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Gastric residual volume during enteral nutrition in ICU patients: the REGANE study

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Abstract *Objective:* To compare the effects of increasing the limit for gastric residual volume (GRV) in the adequacy of enteral nutrition. Frequency of gastrointestinal complications and outcome variables were secondary goals. *Design:* An open, prospective, randomized study. *Setting:* Twenty-eight intensive care units in Spain. *Patients:* Three hundred twenty-nine intubated and mechanically ventilated adult patients with enteral nutrition (EN). *Interventions:* EN was administered by nasogastric tube. A protocol for management of EN-related gastrointestinal complications was used. Patients were randomized to be included in a control (GRV = 200 ml) or in study group (GRV = 500 ml). *Measurements and results:* Diet volume ratio (diet received/diet prescribed), incidence of gastrointestinal complications, ICU-acquired pneumonia, days on mechanical ventilation and ICU length of stay were the study variables.Gastrointestinal complications were higher in the control group (63.6 vs. 47.8%, $P = 0.004$), but the only difference was in the frequency of high GRV (42.4 vs. 26.8%, $P = 0.003$). The diet volume ratio was higher for the study group only during the 1st week (84.48 vs. 88.20%) ($P = 0.0002$). Volume ratio was similar for both groups in weeks 3 and 4. Duration of mechanical ventilation, ICU length of stay or frequency of pneumonia were similar. *Conclusions:* Diet volume ratio of mechanically ventilated patients treated with enteral nutrition is not affected by increasing the limit in GRV. A limit of 500 ml is not associated with adverse effects in gastrointestinal complications or in outcome variables. A value of 500 ml can be equally recommended as a normal limit for GRV.

Keywords Enteral nutrition · Gastric residual volume · Mechanical ventilation · Ventilator-associated pneumonia · Intensive care unit

Introduction

Gastric intolerance of enteral nutrition (EN) is the main gastrointestinal complication during the course of EN in critically ill patients. This has been pointed out in previous investigations by our working group [1–3] and also in other publications [4–6]. Comparing with patients without upper digestive intolerance, intolerant patients receive less volume of diet and have worse prognosis in terms of ICU stay and mortality [1, 7].

Monitoring of gastric residual volume (GRV) is used as an indicator of diet tolerance in clinical practice. The limit for "normal" GRV was proposed as 200 ml for nasogastric feeding in a study from McClave et al. [8] published more than a decade ago. Their recommendation has been applied to clinical practice and, at present, this limit is used for clinical purposes in many ICUs. Nevertheless, recommendations about the normal limit for GRV in critically ill patients treated with EN are not uniform; values between 50 and 500 ml could be found in the literature [9–12].

Holding enteral feeding is a common procedure that is implemented after a situation of high gastric residual volume (HGRV) is appreciated. Nevertheless, to do so in these patients results in a decrease in the volume of diet received by the patient: this could imply an energy deficit that can be deleterious [13].

We hypothesised that if a higher limit is used to define "normal GRV," the frequency of "HGRV" is lessened and also the number of episodes of stopping the diet. So, as a consequence of this, patients could receive more diet and, consequently, the energy deficit would be prevented. Nevertheless, this increase in the limit for GRV would be a risk factor for aspirative pneumonia in these patients. So a careful evaluation is needed to evaluate this effect.

The main aim of this study was to compare the effects of increasing the limit for GRV from 200 ml up to 500 ml on the diet volume received in mechanically ventilated patients with enteral nutrition. Secondary goals were to determine the consequences of this intervention on the incidence of gastrointestinal and pulmonary complications and on several outcome variables.

Methods

Setting

A randomized, multicenter and prospective study was performed in 28 ICUs in Spain.

Patients

Adult patients in the ICU with mechanical ventilation and indication for EN for at least 5 days were included. EN was applied with a nasogastric tube in all the cases. Patients with duodenal or jejunal feeding were not included.

Intragastric position of tube feeding was radiographically confirmed before diet infusion.

Nutritional requirements and type of enteral formula diet were selected by each investigator. Investigators were instructed to follow recommendations of the Spanish Nutritional and Metabolic Working Group [14] for these issues.

A previously described [1] protocol for the definition and management of gastrointestinal complications was used with the only difference in the definition of HGRV; the limit for GRV was set at 200 ml in the control group, whereas in the study group this limit was 500 ml. All patients were managed in the semi-recumbent position (30–45°) in order to decrease pneumonia incidence.

Parenteral Nutrition (PN) was used to complement nutritional requirements in case of underfeeding with EN. Criteria for indication of complementary PN were not protocolized.

