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Comparison of Enteral Erythromycin Plus Intravenous Metoclopramide Versus Enteral Erythromycin Alone in Critically Ill Patients with Enteral Feed Intolerance

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Abstract

Background

Early and adequate enteral nutrition in critically ill patients is associated with decreased rate of infection and improved outcomes. However, enteral feed intolerance (EFI) is common problem in critically ill patients admitted in ICU leading to increased morbidity and mortality. Prokinetics, mainly erythromycin and metoclopramide have been used to address EFI in critically ill patients. This study was carried out to compare the efficacy of erythromycin plus metoclopramide and erythromycin alone for EFI in critically ill patients.

Method

Total 60 patients were enrolled for the study with 30 patients in group A (erythromycin plus metoclopramide) and group B (erythromycin). EFI was diagnosed when gastric residual volume (GRV) was >500ml. Rate of successful feeding at 48 hours, daily accumulative GRV, total daily calorie intake, hospital mortality and 28day mortality were recorded.

Results

The number of patients achieving successful feeding were significantly higher in group A (40%) than in group B (23.3%) at 72 – 96 hours. The ratio of average calorie intake to target calorie intake was also higher in group A (85.32 ± 20.61) than in group B (69.41 ± 35.86), ($p = 0.039$). Average GRV for the first six days was lower in group A then group B ($p<0.05$). Similarly, the average calorie intake was higher for the first six days in group A ($p<0.05$).

Conclusion
In critically ill patients, erythromycin plus metoclopramide is more effective than erythromycin alone in treating enteral feed intolerance.

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Introduction

The significance of nutrition in critically ill patients is increasingly being recognized, particularly in patients with prolonged ICU stay who usually require life sustaining support and go through a state of severe catabolism.[1,2] Early introduction of enteral nutrition is associated with decreased rate of infection, better wound healing and shortened length of hospital stay.[3] Adequate nutritional support during ICU stay has been shown to improve functional and quality of life outcomes, and achievement of optimal calorie and protein intake are associated with decreased morbidity and mortality [4,5].

However, enteral feed intolerance (EFI) is a common problem in critically ill patients admitted in ICU. [6,7] Various observational studies and meta – analyses have shown that more than 30% of critically ill patients experience enteral feed intolerance resulting in not achieving the nutritional targets.[8,9] The inadequate energy and protein delivery leads to exacerbation of catabolism and muscle wasting, lower ventilator free days, prolonged ICU and hospital stay, and increased morbidity and mortality [10,3].

The various mechanisms leading to EFI in critically ill patients are malfunctioning enteric and autonomic nervous system, altered hormonal regulating pathways, smooth muscle dysfunction, effects of various drugs, glucose and electrolyte imbalance, and inflammation. [11,12,13].

EFI is most commonly assessed by measuring the gastric residual volume (GRV). High GRV has been shown to predict delayed gastric emptying and worse outcome [14]. US and European critical care and nutrition society guidelines recommend a GRV of 500ml for the diagnosis of EFI [15,16,17].

Various studies, systemic reviews and meta – analysis have shown that prokinetics have a beneficial role in EFI. Currently, the agents of choice are erythromycin and metoclopramide, either alone or in combination, which are highly effective with relatively low incidence of cardiac, hemodynamic or neurological adverse effects. (19) Metoclopramide (a dopamine antagonist) and low-dose erythromycin (a motilin agonist) are the two most widely used prokinetic agents in critically ill patients. Metoclopramide enhances gastrointestinal intestinal motility through dopamine D2 receptor antagonist and 5 HT4 receptor agonism and primarily affecting the upper GI tract. Erythromycin also act as prokinetic agent by stimulating gastrointestinal motility through its action on motilin receptors agonist, it binds to motilin receptor located on smooth muscle cells located in the gastrointestinal tract especially in the antrum and duodenum. A single intravenous dose of metoclopramide has been reported in studies to improve gastric emptying in critically ill patients [20,21,22], but its effect on the success of feeding is unknown. In contrast, 3 mg/kg of erythromycin is associated with both increased gastric emptying and improved feeding success in previously feed-intolerant critically ill patients. [18,23,24].

