The Effect of Whey Protein Supplementation on Duration of Mechanical Ventilation: A Pilot Study

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Abstract

Introduction: It is important to wean mechanically-ventilated patients as early as possible to avoid complications such as ventilator-associated pneumonia. Supplementing the diet with additional protein may help to stimulate muscle protein synthesis which may enhance respiratory muscle function and ventilator drive. This study aims to determine the effect of whey protein supplementation on the duration of mechanical ventilation in intensive care unit patients of Ospital ng Makati.

Methods: We enrolled forty eligible patients in this open-label randomized controlled trial and were assigned into two groups: Group A (N=20): patients were given enteral feeding using commercial formula with added whey protein, given as one serving every eight hours (equivalent to 18 g of additional protein per day) and Group B (N=20): patients were given enteral feeding using commercial formula alone. Weaning was started as soon as the patient fulfilled the criteria of spontaneous breathing trial and was considered successful if the patient maintained these criteria for 48 hours after extubation.

Results: Our study's results showed that the mechanically intubated patients in Group A have lesser ventilator-dependent days with an average of 5.4 days as compared to those in Group B with an average of 7.45 days (p=0.00). Patients in Group A were also noted to have statistically significant higher increase in serum albumin, mid-arm circumference and triceps skin fold from baseline. Twenty-five percent of patients in Group B developed ventilator acquired pneumonia and none in Group A. No mortality was noted in both groups.

Conclusion: Whey protein supplementation in mechanically ventilated patients can be recommended to facilitate early weaning because of its effect on early muscle protein synthesis leading to improvement of lung function and ventilator drive. It can also help in preventing malnutrition and nosocomial infections during critical illness. With all these benefits of whey protein, its use can potentially lead to shorter duration of mechanical ventilation and hospital stay which can also mean less cost of care delivery.

Keywords: whey protein, weaning, mechanical ventilation, intensive care unit, randomized controlled trial

Introduction

The role of optimal nutritional support in improving the clinical outcomes of critically ill patients is of utmost importance. Malnutrition in this subset of patients is associated with impaired immune function and ventilator drive which lead to prolonged mechanical ventilator dependence. This in turn increases morbidity and mortality which is most commonly due to the development of ventilator acquired pneumonia (VAP).[1] In a study done by Carbon-Cuenca, it was noted that 87% of the patients admitted at the intensive care unit (ICU) of Ospital ng Makati from January 1, 2008 to December 31, 2010 were malnourished. This obtained value surpassed the prevalence of malnutrition identified in other countries.[2]

According to the European Society of Parenteral and Enteral Nutrition (ESPEN) guideline, intensive care unit (ICU) patients who present with evidences of malnutrition or those with a high risk of developing malnutrition during their hospital stay and are not expected to be on a full oral diet within three days should receive enteral and/or parenteral nutritional support.[3] Enteral nutrition is said to be an active therapy that attenuates the metabolic response of the patients to stress and favorably modulates the immune system. It is also less expensive than parenteral nutrition and is preferred in most cases because of less severe complications and better patient outcomes.[1] In case of enteral nutrition, feeding should be started early within the first 24 hours following admission, provided that the patient is hemodynamically stable and has a functioning gastrointestinal tract. This is

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to facilitate diet tolerance, reduce the risk of intestinal barrier dysfunction and infections, and reduce the length of mechanical ventilation and hospital stay.[3]

Mechanical ventilation is one of the most challenging aspects of ICU management. In a study by Ordanza, it was noted that out of 324 admissions at the ICU last January to April 2014, 172 or 53% of them were intubated upon admission.[4] Although mechanical ventilation is a life-saving intervention in patients with acute respiratory failure, critical care clinicians should aim to liberate patients from mechanical ventilation as early as possible to avoid the complications associated with prolonged unnecessary mechanical ventilation, including ventilator-induced lung injury and VAP that result to increased length of hospital stay and cost of care delivery.