Methods

Approval was received from the corresponding institutional review board before initiation of the study. Informed consent was obtained from patients or their legal guardians. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Patients were randomized to be included in the control group (GRV: 200 ml) or in the study group (GRV: 500 ml). Randomization was concealed. A central randomization procedure was performed by the coordinating center by a phone call after each patient was included in each study center.

Measurement of GRV was done at a 6-h interval during the 1st EN day, every 8 h the 2nd EN day and on a daily basis after the 3rd day of tolerated EN. Two methods for measuring GRV were used: (1) gravity drainage by connecting a gastric tube to a drainage bag for 10 min or (2) syringe aspiration (with a 50-ml syringe) through the gastric tube. Investigating centers used one of these two methods according to their clinical routine. The GRV measurements were made in whatever position the patient was in at the time; no attempt was made to control this variable.

Metoclopramide (10 mg every 8 h) was administered intravenously to all the patients as a prophylactic prokinetic agent during the first 3 days of EN.

Variables collected

Demographic variables, admission diagnosis and severity scores [acute physiologic and chronic health evaluation (APACHE II) score and sequential organ failure assessment (SOFA) score] were recorded at admission to the ICU.

Day of EN initiation, calculated energy requirements, type of formula feeding, EN duration and causes of finalization of EN were also recorded.

Patients were daily followed to detect the presence of gastrointestinal complications. Gastrointestinal complications were defined as follows [1]:

1. Abdominal distention: abdominal changes on daily physical exam with tympany and/or absence of bowel sounds.
2. High gastric residuals: gastric residual was considered high if the recovered volume was equal to or greater than 200 ml (control group) or 500 ml (study group). Previous nomogram for management of HGRV episodes was modified for use in the study (Fig. 1).
3. Vomiting: enteral formula ejected through the mouth.
4. Diet regurgitation: enteral formula found in oral or nasal cavities with or without exteriorization.
5. Diarrhea: five or more liquid stools in a 24-h period or an estimated stool volume equal or greater than 2,000 ml/day.

Compliance with the enteral nutrition orders was registered daily. Diet volume ratio (VR), considered as an index of efficacy of nutrient delivery, was calculated as follows:

$$\text{Diet VR } (\%) = (\text{administered volume of diet}/\text{prescribed volume}) \times 100$$

Pulmonary aspiration of enteral diet was also investigated. This complication was diagnosed when feed was detected in the tracheal aspirate.

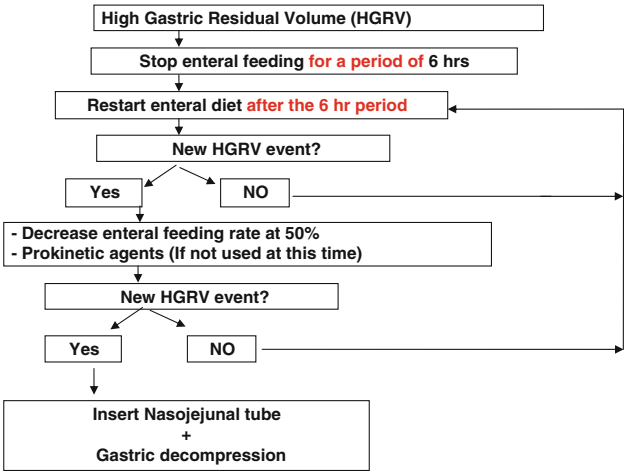

Fig. 1 Nomogram for the management of high gastric residual volume (HGRV). The first step after detecting a HGRV event is stopping diet infusion during a 6-h period to promote gastric rest. Diet infusion is continued after this period. New episodes of HGRV are managed decreasing the infusion rate and introducing motility agents (if not used at this time). Insertion of a naso-jejunal tube was indicated in case of repeated events of HGRV

Pneumonia was defined according to the ATS/IDSA clinical criteria [15]. Pneumonia was diagnosed if a new or progressive radiographic infiltrate was present and at least two of the three following clinical features were also present: (1) fever higher than 38°C, (2) leukocytosis or leucopenia and (3) purulent secretions. Pneumonia was diagnosed prospectively by at least two adjudicators (investigator and another ICU specialist in each participating center). Pneumonia was investigated during all ICU days for each included patient. No microbiological confirmation was required for diagnosis of pneumonia.

Outcome variables, including days on mechanical ventilation, days in the ICU, day 5 SOFA score, final SOFA score and final outcome, were recorded.

Patients were followed until the end of EN or for a maximum of 28 days of EN.

Data collection

The study period was February to September 2006.

