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EDITORIAL

When and how to manage enteral feeding intolerance?

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Introduction

In this issue of *Intensive Care Medicine*, Heyland et al. reported the results of the PROMOTE Trial [1]. In this international multicenter (20 sites, 4 countries) randomized double-blind study, 120 critically ill patients who had enteral feeding intolerance (EFI) were randomized to receive ulimorelin or metoclopramide for 5 days. A volume-based feeding protocol was employed, with a starting feeding rate of 40 mL/h and maximum rate of 150 mL/h. Gastric residual volumes (GRV) were measured every 6 h, and the feeding rate was increased if GRV was < 500 mL, and reduced if GRV was ≥ 500 mL; if GRV ≥ 500 mL persisted in two consecutive measurements with feeding 10 mL/h beyond day 1, the study drug was discontinued.

The study found no difference between ulimorelin and metoclopramide in the primary endpoint of percentage of daily protein prescription (DPP) over 5 days of treatment. There were no differences in the secondary endpoints of feeding success, gastric emptying assessed by paracetamol absorption, incidence of recurrent EFI, vomiting or regurgitation, aspiration, and pulmonary infection. The study highlighted some uncertainties and the need for harmonization.

Definition of enteral feeding intolerance

EFI is common in the critically ill, and often results in not achieving nutritional targets. It may also be associated with significant morbidity, leading to increased mortality and ICU length of stay [2].

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However, there is considerable variation in defining what constitutes EFI. A systematic review of 72 studies estimated prevalence of EFI of 38% (95% CI 31–46), but demonstrated large variability in defining EFI [2]. Upper gastrointestinal tract intolerance reflected by large GRVs (with or without other gastrointestinal symptoms) was used in 63/72 studies, with a median volume defining a "large" GRV of 250 mL (range 75–500 mL) [2].

Efficacy and safety of prokinetic agents

Prokinetic agents to improve gastric emptying are used off-label in critically ill patients. A systematic review of 13 randomized controlled trials ($n = 1341$ critically ill patients) assigned to receive a prokinetic agent (metoclopramide, erythromycin, domperidone) or placebo confirms the reduction in GRVs (RR 0.69; 95% CI 0.52–0.91) and EFI (17.3%; 95% CI 5–26.8%) by prokinetics, with no difference in vomiting, diarrhea, pneumonia or mortality [3]. Importantly, only 5/13 studies reported EFI as an outcome, while increased GRV, vomiting and diarrhea were commonly reported [3].

Side effects and tachyphylaxis are of concern in prokinetic use. In addition, the PROMOTE study demonstrated some differences in the safety profile of the two drugs: serious adverse events occurred more often in the ulimorelin group, but adverse events leading to study drug discontinuation, including atrial fibrillation, were more common in the metoclopramide group. Although most of these differences were not statistically significant, the sample size was too small to draw definitive conclusions.

Indications and contraindications for prokinetic therapy

There is a lack of consensus on indications and contraindications for prokinetic therapy in critically ill patients. EFI can be considered as an adaptive

mechanism during the early course of critical illness [4]. The decrease in plasma ghrelin levels reported by two independent teams was used to support the use of ulimorelin, which acts as a ghrelin agonist [5, 6]. However, the decline in ghrelin release could be considered a signaling pathway sent by the upper gastrointestinal tract as a component of the adaptive response leading to anorexia during the early course of critical illness. Additionally, uncertainty around diagnostic criteria for gastrointestinal dysmotility distal to the stomach warrants caution towards treatment with gastroprokinetics. Improving gastric emptying in cases where the problem lies caudally may worsen bowel distension, leading to complications. Therefore, it is unclear how aggressive we should be in attempting to attain nutritional targets in the first few days of critical illness in patients with EFI. Administration of full calories (100% of energy expenditure) in the early acute phase has not been shown to be beneficial and is not currently recommended [7–11]. The NUTRIREA-2 trial suggests that attempting to achieve full-dose enteral feeding rapidly in patients at risk for gastrointestinal injury may be associated with adverse events [12]. The optimal dose of protein in the acute phase of critical illness is even less certain, and we await publication of data from randomized controlled trials [13, 14].

Accordingly, one approach to patients with one episode of large GRV is to transiently reduce the nutritional target, and consider prokinetic agent only if large GRVs persist or are associated with other gastrointestinal symptoms, whereas small bowel distension is excluded [15]. Additionally, duration of treatment needs to be limited to achieve optimal benefit: risk ratio.

Volume-based protocol was used together with prokinetic agents in all patients in PROMOTE Trial; yet only 51.6% and 55.2% of ulimorelin and metoclopramide patients in the intention-to-treat population achieved feeding success over the 5 days of treatment ($\geq$ 80% of daily protein prescription). At the same time, episodes of EFI declined progressively over the 5 study days in both groups. While all patients had EFI prior to randomization, only 25% had EFI on day 1, and only 15% of patients continued to experience EFI episodes by day 5; only 50.0% had EFI recurrence during the trial.

These findings highlight the transient nature of upper gastrointestinal tract EFI in many ICU patients and raise several important questions. Should a single episode of large GRV trigger prokinetic treatment? In addition, could the treatment effect of prokinetic agents have been "diluted" by including patients with transient EFI? What is the optimal duration of therapy in responders versus nonresponders?

In summary, ulimorelin and metoclopramide administration demonstrated comparable efficacy in treatment of EFI defined as a single GRV $\geq$ 500 ml. In a considerable proportion of patients, the feeding target was not achieved despite volume-based feeding, prokinetic administration for 5 days and a relatively low number of patients with recurrent EFI as defined based on large GRV.

Research addressing EFI and its treatment needs to continue. In the search for new effective and safe molecules, an ultimate goal should be kept in mind: identification of indications for prokinetic treatment (along with a clear definition of EFI) to achieve the optimal benefit-to-risk ratio for such treatment.

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Conflict of interest
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