No study has been made to see the efficacy of enteral erythromycin plus iv metoclopramide in comparison with enteral erythromycin alone in critically ill patients with gastric feed intolerance. Hence this study has been designed to compare the difference between

enteral erythromycin plus intravenous metoclopramide and enteral erythromycin alone in these patients.

Materials and Methods

This prospective randomized study was performed in the medical adult ICU of our centre between February 2024 and February 2025. The Institution Ethical Committee (registration number– ELMC&H/R-Cell/2023/01) approved the research protocol. The patients were enrolled in the study after informed consent from them or their next kin. The trial was registered with Clinical trial registry of India (CTRI number - CTRI/2024/02/062858).

The primary outcome of the study was to study the rate of successful feeding at 48 hours after randomization (successful feeding was defined as achieving 80% of target calorie intake). The secondary outcomes were to record: daily accumulative gastric residual volume (GRV), total daily calorie intake, average daily administered/ target calorie ratio of 7 days, ICU and hospital length of stay, in hospital mortality rate and 28- day mortality rate.

Critically ill patients of either sex and age 18 – 75 years admitted in ICU who had enteral feed intolerance (EFI) were included in the study. Patients with allergy to study drugs, underwent treatment with any prokinetics drugs 24 h before participating in the study, haemodynamic instability or presence of cardiac arrhythmia or prolonged QT interval of >480 msec on a 12-lead ECG, severe brain injury from any cause, small- or large-bowel surgery within six weeks before enrollment in the study, suspicious or confirmed bowel obstruction or perforation, current treatment with carbamazepine, digoxin, warfarin, haloperidol, or perphenazine and pregnant females were excluded from the study.

Sample size

Sample Size at 90% Power

Sample size is calculated on the basis of rate of successful feeding in two study groups using the formula

$$n = d\left(\frac{z_\alpha + z_\beta}{\ln(1-e)}\right)^2\left[\frac{p_1}{1-p_1} + \frac{p_2}{1-p_2}\right]$$

p1 = 0.471 (47.1%), rate of successful feeding in first group

p2 = 0.611 (61.1%), rate of successful feeding in second group

e = 0.9(p1/p2), the risk ratio considers to be clinically significant

d = 1.0, the design effect

Type I error α=5 %, for the significance level of 95%.

Type II error β=10 %, for detecting the results with 90% power of study,

The minimum sample size required comes out to be n = 30 each group

Methodology

A total of 75 patients were screened for enrolment of whom 15 didn't meet the inclusion criteria and were excluded from the study (Figure 1).