Data were prospectively collected in a clinical report formulary (CRF). Each CRF was completed by the responsible physician at each investigating center and then sent to the coordinating center. CRFs were first analyzed in the coordinating center searching for errors or data loss. Discrepancies and transcription errors were discussed and clarified. CRFs were sent for statistical analysis after data validation.

Statistical analysis

We performed a sample-size calculation based on previous results of our working group [1, 2]. We hypothesize that a similar rate of gastrointestinal complications, other than increase in GRV, is expected in both groups. The expected diet supply in the control group was that expected in the previous study: a mean volume ratio of 70% of the volume of diet prescribed. The estimated volume ratio in the study group was set at 90%. A sample size of 143 patients per treatment group was determined in order to obtain 80% power to detect differences with a magnitude expressed as effect size of 0.33 using bilateral tests and a significance level of 0.05. Finally, we decided to enroll 160 patients per group.

Statistical analysis was performed in an independent institution: "Servei d'Estadistica of the Universitat Autonoma de Barcelona" (Barcelona.Spain). Data were analyzed using SAS version 9.1 statistical software (SAS Institute Inc., Cary, NC).

Statistical analysis was blinded for group identification. Chi-square test was used to compare qualitative variables. When application conditions (percentage of cells with expected counts lower than 5 above 25%) were not satisfied, Fisher's exact test or chi-square tests with

Yates correction were used. Quantitative variables were compared using *t* test or one-way ANOVA. When application conditions (normal distribution for model residuals or variance heterogeneity between groups) were not satisfied, the Mann-Whitney-Wilcoxon test or Kruskal-Wallis test were used as indicated. Statistical significance was defined at $P < 0.05$. Values are presented as mean ± standard deviation (SD) if not quoted otherwise.

Results

A total of 329 patients were randomized in the 28 participating ICUs. Seven patients (four in the control group and three in the study group) were inappropriately included (non-mechanically ventilated patients at time of enteral nutrition) and were excluded from the final analysis. A total of 322 patients were analyzed (control: 165, study: 157). There were no differences between groups in age, sex distribution, diagnosis at admission, APACHE II score or SOFA score (Table 1). EN characteristics, including feeding solutions, were also similar in both groups: there were no significant differences in caloric density or in the type of diet between groups (Table 1). Oligomeric diets were not used in this patients.

Frequency of gastrointestinal complications was higher in the control group: 63.6 vs. 47.8% of the patients ($P = 0.004$). Nevertheless, the difference was due only to the frequency of HGRV, which was present in 70 (42.4%) patients in the control group and in 42 (26.8%) in the study group ($P = 0.003$). Mean number of HGRV events per patient was also higher in the control group (0.96 ± 1.59 vs. 0.44 ± 0.88) ($P = 0.001$). The number of events of HGRV in patients with this complication are indicated in Table 2. No differences were appreciated between groups in the method used for GRV measurement: gravity drainage was used in 50.7% of the control group patients and in 63.4% in the study group ($P = 0.19$). Frequency of the remaining gastrointestinal complications was similar in both groups (Table 3). Percentage of patients with complementary PN during their ICU stay was 10.6% for the control group and 17.1% for the study group ($P = 0.11$).

Mean VR was higher for patients in the study group during the 1st week of EN (VR control group: 84.48% VR study group: 88.20%, $P = 0.0002$) and also at day 12 of EN (86.44% vs. 88.25% ($P = 0.035$). After the 2nd week of EN, VR was superior for the control group at week 3 (VR control group: 93.50% VR study group: 89.20%) and at week 4 (97.65% vs. 94.69%); this difference was not statistically significant.

The number of patients with "ICU-acquired pneumonia" was 45 (27.3%) in the control group and 44 (28.0%) in the study group. Outcome variables (days on mechanical ventilation, ventilator-free days, SOFA day 5,