The role of nutrition in weaning patients from mechanical ventilation is already receiving increased attention. In a study by Puthucheary et al., it was noted that in critical illness, loss of muscle mass results from an imbalance between muscle proteolysis and protein synthesis, with proteolysis overwhelming an inadequate synthetic response.[5] Likewise, immobilization which is encountered among patients on mechanical ventilatory support has been recognized to promote muscle wasting. It was then hypothesized that reducing muscle loss by providing enough protein will assist ventilatory function and hasten rehabilitation.[6] Furthermore, in the study by Chan et al., it was noted that hypoalbuminemia with a serum albumin level of <3mg/dl is associated with negative outcome of weaning from mechanical ventilation. The odds that a patient will have failure in weaning was six times more likely in subjects with serum albumin <3 mg/dl.[7] Lastly, in a study done by Novak et al., the extra glutamine present in whey protein as compared with other protein supplemental preparations can promote immune function, prevent gut mucosal atrophy, and reduce septic complications.[8]

In this study, 100% whey protein formula (Beneprotein) was used in addition to the usual commercial formula for enteral feeding. The usual commercial formula being used in our institution contains 19 g/serving. In addition, three servings of Beneprotein (6 g/serving) were given per patient per day. Whey protein is said to be a complete protein because it contains all of the essential amino acids with a high proportion of the branched-chain amino acid leucine—a key amino acid in the stimulation of muscle protein synthesis (MPS). MPS in turn enhances respiratory muscle function and ventilator drive which may lead to early and successful weaning from mechanical ventilation. [9,10]

There were already several studies that have shown that prolonged mechanical ventilation is associated with adverse clinical outcomes such as ventilator-associated pneumonia, ventilator-associated lung injury, respiratory muscle wasting, swallowing dysfunction, increased sedation requirements, sleep disturbance, and neuropsychiatric complications. Hence, strategies that can promote early weaning from mechanical ventilation, such as the intervention done in this study, should be investigated. This is to provide desirable effects to both patients and to all those involved in their medical care.

The primary objective is to determine the effect of whey protein supplementation in the duration of weaning of mechanically ventilated patients admitted at the ICU of Ospital ng Makati. More specifically: (1) to determine the effect of whey protein supplementation in the change in serum albumin, mid-arm circumference and triceps skin fold from baseline, (2) to determine the effect of whey protein supplementation in the development of ventilator-acquired pneumonia, (3) To determine the effect of whey protein supplementation in all-cause mortality, and (4) to determine any adverse effects of whey protein supplementation.

Methods

This open-label randomized controlled trial was a pilot study conducted at the ICU of Ospital ng Makati last October to November 2015 and August-September 2016. All patients who met the inclusion criteria and none of the exclusion criteria were included in this study.

The participants included are all patients admitted due to acute respiratory failure requiring mechanical ventilation admitted at the ICU of Ospital ng Makati from October-November 2015 and August-September 2016 who could be enterally fed were enrolled in this study. Patients were assessed using the Simplified Acute Physiology Score (SAPS II). This is a severity score and mortality estimation tool developed from a large sample of medical and surgical patients in North America and Europe which include the following parameters:

1. Age in years
2. Heart rate
3. Systolic blood pressure in mmHg
4. Arterial oxygen tension in mmHg/fraction of inspired oxygen
5. Urinary output
6. Body temperature in degree centigrade
7. Blood urea nitrogen in mg/dl
8. White blood cell count/mm3
9. Serum potassium in mmol/dl
10. Serum sodium in mmol/dl
11. Serum bicarbonate level in meq/l
12. Serum bilirubin in mg/dl
13. Glasgow coma scale
14. Chronic disease
15. Type of admission

The SAPS II score ranges from 0 to 163 points.[11] All patients included in the study have SAPS II score less than 39.5 as this is the cutoff point below which patients have the same severity of illness and become more likely to survive during the period of mechanical ventilation until weaning.