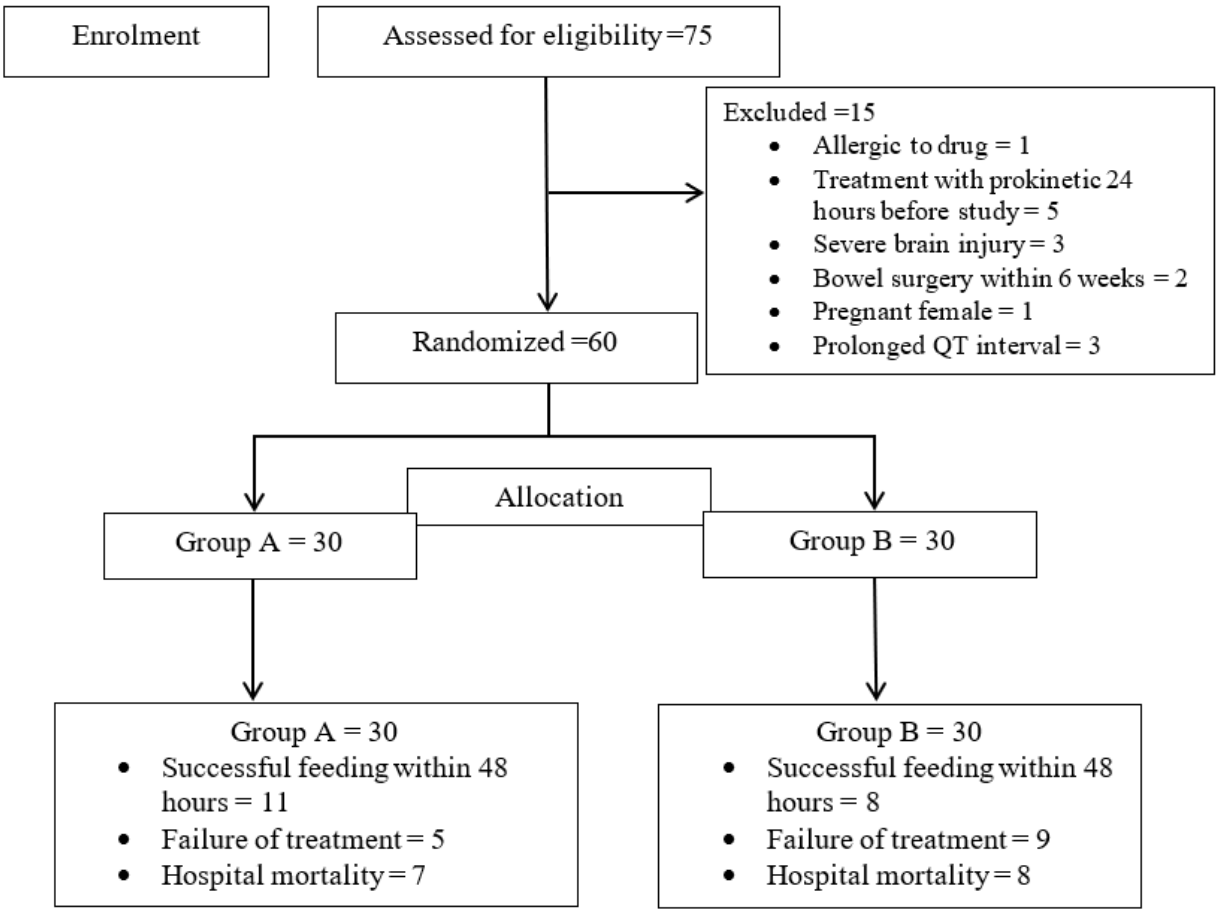

Figure 1: Flow diagram of the study recruitment & outcome

Total 75 patients were screened for enrolment of whom 15 didn't meet the inclusion criteria and were excluded. A total of 60 patients were included in the study (30 in each group).

After written informed consent from patient or the next kin, total 60 patients were included in the study and randomized by Sequentially Numbered Sealed Envelopes (SNOSE) technique into erythromycin plus metoclopramide (Group A) and erythromycin (Group B) groups. As intravenous erythromycin is not available in India, oral erythromycin was used for the study. Group A received 10 mg metoclopramide intravenously every 8 hourly in combination with 250 mg enteral erythromycin for seven days and group B received only enteral erythromycin 250 mg 6 hourly for 7 days. The nursing staff who took care of the patient was blinded to the

intervention. Normal saline in a syringe was administered to the patients of group B as placebo along with the enteral erythromycin. The data was recorded by another blinded investigator.

Enteral feeding protocol

The enteral feed was given through the nasogastric tube, the position of which was confirmed by abdominal x ray and reconfirmation before each feed was done by injecting 10ml of air through a syringe and auscultating over stomach simultaneously.

Daily target energy requirement was calculated as 25kacla/kg/day based on actual body weight of the patient except in patients with BMI ≥ 30 kg/m2 where the daily energy target was 11-14 kcal/kg/day. The feed was given as intermittent boluses every 2 hourly. Total 11 feeds were given each day as break was given after 12 midnight feed to 4 AM. The calculated calorie requirement was divided in 11 feeds. Standard feed preparations were made (1kcal/ml). According to the ICU protocol, feeding intolerance was assessed by a 4-h measurement of gastric residual volume (GRV); patients with ≥500 mL or those who developed vomiting, regurgitation, abdominal pain, or abdominal distension during enteral
feeding indicated EFI.