Table 1 Patients and enteral nutrition characteristics

	Control (GRV: 200)	Study (GRV: 500)	*P*
Patients	165	157	
Age (years[a])	60.0 ± 25.0	65.0 ± 27.5	0.08
Sex[b]			0.28
Male	63.4%	70.6%	
Female	36.6%	29.4%	
Diagnostic group[b]			0.15
Medical	81.5%	84.0%	
Surgical	6.2%	1.9%	
Trauma	12.3%	14.1%	
APACHE II[c]	18.9 ± 7.5	19.4 ± 7.4	0.81
SOFA[c]	7.2 ± 3.1	6.7 ± 3.0	0.17
Feeding tube caliber at start of EN[b]			0.20
<8F	1.2%	4.5%	
8F	6.8%	4.5%	
10 F	14.3%	15.4%	
12 F	37.9%	30.1%	
>12 F	39.8%	45.5%	
Admission to EN time[a] (days)	1.0 ± 1.0	1.1 ± 1.0	0.51
Feeding formula caloric density[b]			0.22
<1.25 kcal/ml	59.3%	65.1%	
>1.25 kcal/ml	40.7%	34.9%	
Type of feeding formula[b]			0.58
Normoproteic	36.4%	45.0%	
Hyperproteic	34.6%	29.4%	
Pulmonary	19.5%	20.2%	
Immunonutrition	9.3%	5.4%	
EN duration[a] (days)	8.0 ± 12.0	11.0 ± 12.0	0.22
Cause of EN finalization[b]			0.28
Oral diet	50.3%	49.0%	
EN-related complications	3.6%	6.4%	
Other complications	11.5%	5.1%	
ICU discharge	18.8%	19.7%	
Dead in ICU	15.7%	19.8%	

EN enteral nutrition, *GRV* gastric residual volume
[a] Median ± IQR
[b] Percentage of patients
[c] Mean ± SD

Table 2 Number of events of high gastric residual volume in patients with this complication

Events	Control (GRV: 200) ($n = 165$)	Study* (GRV: 500) ($n = 157$)
0	95 (57.6%)	115 (73.2%)
1	32 (19.4%)	25 (15.9%)
2	16 (9.7%)	10 (6.4%)
3	10 (6.1%	5 (3.2%)
4	5 (3.0%)	1 (0.6%)
5	3 (1.8%)	1 (0.6%)
6	0	0
7	2 (1.2%)	0
8	2 (1.2%)	0

* Cochran-Armitage trend test. $P = 0.0003$
GRV gastric residual volume

Table 3 Gastrointestinal complications

	Control (GRV: 200)	Study (GRV: 500)	*P*
Patients	165	157	
Patients with gastrointestinal complications	105 (63.6%)	75 (47.8%)	0.004
Patients with HGRV	70 (42.4%)	42 (26.8%)	0.003
Patients with abdominal distension	18 (10.9%)	16 (10.2%)	0.83
Patients with diarrhea	33 (20.0%)	31 (19.7%)	0.95
Patients with vomiting	24 (14.5%)	17 (10.8%)	0.31
Patients with regurgitation	12 (7.3%)	8 (5.1%)	0.41
Patients with aspiration	0	1 (0.6%)	0.48

GRV gastric residual volume, *HGRV* high gastric residual volume

Table 4 Outcome variables

	Control (GRV: 200)	Study (GRV: 500)	*P*
Mechanical ventilation (days)	14.7 ± 13.1	15.6 ± 13.6	0.36
ICU stay (days)	19.8 ± 15.8	20.7 ± 16.2	0.50
Pneumonia[a]	27.3%	28.0%	0.88
Ventilator-free days	5.1 ± 6.4	5.1 ± 8.0	0.28
SOFA day 5	6.3 ± 3.3	6.2 ± 3.2	0.48
SOFA day 10	5.0 ± 3.2	5.3 ± 3.0	0.75
ICU mortality[a]	15.7%	19.8%	0.28
Hospital mortality[a]	33.6%	33.9%	0.53

Values are expressed as percentage or mean ± SD
GRV gastric residual volume
[a] Percentage of patients

SOFA day 10, ICU length of stay and hospital mortality) were also similar in both groups (Table 4).

Discussion

Gastric emptying may be affected in critical illness and contributes to EN intolerance [16–19]. The use of GRV as a tool to evaluate gastric tolerance to EN is accepted as a clinical routine and has been incorporated in nutritional support algorithms in many ICUs [20, 21]. Our working hypothesis was that a limit higher than the 200–250-ml current limit could be used and that this could serve as a "rescue" mechanism for maintaining EN in patients with GRV in the range of 200–500 ml, without increasing complications. We decided to select a limit of 500 ml for GRV in the study group because this value has been suggested in the literature as a clinical end-point needing evaluation [10].

Elevated GRV could be associated with an increase in the incidence of EN-related gastrointestinal complications [7]. Other studies indicate, like in this one, that there is no correlation between the limit used for "normal GRV" and the incidence of diarrhea, regurgitation or abdominal distension [22, 23].

Use of low GRV has not been shown to decrease the incidence of aspiration. The relation between HGRV and aspiration is, nevertheless, controversial. Mentec et al. [7] showed that the incidence of pneumonia after the onset of EN was clearly superior in patients with upper digestive intolerance to enteral feeding. On the other hand, McClave et al. [24] could not find this correlation. Other authors also found no relationship between GRV and aspiration or pneumonia [25–27].