On the other hand, patients were excluded from the study if the reason for intubation is a neurologic cause (e.g cerebrovascular disease) or a neuromuscular cause (e.g. myasthenia gravis, Guillian Barre syndrome) because these are the patients who have respiratory depression secondary to a central cause which is difficult to treat. Patients who have glomerular filtration rate of 60 and below, uncontrolled diabetes mellitus, and hepatic failure are also excluded from the study because these are the conditions wherein a high protein diet is contraindicated.

The study was designed and conducted in accordance with the ethical principles laid down by the Declaration of Helsinki. The protocol was approved by the independent ethics committee of Ospital ng Makati. The primary investigator secured an informed consent from the patients and/or their relatives at the beginning of the study.

Eligible patients were enrolled and randomized using random number sequence contained in sealed opaque envelopes within the first 24 hours of ICU admission to receive either commercial formula with whey supplementation or commercial formula alone for enteral feeding.

The brand of commercial formula used was Peptamen, which has a protein source from enzymatically hydrolyzed whey protein. It's protein content is 16% of the total caloric distribution and it provides 10 grams of protein per serving. Moreover, the whey protein preparation used in this study was Beneprotein, a 100% whey protein supplement that contains six grams of protein per serving.The patients were randomly allocated into two groups as follows:

Group A: Patients given enteral feeding using commercial formula with added whey protein.
Group B: Patients given enteral feeding using commercial formula alone.

Patients' caloric requirements were computed using their ideal body weight computed based on height multiplied by their individual stress condition (using 25-30 kcal/kg) as advised by the American Society for Parenteral and Enteral Nutrition (ASPEN).[9] Calories were distributed as follows: carbohydrates: 50-60%, protein: 12-15% and fats: 25-35%. Patients on the intervention group were given additional three servings of whey protein every eight hours (six grams of protein per serving). Trained dieticians were the ones who prepare the formula using standard weight measures. The feeding regimen, given as intermittent bolus feeding by trained ICU nurses, was only started after a stable ventilatory state had been achieved at which patient is already hemodynamically stable.

On admission, the following laboratories were requested: complete blood count, serum albumin, bilirubin, blood urea nitrogen, creatinine, and electrolytes and were repeated on Days III, Day VII and/or prior to discharge. Nutrition risk assessments were done and anthropometric measurements were taken including mid-arm circumference and triceps skin fold by an independent personnel using a standard measuring tape and caliper respectively, during admission and daily thereafter. Any adverse events, although none in this study, were to be reported by the resident in charge of the patient to the assigned consultant and investigated and managed accordingly.

The patients participating in this study were on controlled ventilation through a cuffed endotracheal tube with a time cycled ventilator. Normal clinical criteria were used to determine the initial settings of the tidal volume (6-8 ml/kg ideal body weight) and frequency of ventilation (14–20 breaths/min). Arterial blood gas (ABG) measurements were taken at the start ventilation and daily thereafter. Inspired oxygen concentrations were adjusted according to the result of the latest ABG.

Weaning was performed using either synchronized intermittent mandatory ventilation (SIMV) or continuous positive airway pressure (CPAP) mode of the ventilator and was started as soon as the patient's reason for intubation was already partially or fully reversed and the patient fulfilled the criteria of spontaneous breathing trial (SBT) as follows:

- Rapid Shallow Breathing Index (RSBI) <105
- Oxygen saturation ≥ 90%, PaO2 ≥ 60, PaCO2 ≤ 10 from start
- Respiratory Rate <35
- Heart Rate<120-140 or did not change by 20%
- Systolic Blood Pressure >90 and <180 or change <20%
- No increase in anxiety, dyspnea, and work of breathing
- No change in sensorium

Each patient was assessed daily and the weaning process implemented as long as the above criteria were met. Weaning was considered successful if the patient maintained these criteria for 48 hours after extubation.