Firstly, the assigned drugs were given alone in patients with EFI in each group. Thereafter, manual aspiration of gastric contents was measured before the next due feed. If GRV was less than 500 ml, enteral feed was continued and GRV was then measured every 4 hourly. However, if GRV was more than 500ml, the due feed was withheld and the aspirate was discarded. The feed was then restarted after 2 hours. The next GRV was measured according to the protocol. If this GRV was also more than 500ml, it was labelled as enteral feed failure and feed was withheld for 4 hours. It was then restarted as per the initial protocols. Intravenous maintenance fluid was given during the period when the feed was withheld. The data of primary and secondary outcomes were recorded. Total parenteral nutrition was started according to standard ICU protocol in case of treatment failure.

Statistical analysis

The results were analyzed using descriptive statistics and making comparisons among various groups. Categorical data were calculated using chi- square test and summarized as proportions and percentages (%) and quantitative data were calculated using Student's t-test and summarized as mean ± SD. A p value < 0.05 was considered statistically significant. The analysis was done in IBM SPSS ver 23.

Results

The baseline characteristics of the participants were comparable between the two groups

Table 1: Baseline patient characteristics

Characteristics of the patient		Group A (N=30)	Group B (N=30)	p value
Age (years) (mean ± SD)		54.47 ± 19.66	5 2.20± 16.63	0.632
Male [n (%)]		15 (50.0)	18 (60.0)	0.436
Female [n (%)]		15 (50.0)	12 (40.0)	
BMI (kg/m2) (mean ± SD)		23.85 ± 2.52	24.69 ± 2.81	0.227
Comorbidities	No comorbidity [n (%)]	9 (30.0)	14 (46.7)	0.639
	T2DM [n (%)]	4 (13.3)	3 (10.0)	
	COPD [n (%)]	2 (6.7)	1 (3.3)	
	HTN [n(%)]	7 (23.3)	9 (30.3)	
	COPD+ HTN [n (%)]	2 (6.7)	1 (3.3)	
	T2DM + HTN[n (%)]	4 (13.3)	1 (3.3)	
Diagnosis	Acute febrile illness [n(%)]	3 (10.0)	5 (16.7)	0.128
	Sepsis [n(%)]	4 (13.3)	5 (16.7)	
	Meningitis [n(%)]	2 (6.7)	1 (3.3)	
	Pneumonia [n(%)	2 (6.7)	1 (3.3)	
	CAD [n(%)]	3 (10.0)	0 (0.0)	
	CVA [n(%)]	3 (10.0)	9 (30.0)	
	RTI [n(%)]	1 (3.3)	3 (10.0)	
	Others [n(%)]	8 (26.7	6 (20.0)	
APACHE II score (mean ± SD)		19.40 ± 3.16	20.50 ± 3.64	0.216
Modified NUTRIC score (mean ± SD)		4.13 ± 1.41	4.93 ± 1.91	0.070
Time to start after admission (days)		2.13 ± 0.73	2.00 ± 0.83	0.512
Average calorie target		1523.33 ± 249.22	1587.50 ± 218.51	0.293
80% of target, the criteria of successful feeding		1218.67 ± 199.37	1270.00 ± 174.81	0.293

Data are reported as n (%) or mean (range)
SD – Standard Deviation, BMI – Body Mass Index , T2DM – Type 2 Diabetes Mellitus, COPD – Chronic Obstructive Pulmonary Disease, HTN -Hypertension , APACHE – Acute Physiology and Chronic Health Evaluation, NUTRIC – NUTrition Risk in the Critically ill
No significant difference was found between the two groups with respect to the baseline characteristics.

Table 2: Primary and secondary outcome

Outcome		Group A (N=30)	Group B (N=30)	p value
time to achieve successful feeding (hours)	24 - 48 [n (%)]	11 (36.7)	8 (26.7)	0.405
	72 - 96 [n (%)]	12 (40.0)	7 (23.3)	0.045
	> 96 [n (%)]	2 (6.7)	6 (20.0)	0.604
Average daily admission / target (mean ± SD)		85.32 ± 20.61	69.41 ± 35.86	0.039
Length of stays in hospital (days) (mean ± SD)		12.90 ± 3.77	11.37 ± 2.61	0.072
Hospital mortality [n (%)]		7 (23.3)	8 (26.7)	0.766
28 day mortality [n (%)]		8 (26.7)	10 (33.3)	0.573
Failure of treatment [n (%)]		5 (16.7)	9 (30.0)	0.222

Data are reported as n (%) or mean (range)
SD – Standard Deviation

Number of patients achieving successful feeding at 72-96 hours were significantly higher in group A. The average daily administered calorie -to-target calorie ratio was significantly more in group A then in group B. Rest of the secondary outcomes were comparable between the two groups.