Our results agree with these considerations about the absence of a relationship between GRV and pulmonary aspiration. Nevertheless, we do not investigate the issue of pulmonary aspiration because this requires procedures such scintigraphy studies [28, 29], colored microspheres [24] or pepsin detection in tracheal aspirate [30], tests that were not routinely used in the participating centers in this study. Instead, we planned a clinical study and, consequently, the incidence of ventilator-associated pneumonia was the parameter used to explore the risk associated with GRV. Control and study groups had a similar frequency of VAP in our study, indicating that a direct relation between GRV and VAP does not seem to exist.

Prokinetic drugs have been recommended to increase EN tolerance in critically ill patients, but this is also a controversial issue [31–33]. In this study, metoclopramide was used as a prophylactic measure to increase diet tolerance and decrease aspiration risk in all the patients. Nevertheless, the study was not designed to test the hypothesis that prophylactic prokinetic treatment is beneficial in these situations. Prophylactic use of prokinetic drugs from the onset of EN in all the cases remains speculative and could not be recommended as a clinical routine. Nevertheless, we cannot exclude a beneficial effect of metoclopramide in improving diet tolerance in our patients.

Mentec et al. [7] showed that increased residual volumes were associated with decreased mean caloric intake in their patients. Nevertheless, other published trials [22, 23] report that using a higher GRV has benefits in terms of greater formula intake. This occurred also in our study. As a beneficial effect of using a 500-ml limit for GRV, instead of the more common limit of 200 ml, our patients received more enteral diet during the first 12 days of EN. Cumulative data for the 1st week of EN and at day 12 (the mean duration for EN in our series) indicate this fact. This is of interest because a negative energy balance has been correlated to the occurrence of complications in the ICU [12, 34]. According to the presented data, increasing the limit in GRV can be considered as a measure that could be implemented in order to decrease the energy deficit. Nevertheless, our data about differences in diet VR could be considered as "unimportant" for clinical implications; the accumulated difference in diet VR for the 1st week was only 3.7% (less than 100 kcal). This minimal difference in

energy administration probably could explain the absence of effect on outcome variables in our patients. Recent data about the importance of tight caloric control on outcome variables suggest that a more important effect on caloric intake would be necessary to appreciate outcome effects, such as a decrease in mortality [35]. More investigation is needed to confirm the effect of increasing GRV in the efficacy of diet administration in critically ill patients receiving enteral nutrition.

The increase in diet VR after the 2nd week of EN in control group patients was an unexpected finding. We have no clear explanation for this. Nevertheless, the importance of this finding would be anecdotal if we consider that a great number of our patients receive EN in the first 2 weeks and that this period is also when EN-related GI complications preferentially occur. Other authors [7, 27] have also pointed out that the increase in gastric residuals is appreciated mainly during the 1st days of EN, a period in which the impairment in gastric motility also occurs preferentially.

The clinical value of GRV in the evaluation of enteral feeding tube tolerance has been criticized because of the methodological problems associated with the measurement of GRV and the interpretation of the results. Several authors have suggested that the trend in GRV may be more useful than use of a cutoff value and, also, that GRV measurement must be accompanied by a clinical evaluation before a decision "to feed or not to feed" is taken [10, 24, 26]. Nevertheless, measurement of GRV is a universally used clinical practice and investigation in this field merits consideration. Existing data to assume a "safe" limit for GRV in tube-fed ICU patients are based on expert opinions and not on clinical investigations. The present study helps to clarify this issue.

Our study is the first published multicenter and randomized study that compares two limits for GRV in tube-fed ICU patients with mechanical ventilation. According to the data presented, we can conclude that increasing the limit for normal GRV to 500 ml is associated with an increase in the diet VR of ICU patients treated with EN. This is not associated with adverse effects in gastrointestinal complications or in outcome variables. In conclusion, a value of 500 ml could be recommended as a limit for GRV in mechanically ventilated ICU patients treated with enteral nutrition by nasogastric tube and receiving also metoclopramide as a motility agent from the beginning of the EN. Nevertheless, before generalizing the clinical use of our recommendation, it is necessary to consider some issues that could limit the generalization of our results. These have been mainly obtained in medical patients, by a homogeneous group of investigators experienced in the application of EN to critically ill patients (as can be seen in previous publications of our working group [1, 2]) and using a "prophylactic" treatment with motility agents to theoretically protect against EN pulmonary complications. More studies are needed in this field. Nevertheless, with these considerations, our results suggest that feeding protocols that use a cutoff value for GRV could consider the 500 ml limit.

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Appendix

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