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Microbial cell preparation in enteral feeding in critically ill patients: A randomized, double-blind, placebo-controlled clinical trial☆

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ABSTRACT

Gut failure is a common condition in critically ill patients in the intensive care unit (ICU). Enteral feeding is usually the first line of choice for nutrition support in critically ill patients. However, enteral feeding has its own set of complications such as alterations in gut transit time and composition of gut eco-culture. The primary aim of this study was to investigate the effect of microbial cell preparation on the return of gut function, white blood cell count, C-reactive protein levels, number of days on mechanical ventilation, and length of stay in ICU. A consecutive cohort of 60 patients admitted to the ICU in University Malaya Medical Centre requiring enteral feeding were prospectively randomized to receive either treatment (n = 30) or placebo (n = 30). Patients receiving enteral feeding supplemented with a course of treatment achieved a faster return of gut function and required shorter duration of mechanical ventilation and shorter length of stay in the ICU. However, inflammatory markers did not show any significant change in the pretreatment and posttreatment groups. Overall, it can be concluded that microbial cell preparation enhances gut function and the overall clinical outcome of critically ill patients receiving enteral feeding in the ICU.

1. Introduction

Gastrointestinal dysfunction is a major complication encountered in the critically ill, especially in the intensive care unit (ICU) setting, whereby patients commonly experience dysmotility of the gastrointestinal system [1]. An approximate 50% of mechanically ventilated patients exhibit antral hypomotility-reduced gastric emptying, lesser migrating motor complexes, and higher risks to infections, usually leading to infectious diarrhea [2]. Enteral feeding is a major factor that contributes to the clinical outcome and duration of stay of critically ill patients in the ICU, and in that sense, tolerance to enteral feeding is of great importance [2]. A functional gastrointestinal tract has now been recognized as an important factor in the clinical outcome of ICU patients [1].

Nutritional support in critically ill patients is one of the major aspects of patient care in the ICU. Because of the nature of their illnesses, critically ill patients are usually under physiologic and psychosocial stress, thus placing them in a hypercatabolic state; thus, the provision of adequate nutrition is of utmost importance for their recovery [3]. Enteral feeding is the first-line and commonly used nutritional support system in critically ill patients as an adjunct therapy with the primary goal of achieving the caloric requirement of the patient and preventing the patient from developing malnutrition. However, enteral diets are known to affect the physiologic state of the gut due to modification in gut transit time and alteration of the secretory and absorptive capacity of the intestines, as well as modification to the gut ecosystem. However, delivery of calories could be limited by the set pump itself, mainly due to nursing protocols and frequent cessation of feed due to medical reasons or surgical procedures [4]. This reduced tolerance would result in high gastric residual volumes (GRV) [4]. In 2008, Gatt [5] defined the *return of normal gut function* as at least 80% tolerance of an individual's daily caloric requirement for a consecutive period of 48 hours or more. Tolerance of less than this value may be associated with poor clinical outcome and may indicate the lack of gut function [5]. Thus, in this study, the return of normal gut function would be defined as being able to achieve at least 80% of caloric requirement for a consecutive period of 48 hours.

Furthermore, bacterial strains, such as *Lactobacillus* and *Bifidobacterium*, are defined as preparations of microorganisms that exert therapeutic effects when administered in specific recommended

Abbreviations: AIDS, acquired immune deficiency syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; BALT, bronchus-associated lymphoid tissue; CFU, colony-forming unit; CRP, C-reactive protein; GALT, gut-associated lymphoid tissue; GCP, Good Clinical Practice; GRV, gastric residual volume; GSN, gut-specific nutrients; ICU, intensive care unit; IRB, institutional review board; MALT, mucosa-associated lymphoid tissue; MCP, microbial cell preparation; MEC, Medical Ethics Committee; MODS, multiple-organ dysfunction syndrome; UMMC, University Malaya Medical Centre; WBC, white blood cell.

☆ ClinicalTrial.gov: NCT01792401; MEC Registration No.: 835.1 (institutional review board, University Malaya Medical Centre, Malaysia).

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dosages [6]. They can colonize the human intestine and modulate the gut ecosystem, which serves as a defense mechanism hindering the growth and colonization of pathogenic bacteria. The term "probiotic" was coined in 1965 by Lilly and Stillwell [7]. In light with current scientific progresses, probiotics are more specifically referred to as microbial cell preparation (MCP) or components of microbial cells that exert beneficial effects on the health and overall well-being of the host [8]. Henceforth, we would refer to probiotics as MCP in the context of this study. Current scientific research has not fully tapped and elucidated the various mechanisms of action of MCP and its role in improving gut function. Diarrhea is commonly seen in ICU patients on enteral feeding, with almost 15% to 50% of patients reported to be affected [9]. Replenishing the altered ecosystem of the gut with MCP may prove beneficial to reestablish the favorable homeostatic environment in the gastrointestinal tract [6,10]. Slow bowel movements are common in ICU patients, with an estimated 80% of patients having no bowel movements in the first 72 hours of admission [9]. Several hypotheses exist to explain the delayed gastric motility of patients in the ICU, namely, sepsis and shock, elevated levels of endotoxins, inflammatory mediators, nitric oxide production, and lastly, drugs such as sedatives, opiates, and vasoactive drugs [9]. It is believed that the acidic environment induced by MCP may stimulate the motility of the intestines, as shown in patients with chronic constipation [11].

