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RESEARCH ARTICLE

Optimal dose and duration of enteral erythromycin as a prokinetic: A surgical intensive care experience

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ABSTRACT

Background: Enteral feeding has various advantages over parenteral feeding in critically ill patients. Acutely ill patients are at risk of developing enteral feeding intolerance. Prokinetic medications improve gastrointestinal mobility and enteral feed migration and absorption. Among the available prokinetic agents, erythromycin is the most potent. Erythromycin is used in different dosages and durations with variable efficacy. Intravenous erythromycin has an early and high rate of tachyphylaxis; hence, enteral route is preferred. Recently, the combination of prokinetic medications has been increasingly used because they accelerate the prokinetic action and decrease the adverse effects.

Aim: This study aimed to determine the optimal effective prokinetic dose and duration of administering enteral erythromycin in combination with metoclopramide in critically ill patients.

Patients and methods: This study has a prospective observation design. After obtaining permission from the medical research center of the institution, all patients in the surgical and trauma intensive care unit having enteral feed intolerance and those who were already on metoclopramide for 24 hour (h) were enrolled in the study. Patients' demographic data, diagnosis, surgical intervention, disease severity scores, erythromycin dose, duration of administration, any adverse effects, factors affecting erythromycin response, and outcome were recorded. All patients received 125 mg syrup erythromycin twice daily through a nasogastric tube (NGT). The NGT was clamped for 2 h, and half amount of previous enteral feeds was resumed. If the patient did not tolerate the feeds, the erythromycin dose was increased every 24 h in the increment of 250, 500, and 1000 mg

(Figure 1). Statistical significance was considered at $P < 0.05$. A total of 313 patients were enrolled in the study. Majority of the patients were male, and the mean age was 45 years.

Results: Majority (48.2%) of the patients (96) with feed intolerance were post laparotomy. Ninety percent (284) of the patients responded to prokinetic erythromycin therapy, and 54% received lower dose (125 mg twice daily). In addition, 14% had diarrhea, and none of these patients tested positive for *Clostridium difficile* toxin or multidrug resistance bacteria. The mean duration of erythromycin therapy was 4.98 days. The most effective prokinetic dose of erythromycin was 125 mg twice daily ($P = 0.001$). Erythromycin was significantly effective in patients with multiple organ dysfunction and shock ($P = 0.001$). Patients with high disease severity index and multiple organ dysfunction had significantly higher mortality ($p < 0.05$). Patients not responding to erythromycin therapy also had a significant higher mortality ($p = 0.001$).

Conclusion: Post-laparotomy patients had high enteral feed intolerance. Enteral erythromycin in combination with metoclopramide was effective in low dose and was required for short duration. Patients who did not tolerate feeds despite increasing dose of erythromycin had higher mortality.

Keywords: Brain injury, erythromycin, diarrhea, gastroparesis, gastrointestinal hypo mobility, laparotomy, metoclopramide, multiorgan dysfunction

INTRODUCTION

Enteral feeding in acute and critically ill patients has several advantages over parenteral feeding because it is cost effective, is easy to administer, facilitates efficient absorption of nutrients, stimulates intestinal blood flow, maintains gastrointestinal (GI) mucosal barrier to prevent bacterial translocation, reduces gut-associated lymphoid system stimulation to prevent pro-inflammatory stimulants, reduces septic complications, avoids total parenteral nutrition-induced immunosuppression, hastens healing, promotes weaning and recovery, and reduces muscle catabolism.[1] GI hypomobility, which hampers the tolerance of enteral feeds, is common in critically ill patients because of various reasons, such as medications, hyperglycemia, organ dysfunction, mechanical ventilation, and critical illness.[2] Prokinetic