Outcome Measures

Primary Outcome

1. Duration of mechanical ventilation

Secondary Outcomes

1. Change in serum albumin from baseline
2. Change in mid-arm circumference and triceps skin fold from baseline
3. Development of ventilator-acquired pneumonia
4. All-cause mortality and any adverse events

Sample size calculation was done using Open Source Epidemiologic Statistics for Public Health (OpenEpi) which estimated a total of 186 patients (93 patients in each arm) to be enrolled in this study to ensure 80% power. This was based on the study of Ordanza on the prevalence of intubated patients admitted at the ICU of Ospital ng Makati last 2014. Descriptive statistics using means and percentages were used for the patient demographics. The primary outcome which is duration of mechanical ventilation was compared using paired T-test and the secondary outcomes including the changes in serum albumin, mid-arm circumference and triceps skin fold were measured using analysis of variance (ANOVA). A *p*-value of <0.05 was considered statistically significant.

Results

During the four months course of the study, a total of 93 patients were admitted at the ICU. However, only 40 patients were able to fulfill the inclusion criteria set in this study. The 40 eligible subjects were then enrolled and were randomly assigned to either Group A or B. Twenty subjects were allocated in Group A (Patients given enteral feeding using commercial formula with added whey protein) and twenty in Group B (Patients given enteral feeding using commercial formula alone) (Figure 1). All the 40 subjects were followed-up and were included in the data analysis.

The baseline characteristics were almost similar between the two groups as seen in Table I which probably occurred by chance given the small number of subjects.

Outcome measures

1. Effect of Whey Protein on Duration of Weaning from Mechanical Ventilation

The mechanically intubated patients who received whey protein supplementation (Group A) have lesser ventilator dependent days with an average of 5.4 days as compared to those who did not receive whey protein (Group B) with an average of 7.45 days (Figure 2). The result was statistically significant (*p*=0.00).

2. Effect of Whey Protein Supplementation in Serum Albumin

Both groups have increased serum albumin at the end of the study however it was noted that the patients who received whey protein supplementation have greater increase in serum albumin from baseline as compared to those who did not receive whey protein (*p*=0.00) (Figure 3).

3. Effect of Whey Protein in Mid-Arm Circumference and Triceps Skin Fold

In this study, those patients who received whey protein supplementation have increased mid-arm circumference (*p*=0.00) and triceps skin fold (*p*=0.00) from baseline as

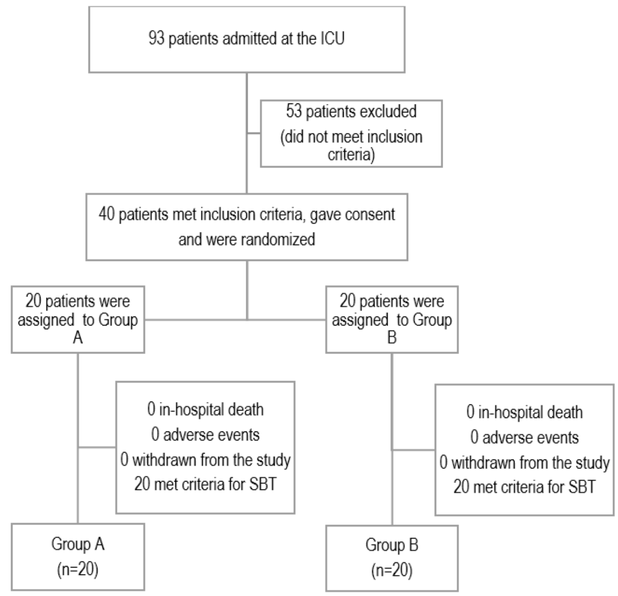

Figure 1. The allocation of patients to treatment groups.