Table 3 : Comparison of average GRV and average total Calorie

Average GRV ml (mean ± SD)	Group A	Group B	p-value
Day 1	741.43 ± 412.71	1362.67 ± 305.17	<0.001
Day 2	468.03 ± 281.27	1276.00 ± 248.47	<0.001
Day 3	412.70 ± 241.14	1056.77 ± 265.07	<0.001
Day 4	382.00 ± 330.51	953.00 ± 324.44	<0.001
Day 5	298.67 ± 296.98	763.60 ± 428.42	<0.001
Day 6	242.37 ± 278.60	630.67 ± 528.60	<0.001
Day 7	225.93 ± 317.16	860.47 ± 2273.09	0.135
Average total calorie (kcal) (mean ± SD)	**Group A**	**Group B**	**p value**
Day 1	781.90 ± 303.01	224.83 ± 198.79	<0.001
Day 2	1055.30 ± 331.27	311.50 ± 192.62	<0.001
Day 3	1110.63 ± 350.16	530.73 ± 242.78	<0.001
Day 4	1141.33 ± 398.24	634.50 ± 345.47	<0.001
Day 5	1224.67 ± 377.49	823.90 ± 436.34	<0.001
Day 6	1280.97 ± 353.88	956.83 ± 535.40	0.008
Day 7	1297.40 ± 408.26	1144.70 ± 590.63	0.249

The average Gastric Residual Volume (GRV) was lower in group A than in group B on the first 6 days. It was insignificantly different only on day 7. The average calorie intake was significantly higher in group A than in group B on the first six days.

Table 4 : Logistic regression analysis showing relationship of Failure to Treatment with probable predictors

Dependent : Failure of treatment

Predictors	B	S.E.	p- value	Exp(B)/OR	95%CIL for Exp(B)	95% CIU For Exp(B)
Group A	0.37	0.87	0.67	1.45	0.27	7.94
Group B	Ref.					
APACHE II score	0.21	0.17	0.21	1.24	0.89	1.73
Modified nutric Score	0.67	0.27	0.01	1.95	1.14	3.32
BMI	0.19	0.18	0.29	1.21	0.85	1.72
Constant	-13.77	6.55	0.04	0.00		

APACHE - Acute Physiology and Chronic Health Evaluation , BMI – Body Mass Index

The logistic regression analysis investigating the relationship between failure of treatment and its probable predictors revealed that higher nutrition scores increase the likelihood of treatment failure. APACHE II score and BMI did not have a significant effect on treatment failure.

Table 5 : Logistic regression analysis showing relationship of Time to achieve Successful feeding with probable predictors

Dependent : time to achieve successful feeding	Predictors	B	Std. Error	p- value	Exp(B)/ OR	95% CIL for Exp(B)	95% CIU for Exp(B)
72 - 96 hours	Intercept	-4.59	5.48	0.402			
	BMI	0.11	0.17	0.520	1.11	0.80	1.55
	APACHE II score	0.11	0.17	0.520	1.12	0.80	1.56
	Modified nutric score	0.00	0.64	1.000	1.00	0.29	3.51
	Group A	0.73	1.18	0.532	2.09	0.21	20.94
	Group B	Ref.					
> 96 hours	Intercept	-5.79	6.57	0.378			
	BMI	0.04	0.21	0.866	1.04	0.69	1.57
	APACHE II score	0.34	0.20	0.089	1.41	0.95	2.09
	Modified nutric score	0.18	0.75	0.810	1.20	0.28	5.18
	Group A	-3.06	1.19	0.010	0.05	0.00	0.48
	GroupB	Ref.					

Ref: 24-48 hours

The logistic regression analysis exploring the relationship between the time to achieve successful feeding and probable predictors showed that for the "72 - 96 hours" category, the "BMI" and " APACHE II score" variables did not significantly predict the time to successful feeding. Similarly, the "Modified NUTRIC score" showed no effect.