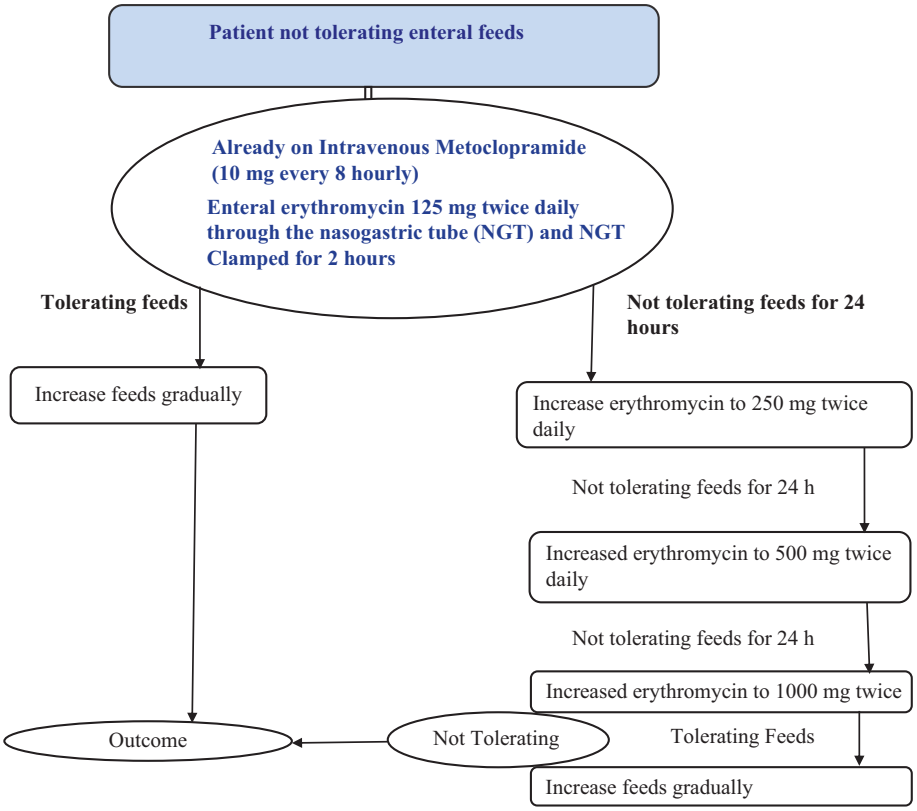


Figure 1. Administration method and increment of erythromycin dose with patient outcome.

medications are used to improve the GI motility and strengthen the enteral nutrition in critically ill patients. Commonly used prokinetic medications are cisapride, metoclopramide, domperidone, and erythromycin. However, cisapride is not used currently because of its cardiac toxicity.[2,3] Domperidone is a mild prokinetic rarely used in acutely ill patients because it causes hyperlactatemia and arrhythmia.[3] Metoclopramide is a milder prokinetic that causes tachyphylaxis and other side effects in critically ill patients.[4] A Chinese meta-analysis reported that intravenous erythromycin is effective in small doses and is more potent than metoclopramide.[5]

Enteral and intravenous (IV) erythromycin are used as a prokinetic agent. The enteral route of erythromycin is easy to administer and causes less tachyphylaxis and cardiac adverse effects compared with the intravenous route of administration.[6]

The effective oral or enteral prokinetic erythromycin dose and duration of therapy vary. Although the prokinetic dose of erythromycin is significantly lower than the antibiotic one, the prokinetic dosages of enteral erythromycin range from 100 – 125 mg two to three times per day to 250 – 500 mg every 8 h for 2 to 4 weeks.[7] The optimal prokinetic dose and duration of enteral erythromycin therapy have yet to be determined.[8]

Compared with single agents, the combination of metoclopramide and erythromycin exerts stronger prokinetic effect with decreased tachyphylaxis and other side effects.[8] *van der Meer et al.*, reported that the combined metoclopramide and intravenous erythromycin therapy exhibits stronger prokinetic action than either medication alone.[4]

This study aimed to determine the optimal prokinetic dose and duration of enteral erythromycin in combination with metoclopramide for the treatment of intensive care patients.

PATIENTS AND METHODS

Permission for this prospective observational study was obtained from the medical research committee (MRC) (permission number 9018/09). Given the study design and the common use of erythromycin as a prokinetic agent, the MRC waived the consent. Patients admitted in the surgical and trauma intensive care units (SICU and TICU, respectively) of the single tertiary health care facility from January 2009 to December 2018 were enrolled in the study.