Table I. The baseline characteristics of the subjects in both groups

	Group A (N=20)	Group B (N=20)
Age (in years)	57 (47-70)	59 (45-72)
Male (%)	55%	45%
Systolic blood pressure (mmHg)	120 (100-140)	115 (90-140)
Diastolic blood pressure (mmHg)	80 (60-90)	70 (60-90)
Heart Rate (beats/min)	90 (74-103)	91 (79-104)
Body Mass Index (kg/m^2)	22.23 (19.6-25.7)	23.21 (18.8-26.1)
Nutritional Status (SGA grade)*	B	B
Comorbidities		
Hypertension	14/20	12/20
Diabetes Mellitus	8/20	10/20
Bronchial Asthma	3/20	4/20
Chronic Obstructive Pulmonary Disease	9/20	7/20
Kidney Disease	2/20	2/20
GCS score**	15	15
Lab Results		
Hemoglobin (mg/dl)	13.3 (12-14.5)	12.4 (11-14.6)
WBC Count (blood) (x10^9/L)	17.7 (14-24)	15.5 (12-21)
Blood Urea Nitrogen (g/L)	6.3 (5.4-9.2)	8.5 (5.5-13)
Serum Creatinine (g/L)	83.0 (64-94)	80.0 (54-94)
• Serum Sodium (mmol/L)	132.0 (126-136)	133.9 (128-136)
• Serum Potassium (mmol/L)	3.6 (3.2-4.6)	3.4 (3.0-3.8)
• Serum Bilirubin (mmol/L)	11.0 (7.5-21)	10.9 (7.6-13)
• Serum Albumin (g/L)	28.55 (22-32)	27.65 (24-32)
SAPS II Score	23.5 (19-34)	25.7 (19-36)

*Subjective Global Assessment
**Glasgow Coma Scale

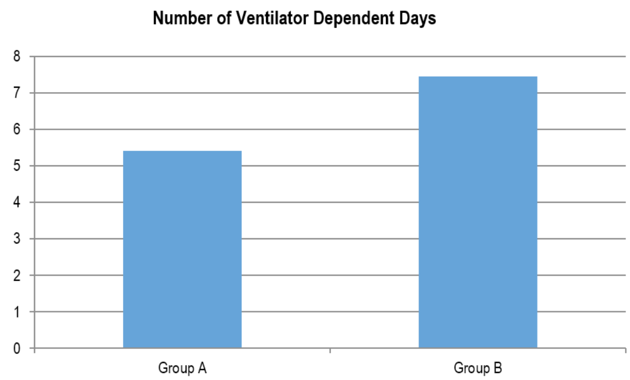

Figure 2. The number of ventilator dependent days of the two groups.

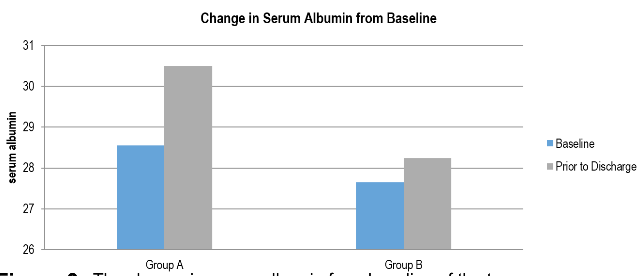

Figure 3. The change in serum albumin from baseline of the two groups

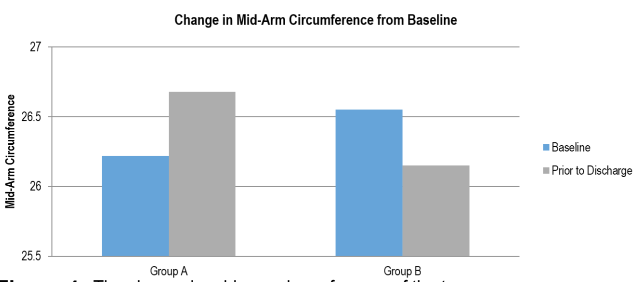

Figure 4. The change in mid-arm circumference of the two groups

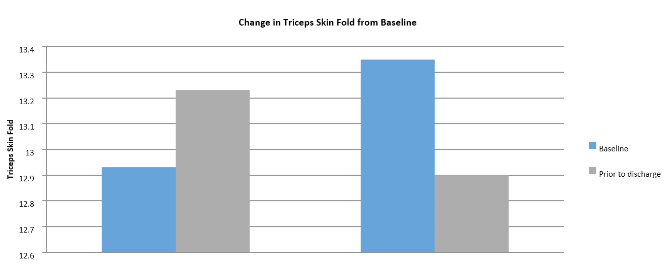

Figure 5. The change of triceps skin fold from baseline of the two groups.

compared to those who did not receive whey protein supplementation (Figure 4 and 5). The latter group also showed some decline in the two parameters mentioned as also seen in the figures.