The same was observed for the “>96 hours” category. However, group A showed a significant negative association with achieving successful feeding beyond 96 hours, with an OR of 0.05 (95% CI: 0.00 to 0.48) and a p value of 0.010, indicating that this treatment was likely to reduce the time to successful feeding compared to group B

For the "72 - 96 hours" category, the "BMI" and " APACHE II score" variables did not significantly predict the time to successful feeding, with p-values of 0.520 and 0.520, respectively, and odds ratios (OR) of 1.11 and 1.12, indicating minimal impact. Similarly, the "Modified nutric score" showed no effect, with a p-value of 1.000 and an OR of 1.00. Group A showed a higher OR of 2.09 (95% CI: 0.21 to 20.94) with a p-value of 0.532, indicating no significant effect on the likelihood of achieving feeding success in 72 - 96 hours when compared to the reference group B. For the "> 96 hours" category, the "BMI" variable again had no significant impact, with a p-value of 0.866 and an OR of 1.04. The " APACHE II score score" had a marginal significance with a p-value of 0.089, showing an OR of 1.41 (95% CI: 0.95 to 2.09), suggesting a potential association with the time required to achieve successful feeding, though not statistically conclusive. The "Modified nutric score" did not significantly influence the outcome, with a p-value of 0.810 and an OR of 1.20. However, Group A showed a significant negative association with achieving successful feeding beyond 96 hours, with an OR of 0.05 (95% CI: 0.00 to 0.48) and a p value of 0.010, indicating that this treatment was likely to reduce the time to successful feeding compared to Group B.

In summary, the findings suggest that while BMI, Apache score, and Modified nutric score did not significantly affect the time to successful feeding, the group A was significantly associated with achieving successful feeding in fewer attempts, especially in those requiring more than 96 hrs.

Discussion

During critical illness, enteral nutrition is an important method for nutritional support, as it has greater benefits in preserving intestinal mucosal barrier function and fewer infective complication as compared to total parenteral nutrition. However, gastric motility is frequently impaired in patients with critical illness, thereby leading to feeding intolerance and may result in vomiting, feed reflux or regurgitation and pulmonary aspiration. These complications are associated with inadequate delivery of nutrition, high financial burden and high morbidity and mortality. Hence, it is important to identify and treat feeding intolerance in critically ill patients.

Prokinetic agents are currently considered as the first line of therapy for feeding intolerance. American Society for Parenteral and Enteral Nutrition (EN) and European Society for Parenteral and EN recommend the use of metoclopramide or erythromycin in critically ill patients with intolerance to enteral nutrition. [25] However, there are limited studies and data to compare the effects of prokinetics on EFI in critically ill patients.

In our study, the baseline demographic data were comparable in both the groups similar to the previous study done by Makkar et al. [26] who randomized 115 traumatic brain injury patients with feeding intolerance to receive metoclopramide, erythromycin or placebo eight hourly and Charoensareerat T et al. [27] who randomized 35 mechanically ventilated with feeding intolerance into metoclopramide with erythromycin and placebo group. They too didn’t find any significant difference in baseline characteristics of the study population.

The current study enrolled patients with multiple diagnosis, seizures and sepsis being the most common diagnosis in group A (13.3%) while cerebrovascular accident was the most common diagnosis in group B (30%), while Makkar et al. [26] included patients with traumatic brain injury only. Another study done by Nam Q. Nguyen et al. [28] included two groups, one that received only metoclopramide and other received only erythromycin, maximum patients in both the groups had respiratory failure. The chi square test

showed there was no statistically significance in the distribution of diagnosis. It was indicated that for whatever is the diagnosis for which the patient has been admitted in ICU, prokinetics are required for the feeding intolerance.

The severity of illness was classified according to the APACHE II score and Modified Nutric score in both groups, the difference was comparable between the two groups. Similarly, the study done by Makkar et al. [26] included only APACHE II score for severity but there was no co- relation between three groups while the study done by Charoensareerat T et al. [27] included both the scoring system for the severity and did not show any co relation with the outcome of the study.