Inclusion and exclusion criteria

Inclusion criteria were adult patients who were on metoclopramide and still not tolerating the enteral feeds in the SICU and the TICU.

Pediatric patients; patients with mechanical bowel obstruction, allergy to metoclopramide or erythromycin, and hepatic dysfunction or failure; and patients receiving other prokinetic agents (azithromycin, domperidone) and on intravenous erythromycin therapy were excluded from the study.

Data collection

Patients' demographic data, severity of the disease by Glasgow coma score (GCS), sequential organ failure assessment (SOFA) score, severity of trauma by injury severity score (ISS), type of shock, multiple organ dysfunction, use of opioids or patient in coma, amount of enteral feed up on feed intolerance, dose of erythromycin, response to erythromycin, cardiac arrhythmias, diarrhea, and outcome were recorded before removing the patients from the SICU.

A total of 313 patients were enrolled in the study. Majority of patients were male (77.6% vs 22.4), and the mean age was 45 years.

Prokinetic medication dosage

All patients who did not tolerate feeding for the initial 24 – 48 h and already on regular intravenous metoclopramide (10 mg every 8 hour) were included in the study. The initial dose of erythromycin was 125 mg twice daily through a nasogastric tube (NGT). The NGT was clamped for 2 h, and the feed restarted with half of the previous amount of enteral feeds. If patients continued to have enteral feed intolerance, the dose of erythromycin was doubled every 24 h up to the maximum of 1000 mg twice daily. For instance, if the patient did not tolerate feeds for 24 h on the initial dose, the enteral erythromycin dose was increased to 250 mg twice daily; if the patient still did not tolerate the feed for 24 h on 250 mg erythromycin, the dose was increased to 500 mg twice daily; and if the patient still did not tolerate the feed by the next 24 h, the erythromycin dose was increased to a maximum of 1000 mg twice daily (Figure 1). Patients were retained in the same dose group if they started to tolerate the enteral feeds. For instance, patients who started to tolerate the feed at 125 mg of erythromycin were placed in the 125 mg dose group.

Enteral feeding intolerance was diagnosed if the patient had a gastric residual volume of more than

500 mL, regurgitation, abdominal distension or evidence of gastroparesis on X-ray within 24 – 48 h of starting enteral feeds. Gastric residual volume was calculated by aspirating every 4 h from the NGT.

Optimal dose and duration of prokinetic action of erythromycin and other definitions

The optimal prokinetic dose of erythromycin is the dose at which patients started to tolerate the enteral feeds. The optimal duration of erythromycin is the time duration of erythromycin therapy on which the patient started to tolerate the enteral feeds. The amount of enteral feeding is the amount of enteral feed received by the patients when feed intolerance started. The calculated QT (QTc) interval was calculated as the time from the start of the Q wave to the end of the T wave.

Statistical analysis

Data were entered and analyzed using SPSS version 23. Descriptive statistics in the form of mean and standard deviations (Mean ± SD) was performed for interval variables. Frequency with percentages was calculated for categorical variables. Chi-square tests were performed to determine the association between categorical variables, between prokinetic erythromycin response and nonresponse groups, and between the survived and nonsurvived groups. Student t tests (Un-paired) were performed to determine statistically significant mean differences between interval variables and survived vs. non-survived groups as well as prokinetic erythromycin response vs nonresponse groups. The interval variables were detected as normal by Kolmogorov – Smirnov tests. Multivariate logistic regression analysis was performed for important and significant variables at univariate analysis to identify risk factors for mortality. Adjusted odds ratios and 95% C.I. with p value were presented. Multivariate analysis for prokinetic erythromycin response was not performed because of the insufficient sample size in the nonresponder category. Statistical significance was considered at $P \leq 0.05$ (two tailed).