4. Effects of Whey Protein in Development of Nosocomial Infections, and All-Cause Mortality

The study showed that five out of 20 or 25% of patients in Group B developed VAP and none in Group A. Furthermore, no mortality was noted in both groups.

5. Adverse Events

No adverse events that can be attributed to the supplementation of whey protein were noted in the subjects in Group A.

Discussion

It was noted in the study of Ordanza (2014) that 66% or eight days out of the 11.58 days of patient's average stay in the ICU were spent with mechanical ventilator support.[4] In the present study, the addition of whey protein may be beneficial in decreasing the ventilator dependent days to 5.4 as compared to the eight days average in the setting of Ospital ng Makati. This result could be attributed to the positive effect of whey protein in muscle protein synthesis which in turn provided improvement in respiratory muscle strength and function.

Serum albumin levels in the study were noted to be increased in both groups but with greater increase in Group A. This may be attributed to the fact that albumin levels have been known to decrease during critical illness because it is also an acute-phase reactant especially among patients who are on bed rest and are mechanically ventilated but will recover once their condition improves. Hence whey protein supplementation is a promising intervention that can prevent hypoalbuminemia in mechanically ventilated patients.

The loss of muscle mass which was observed in patients of Group B may again be explained by the muscle breakdown that happens during acute illness and muscle atrophy during period of immobilization. On the other hand, patients who received additional whey protein had increased muscle mass which can be attributed to its significant effect in promoting muscle protein synthesis.

Although all patients on mechanical ventilator have risk of developing VAP, an important factor of its development would be the duration of the mechanical ventilation because the longer the ventilator-dependent days, the higher the risk of developing VAP. As described earlier, patients who received whey protein were weaned earlier than those who did not receive the supplement, hence shorter time on ventilator support leading to less likelihood of developing VAP.

No adverse events that can be attributed to the additional whey protein were noted in both groups which may be due to the safe components of the used formula. Likewise, no mortality was noted in both groups which may be accounted to the relatively low baseline SAPS score in all subjects, and further could imply that whey protein supplementation is generally safe among mechanical ventilated patients admitted at the ICU.

Conclusion

Whey protein supplementation can be recommended to mechanically ventilated patients without contraindications to high protein diet to facilitate early weaning because it contains all essential elements that could stimulate early muscle protein synthesis promoting improvement in lung function and ventilatory drive. Whey protein can also promote greater increase in serum albumin during the recovery period and can prevent malnutrition during critical illness. In addition, whey protein has been associated with enhanced immune function due to its extra glutamine content which may contribute in the prevention of nosocomial infections especially ventilator-acquired pneumonia. Moreover, in the setting of the ICU of Ospital ng Makati, there are only limited numbers of hospital beds, mechanical ventilators as well as hospital staff and resources in spite of the continuously growing number of patients who are in need of mechanical ventilation and ICU admission. The use of additional whey protein can potentially lead to shorter duration of mechanical ventilation and hospital stay which can also mean less cost of care delivery. All these mentioned benefits of whey protein supplementation were seen in this study with a relatively small sample size. The authors recommend to retest it in a larger study population with a longer study duration to strengthen the correlations.

The main limitations of this study were its research design which is an open label randomized controlled trial. It would also be better if prealbumin (not available in our institution) was used instead of albumin because it has a shorter half-life making it a more favorable marker of acute change in nutritional status.

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