We hypothesize that enteral feeding supplemented with MCP improves the time required for the return of normal gut function in critically ill patients in the ICU.

2. Materials and methods

This study protocol was approved by the institutional review board of University Malaya Medical Centre (Reference No. 835.1) prior to the commencement of the study. This study was conducted in accordance to Good Clinical Practice Guidelines and was registered at the US National Institutes of Health Web site (http://www.clinicaltrials.gov; Reference No. NCT01792401). The data obtained from the patients were with prior consent either by the patient themselves or their respective next of kin. No ethical restraints were noted in regard to the execution of this study or in the treatment modalities used.

The primary end point for this study was the duration to return to normal gut function, which is defined as the time (in hours) taken to achieve a minimum of 80% of calculated caloric requirement for a consecutive 48-hour period.

The sample size was calculated based on published data [12], which showed that a minimum number of 24 patients in each group was required to demonstrate a difference in hours in the return of normal gut function at a level of 5% significance with a power of 95% according to Altman's formula. This study was a prospective, randomized, double-blind, placebo-controlled trial. The random allocation sequence was generated by a computerized system to randomly allocate 30 subjects in each group. All researchers and subjects remained blinded to the allocation until the end of the study.

2.1. Subject recruitment criteria

The inclusion criteria were as follows: critically ill patients 18 years and older; admitted to the ICU of University Malaya Medical Centre, Kuala Lumpur, for more than 48 hours; requiring enteral feeding via nasogastric tube feeding alone; and not taking any forms of MCP prior to commencement of the study.

The exclusion criteria were as follows: patients admitted to the ICU for monitoring purposes, patients on immunosuppressive treatment, patients with hematological diseases, patients with AIDS, pregnant patients, patients who were known to have allergy to MCP, contraindication to placement of nasogastric feeding tube, on parenteral feeding alone or combined with enteral feeding, and enrolled in other studies and on other forms of MCP prior to commencement of the study.

2.2. Product, dosage, and administration

The random allocation was generated by a computer model, and both researcher and participants remained blinded to the contents of the sachets throughout the study procedure and statistical analysis. Un-blinding was performed after completion of analysis.

The treatment sample is an orange-flavored granule, containing 30 billion colony-forming units of highly compatible, acid- and bile-resistant strains of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and *Bifidobacterium infantis*. The placebo mixture samples have similar appearance and taste, but without fermentation. Both preparations were prepared in sealed aluminum foil of 3 g labeled A (placebo) and B (treatment). These were administered twice daily at 0800 and 2000 hours for a consecutive 7 days [11] once the patient was started on enteral feeding. The trial product (treatment or placebo) was diluted in 5 mL of water and was administered to the patient via the nasogastric tube. After administration, flushing of the tube with 5-10 mL of water was done to make sure that the test sample passes through the tube completely.

2.3. Enteral feeding regimen

Enteral feeding regimen in the ICU was as follows: Osmolite 1 cal (standard formula), Glucerna (glucose intolerance formula), Peptamen (semielemental formula), and Novasource Renal (electrolyte and fluid restriction). The feeding regimen was in accordance to the Enteral Feeding Flowsheet (Fig. 1). Feeding was started within the first 24 to 48 hours after admission to ICU. Feeding was administered continuously using a feeding pump for 24 hours. The energy requirements for all subjects were calculated based on a weight-based formula (weight obtained from weighing bed in ICU) at the time of patient recruitment, which is 25 kcal kg^{-1} d^{-1} [13]. Moreover, complications of feeding such as feeding intolerance in terms of abdominal distension/discomfort, lack of bowel activity and any subjective symptoms reported by patients, vomiting, GRV, diarrhea, refeeding syndrome, and suspected aspiration of feed were monitored. Return of gut function was monitored through records of input output chart, and the tolerance and absorption of the enteral feed was measured based on GRV. The GRV was checked every 6 hours for continuous feeding. A GRV less than 200 mL would result in readministration of the GRV to the patient and continuation of the enteral feeding protocol. A GRV more than 200 to 500 mL would be based on 2 episodes, whereby the first episode would be to continue enteral feeding and start the patient on prokinetic agent, whereas the second consecutive episode would require notification of medical staff and dietitian. A GRV more than 500 mL would result in cessation of enteral feeding.

3. Results

Data were collected between March 2011 and December 2011, from the time of enrollment of the patient into the trial to the time of completion of treatment. It included demographic data, diagnosis on admission to ICU, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and anthropometric measures included weight that was the adjusted body weight [14], caloric requirement calculated based on Cerra et al [13], inflammatory markers, ventilation days, and days of ICU stay. SPSS 17 for Mac (Chicago, Ill) was used for the statistical analysis. *P* value less than .05 was considered statistically significant.

3.1. Demographic data

Fig. 2 shows the flowchart of patient recruitment and analysis. Although 70 patients were screened, only 60 patients were recruited to participate in the study due to failure to obtain consent. These 60 patients were randomly allocated to either treatment or placebo group in equal number, via sealed envelope method. During the trial period,