RESULTS

Distribution of demographic and clinical characteristics

Majority of the patients (49.86%) were post-surgical, 37.39% post-trauma, and 10.8% patients were of spontaneous subarachnoid hemorrhage and intracerebral hemorrhage (Table 1)). The patients' division by diagnosis are shown in Figure 2. Majority of the patients were post laparotomy for acute abdomen followed by traumatic brain injury patients. Majority of our patients were without any comorbidities (66.5%), and 17.57% of the patients had diabetes mellitus and hypertension (Table 1). In addition, 50% of the patients had septic shock, 77% were complicated by septic shock, and 85% were mechanically ventilated. Majority (90%, 284) of the patients responded to the prokinetic action of erythromycin and started to tolerate the enteral feeds. Majority of the patients (54%) received minimal dose of erythromycin (125 mg twice daily). The frequent adverse effect of erythromycin was diarrhea (14.08%), and prolongation of QTc occurred in 2.8% of cases. None of the patients were positive for *Clostridium difficile* (CD) toxins in the stool and none of the patients showed growth of resistant bacteria to erythromycin. (Table 1)

Demographic and clinical variables

Table 2 shows the descriptive demographic and clinical variables. Patient's mean GCS was 11, the ISS was 35, and the mean SOFA score was 9.65. The mean feeding amount was 49.18 mL at the time of intolerance, the mean duration of erythromycin therapy was 4.98 days, and the mean length of ICU stay was 16.51 days. (Table 2)

Variables associated with prokinetic response of erythromycin

Table 3 shows the various variables affecting the erythromycin prokinetic response. No significant difference in response to erythromycin was found between patient sex and comorbidities. Erythromycin exerted significant prokinetic effects on patients with multiple organ dysfunction ($p = 0.001$) and patients in shock ($p = 0.001$). The lower erythromycin dose of 125 mg twice daily elicited significantly higher prokinetic response ($p = 0.001$) than the higher dosages.

The prokinetic response of erythromycin was not significant in ventilated patients and in patients on opioid or thiopental medications. (Table 3)

With regard the age group of the patients, the younger patients (45 ± 17.03 years vs. 48 ± 21.05 years) had a significant response to the prokinetic effect of erythromycin ($p = 0.03$). The GCS was significantly higher (11.32 ± 3.6 vs. 9.31 ± 4.7) in

Table 1. Distribution of demographic and clinical characteristics

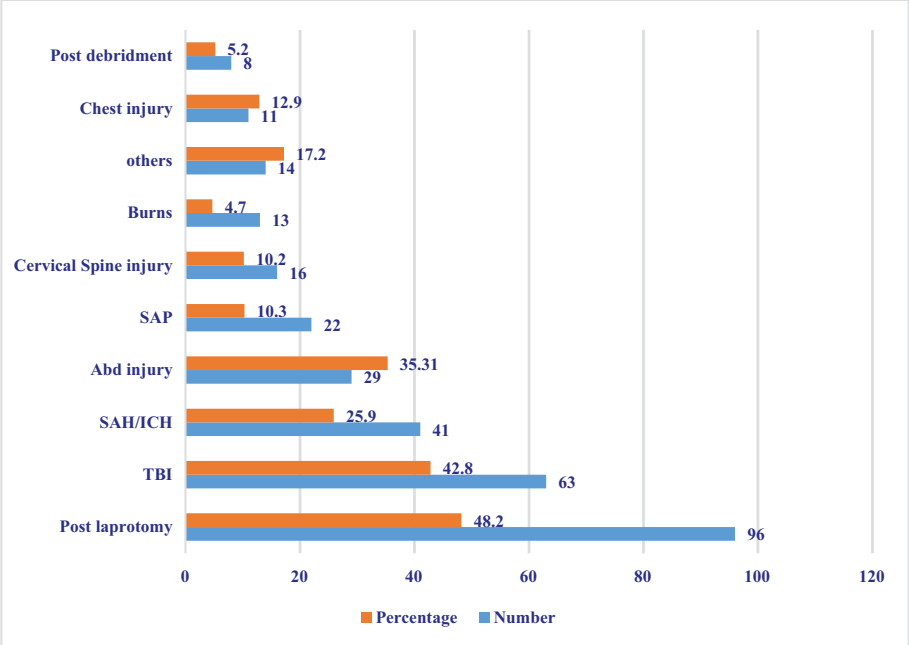
Variable		Frequency (n)	Percentage (%)
Sex	Male	243	77.6
	Female	70	22.4
Diagnosis	Post-surgical	156	49.86
	Post Trauma	119	37.39
	*SAH/ICH	34	10.88
	Post Cardiac arrest	4	1.28
Co morbidities	None	208	66.5
	DM	58	17.57
	HTN	58	17.57
	Others	12	3.8
Shock	None	112	35.8
	Septic	159	50.8
	Hemorrhagic	24	7.7
	Cardiogenic	18	5.8
MODS (Multiorgan dysfunction)	Yes	241	77
	No	72	23
Erythromycin dosage	125 mg	169	54
	250 mg	96	30.7
	500 mg	32	10.2
	1000 mg	16	5.1
Ventilated	Yes	268	85.6
	No	45	14.4
Medications	Opioids	298	95.2
	Thiopental	10	3.2
	None	5	1.6
Response to Erythromycin	Yes	284	90.7
	No	29	9.3
Adverse effects of Erythromycin	Diarrhea	44	14.05
	**Prolonged QTc interval	9	2.8
	Clostridium defile	0	0
	Bacterial Resistance	0	0
Outcome	Survived	274	87.6
	Died	39	12.5

