 mmol/l), (ii) Peripheral oedema or acute circulatory fluid overload, and (iii) Disturbance to organ function including respiratory failure, cardiac failure and pulmonary oedema.

Table 4: Enteral supplementation data and refeeding hypophosphataemia.

	All Patients (n=18)	RH (n=7)	No RH (n=11)	p-value
Nutrition started after ICU admission	11 (4 - 23.5)	14 (9 – 23)	8 (4 – 25)	0.50
Calories (25 Cal/kg/day)	1431 ± 294	1462 ± 304	1411 ± 301	0.73
Reach full calories after started feeding (hours)	32.6 ± 8.6	35.7 ± 9.4	30.4 ± 7.8	0.22

For this study we utilised the definition based on a study by Marik *et al.* [8] Interestingly, its incidence in our local population was almost similar. [8] In a previous study done in our ICU, 29% of 41 patients were reported to have hypophosphataemia of less than 0.8 mmol/l.[16] Hypophosphataemia is more common in the intensive care setting, occurring in about 45% of hospitalised patients. [17] In 208 surgical ICU patients, hypophosphataemia of less than 0.80 mmol/l was reported in 29% of their patients. [18] Utilising a more severe form of hypophosphataemia, 0.43% of more than 10 thousands hospitalised patients. [7] We reported two of our patients had severe hypophosphataemia of less than 0.32 mmol/l. Severe hypophosphataemia could be life threatening if not corrected. [8, 19] We showed that utilising different defintiions involving other electrolytes, yielded a higher incidence of 72%, whereas the incidence is much lower using a more rigid definition of severe electrolyte imbalance. Sixteen patients had cardiovascular or respiratory failure on ICU admission; hence assessment of these organ failures for refeeding syndrome were not accurate as they may be due to primary diseases rather than refeeding syndrome. [5, 6]

Prolonged fasting was associated with RH; it was initially reported in prolonged starvation in prisoners and victims of famine. [2] In critically ill patients, patients with negligible food intake for more than five days appeared more likely to have these problems. [20] However it was reported in those who starved to as short as 48 hours. [4] Of interest, we showed that RH occurs regardless of duration of fasting, even in patients who were fasted less than two days. This may reflect that most of our ICU admission were quite ill and were not taking adequate nutrition for duration of time prior to ICU admission.

Risk stratification could identify those at risk, and commencement of preventive measures. The NUTRIC score that consist of points from age, SOFA score, APACHE II Score, numbers of co-morbdities and days from hospital to ICU admission, were derived from data of 597 ICU patients. [14] The scoring algorithm may be used to risk stratify patients at risk of malnutrition. We showed that sum of NUTRIC score was higher in patients with RH. Low baseline serum magnesium was shown to be an independent predictor of this syndrome. [6] Here, we showed a trend of lower potassium, magnesium, calcium and albumin in patients; however these were not statistically significant, probably due to small sample size in our study.

We also analysed its association with outcome including mortality, length of hospital and ICU stay, and duration of mechanical ventilation. We found that none of them were associated with RH. Several studies showed the association of hypophosphataemia with mortality.[18,19] However, when adjusted for other risk factors, hypophosphataemia were not independently associated with ICU mortality or hospital mortality in 2,730 critically ill patients, [21] or in 321 acute kidney injury patients on dialysis. [22] Refeeding syndrome was associated with longer hospital stay, [4, 21, 23] and duration of mechanical ventilation. [4, 21] These differences were probably due differences in definition used and small sample size in our study.

Phosphate is essential for various

physiological function of the body. [24] Hypophosphataemia could results in an array of organ dysfunction including the cardiovascular, respiratory, or neurological. [2, 24] Hence, intravenous supplementation of phosphate is commonly instituted to prevent organ dysfunction. Sixty-six percent of patients received intravenous phosphate supplementation. There was no difference in the proportion of patients who received phosphate, however the total amount given was significantly higher in patients with refeeding syndrome. These patients received a mean of 40 ± 22 mmol/l of intravenous phosphate supplementation. Several studies had shown that intravenous phosphate is safe for doses up to 45 mmol/l with rate of 20 mmol per hour. [24]

The time to start enteral feeding from ICU admission and time to reach full nutritional status after feeding were calculated in a sub-cohort of 18 patients who received enteral feeding. RH also was not associated with the duration of starting nutrition after ICU admission, amount of calories needed, and time required to achieve full calories after started feeding. Progressive calories introduction until metabolic abnormalities were corrected is important in managing these patients. [2]

This study has several limitations. First, it was conducted in single centre. Second, it involved only a small sample size. This is limited due to short duration to conduct the study. Further larger studies could evaluate the association between risk factors and outcome. Third, the study includes patients who are on oral feeding as well as those who received enteral nutrition. Further study limiting patients who received enteral nutrition would better evaluate its association with nutrition risk. Finally, body weight was not measured, but estimated from the knee height and mid-arm circumference. [15] However, univariate analysis showed no differences in body weight.

In conclusion, Refeeding hypophosphataemia is common, occurring in 45% of ICU admission regardless of their fasting status. Higher NUTRIC score and hypomagnesaemia were the risk factors, however we showed no differences in outcome. Future larger studies could evaluate the association between its risk factors and outcome in our local population.

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