The mean days from the admission to start of the both of the prokinetics was 2.13 days in group A while for group B was 2.00 days and the average target calories requirements in the group A was 1523.33 ± 249.22 kcal and for group B was 1587.50 ± 218.51 kcal. Achieving the target calorie, especially in critically ill patients with high nutrition risk, can improve the clinical outcome and also there is decrease in the mortality. However, no significant difference was observed in achieving 80% of the target calorie intake, which is a criterion for successful feeding, between the two groups. In both the groups the calories requirements were similar between the combination group and monotherapy with erythromycin, similar to the study done by Charoensareerat T et al. [27]. Heyland et al. [30] compared ulimorelin and metoclopramide for EFI in 120 patients and they too found similar rate of feeding success and no difference of safety profile between the two groups.

In the present study, the average GRV was calculated in each day for 7 days in both the group and was compared. According to a study by Mentec H et al. [29] GRV of > 500 ml is defined as the threshold to determine large GRVs and signifies withholding of enteral feeding. Heyland et al. [14] also diagnosed EFI when GRV was ≥ 500 ml. According to the recent American recommendations, a GRV of 250 mL is defined as the threshold for the early recognition of feeding intolerance and prompt therapy initiation in asymptomatic patients. We took the cut off of >500ml GRV to label as gastric feed intolerance.

On each day the values were compared between the groups and was clinically significant with p value of <0.05 while only on day 7 the GRV in between the two groups showed no statistical difference. It was concluded that the group receiving both the drugs had a lower GRV than only the erythromycin group, thereby indicating that patients with both the prokinetics had a better gastric tolerance than the group of patients receiving only one prokinetics. Landry et al. [30] showed that there was no difference in total GRV following administration of oral and intravenous erythromycin in normal subjects, whereas Pinto et al. [31] demonstrated the benefit of adding oral erythromycin to oral metoclopramide in improved feeding intolerance by lowering GRV in patients with traumatic brain injury who failed to respond to metoclopramide monotherapy.

Enteral nutritional intolerance manifests as increased gastric residual volume, abdominal distension and diarrhoea, and this poor feeding tolerance can result in increased risk of aspiration and pneumonia. All of these result in increased stay at ICU and increased mortality rates.[28] Prokinetics solves the problem by resolving feeding intolerance and reducing the average length of stay at the hospital. In our study the average duration of stay in patients of group A and group B were almost same, hence was statistically insignificant with p value of 0.072 ($p<0.05$) similar to the study by Charoensareerat T et al. [27].

In our study the mortality rate was less in group A that was (23.3%) while the group had more mortality rate of (26.7%), though non significantly. Similarly, Charoensareerat T et al. [27] found that the mortality rate was more in patients receiving only one pro kinetic. If we see the pattern of 28day mortality, there was not much difference among both the groups.
In our study the failure was more in patients receiving only erythromycin as the prokinetic as also seen by Charoensareerat T et al. [27] in their study in which the patients receive only one pro kinetic which was metoclopramide.

From the above study, we found that to improve feeding intolerance in critically ill patients, the need for pro kinetic therapy is a necessity and the combination therapy with metoclopramide with erythromycin can prove to be better modality in treating patients with

enteral feed intolerance.

Limitations

Our study had few limitations. Firstly, it was a single center study with its own standardized feeding protocol hence results can be different with different feeding protocols. Secondly, as intravenous erythromycin is not available in our country, enteral erythromycin preparation was used. Thirdly, the antibiotic effect of erythromycin was not taken into consideration, however, no adverse effect was noted in the groups.

Conclusion

The present study was carried out to compare the prokinetic effect of the monotherapy that is erythromycin alone versus the combination therapy with enteral erythromycin and intravenous metoclopramide in critically ill patients. In this study it was found that enteral erythromycin and intravenous metoclopramide given in combination had a better outcome in terms of time to achieve successful feeding, decreased GRV and improved calorie intake with no significant adverse effects.

Hence, the combination therapy may serve as a valuable strategy for optimising enteral nutrition delivery in the ICU. However, further larger studies are needed before integration of such combination regimen into clinical protocols.

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