*Spontaneous Subarachnoid hemorrhage/Intracerebral hemorrhage
**Calculated QT interval in electrocardiogram

the patients who responded to erythromycin ($p = 0.001$). When the enteral feeding amount at feed intolerance was high (49.76 ± 35.61 mL vs. 43.57 ± 30.69 mL), erythromycin was significantly effective ($p = 0.02$). The duration of erythromycin therapy (4.76 ± 4.07 days vs. 7.10 ± 3.69 days) was significantly lower in the response group than in the nonresponse group ($p = 0.003$). (Table 3)

Comparison of variables to patient outcome

Table 4 shows the variables affecting patient outcome. Patient sex, age, and injury severity score exerted no significant influence on patient outcome. The SOFA score was significantly high and the GCS was significantly low in patients with poor outcome ($p = 0.04$ and 0.05 respectively). Patients with multiorgan dysfunction and ventilation had a significantly higher mortality than their counterparts ($p = 0.001$ and 0.05 respectively). Patients not responding to the prokinetic effect of erythromycin and unable to tolerate the feeds had a significantly higher mortality than their counterparts ($p = 0.001$). The duration of erythromycin therapy and the length of intensive care stay were significantly higher in patients who died than in patients who survived ($p = 001$). Overall, 39 patients died (12.5%) in our study.



TBI: Traumatic brain injury
SAH/ICH: Spontaneous subarachnoid hemorrhage/Intracerebral hemorrhage
Abd Injuries: Abdominal injuries
SAP: Severe acute pancreatitis

Figure 2. Patient division by diagnosis

Multivariate analysis of risk factors associated with mortality

Table 5 shows the variables for mortality. Hypertensive patients, no prokinetic response, and long ICU stay were associated with the increased risk for mortality. Multivariate analysis for prokinetic erythromycin response was not performed because of the insufficient sample size in the nonresponder category.

DISCUSSION

Enteral feeding intolerance frequently occurs in critically ill patients because of acute critical illness and multiple organ dysfunctions, causing GI hypomobility. Prokinetic medications improve gut motility and nutrient absorption.[9] Approximately 60% of critically ill patients develop enteral feeds intolerance, and more than half of these patients require prokinetic medications.[10]

Erythromycin is a potent prokinetic agent available in the market, after many countries had withdrawn cisapride from medical practice.[2,3] Although erythromycin has been available since the 1950s, its use as a prokinetic drug started only in the early 1990s.[11] Erythromycin acts on motilin receptors in the stomach and the duodenum, improving gastric emptying and motility

Table 2. Descriptive statistics of demographic and clinical variables

Variables	Mean and Standard Deviation (± SD)
Age (years)	45 ± 17.43
GCS (Glasgow coma scale)	11.14 ± 3.82
ISS (Injury Severity score)	35.4 ± 13.7
*SOFA Score	9.65 ± 4.61
Enteral Feeding Amount (ML)	49.18 ± 35.13
Erythromycin Duration (Days)	4.98 ± 4.1
ICU (Intensive care Unit) Stay (Days)	16.51 ± 21.45

*SOFA Score: Sequential Organ Failure Assessment Score

Table 3. Variables associated with prokinetic response of erythromycin

Variable	Response (284)	No Response (29)	P value
Age (years)	284(45 ± 17.03)	29 (48 ± 21.05)	0.03
Sex (Male)	223 (78.5%)	20 (69.0%)	0.17
Nationality Qatari	71 (25%)	8 (27.6%)	0.76
DM	47 (16.5%)	8 (27.6%)	0.14
HTN	47 (16.5%)	8 (27.6%)	0.14
Others	11 (3.9%)	3 (10.3%)	0.10
*MODS	212 (74.6%)	29 (100%)	0.001
Ventilation	241 (84.9%)	27 (93.1)	0.20
Shock	133 (46.8%)	26 (89.6%)	0.001
Erythromycin Dosage			
125 mg	166(58.5%)	3(10.3%)	0.001
250 mg	92(32.4%)	4(13.8%)	
500 mg	21(7.01%)	11(37.9%)	
1000 mg	5(1.8%)	11(37.9%)	
Opioids	266(95.3%)	26(92.9%)	0.75
Thiopental	8(2.9%)	2(7.1%)	0.61
ISS (Injury Severity score)	95 (35.29 ± 13.90)	6 (36.66 ± 11.97)	0.70
**SOFA Score	280 (9.23 ± 4.5)	29 (13.72 ± 3.4)	0.12
GCS (Glasgow coma scale)	284 (11.32 ± 3.6)	29 (9.31 ± 4.7)	0.001
Feeding Amount	270 (49.76 ± 35.61)	28 (43.57 ± 30.69)	0.02
Erythromycin Duration	284 (4.76 ± 4.07)	28 (7.10 ± 3.69)	0.003
ICU stay in days	283, 16.07 ± 20.92	29 (20.79 ± 26.14)	0.12

Figures are given frequency n (%) and mean ± standard deviation (SD)
*MODS: Multiple organ dysfunction syndrome
**SOFA: Sequential organ failure assessment

Table 4. Variables associated with patient outcome

Variable	Survived (274)	Dead (39)	P value
Age (Years)	274 (44± 16.99)	39 (49± 20.02)	0.10
Sex (Male)	217 (79.2%)	26 (66.7%)	0.06
Nationality Qatari	66 (24.1%)	13 (33.3%)	0.21
DM	46 (16.8%)	9 (23.1%)	0.22
HTN	42 (15.3%)	13 (33.3%)	0.01
Others	11 (40%)	3 (7.7%)	0.24
*MODS	203 (74.1%)	38 (97.4%)	0.001
Ventilation	231 (84.3%)	37 (94.9%)	0.05
Shock	143 (58.4%)	16 (64%)	0.23
Erythromycin response	265 (96.7%)	19 (48.7%)	0.001
Opioids	255 (95.1%)	37 (94.9%)	0.75
Thiopental	8 (3.0%)	2 (5.1%)	0.61
ISS (Injury Severity score)	87 (34.31± 13.51)	14 (42.00± 13.83)	0.61
***SOFA Score	270 (9.02± 4.43)	39 (13.97± 3.26)	0.04
GCS (Glasgow coma scale)	274 (11.43± 3.65)	39 (9.07± 4.27)	0.05
Feeding Amount	260 (45.25± 33.37)	38 (76.05± 35.45)	0.30
Erythromycin Duration	273 (4.28± 2.54)	39 (9.79± 7.95)	0.001
ICU (Intensive care unit) Stay (days)	273 (14.89± 19.987)	39 (27.79± 27.545)	0.001

Figures are given frequency n (%) and mean± standard deviation (SD)
*MODS: Multiple organ failure
**SAH/ICH: Spontaneous subarachnoid hemorrhage/Intracerebral hemorrhage
***SOFA: Sequential organ failure assessment

Table 5. Risk factors associated with mortality

Variables	Adjusted Odds ratio	95% C.I.	P value
Age (year)	0.99	0.97 – 1.02	0.64
Sex (Male)	0.95	0.35 – 2.56	0.91
Nationality Qatari	1.04	0.39 – 2.82	0.94
Hypertension (HTN)	3.16	1.07 – 9.36	0.04
Prokinetic response	0.05	0.02 – 0.15	0.001
*ICU stay (days)	1.02	1.01 – 1.04	0.02

*ICU: Intensive care unit

with the accelerated amplitude and frequency of gastric and duodenal smooth muscle contractions.[12] Although IV erythromycin in various dosages is commonly used as a prokinetic drug, low doses of IV erythromycin are equally effective.[13,14] In addition, enteral erythromycin administration is easy and has few side effects.[6,13,15] However, the optimal prokinetic dose and duration of enteral erythromycin remain unknown.

Maclaren et al compared sequential single doses of metoclopramide, erythromycin and cisapride in a randomized study and concluded that metoclopramide and cisapride exert better prokinetic response than erythromycin.[16] A recent prospective multicenter study has compared metoclopramide and erythromycin and concluded that both exert equal prokinetic effects.[17] Recent studies comparing cisapride and domperidone with erythromycin are lacking, considering that these agents are infrequently used in ICU patients because of their high rate of adverse events and the questionable use of metoclopramide as a prokinetic in these patients.[4,11,13]

The combination of mild prokinetic and intravenous erythromycin is effective with few adverse effects.[18,19] We used enteral erythromycin in incremental doses in patients not responding to intravenous metoclopramide.

Lu et al. performed a prospective randomized study and found that the combination of metoclopramide and intravenous erythromycin has better prokinetic effect than either of the prokinetic agents with lesser adverse effects in intensive care patients.[20] *Sebrechts et al.* performed a serial ultrasound evaluation of gastric emptying and recommended the combination of centrally acting prokinetic domperidone or metoclopramide and locally acting erythromycin for enhanced gastric empyting.[21] *Shah S et al.* mentioned that "pulse therapy" comprising a combination of metoclopramide and erythromycin is effective in patients with severe gastroparesis.[22]

Majority of our patients with enteral feed intolerance are those that underwent laparotomy and those with traumatic or atraumatic brain injury. To feed or not to feed after laparotomy is a practical clinical question, and the answer is to go early for enteral feeding, considering that postoperative dysmotility predominantly affects the stomach and colon, with the small bowel recovering normal function 4 – 6 h after laparotomy.[23] Up to 80% of patients with brain injury have gastroparesis because of the raised intracranial pressure.[24]

Various patient comorbidities affect GI motility. Majority of our patients were without comorbid conditions, but they were critically ill, having multiorgan dysfunction and shock. These comorbidities cause GI hypomobility and feed intolerance, and 59% of shock patients are expected to have gut hypomobility.[25] Majority of our patients responded to the prokinetic effect of erythromycin; interestingly, a majority of these patients received a low enteral dose of erythromycin (125 mg twice daily). The adverse effects of erythromycin were comparatively less in our patients because diarrhea occurred in only 14% patients, and none of them tested positive for CD toxins. *Nguyen et al.* 2008 reviewed 143 patients receiving erythromycin prokinetic dose for a week and had diarrhea, but none of them were tested positive for CD toxins.[26] The hypothesis for not developing CD toxins after erythromycin therapy is that the prokinetic effect and increased GI mobility prevent the colonization and growth of the pathogenic bacteria in the GI tract.[27] The reported incidence of diarrhea in patients with prokinetic erythromycin therapy is dose dependent and is 30%, whereas that in patients with the combination of erythromycin and metoclopramide therapy is 49%.[27] The low incidence of diarrhea in our study may be due to the low dosage of erythromycin. Our patients with increased stool frequency also tested negative for CD toxins. Limited reports are available in the literature about the prokinetic use of erythromycin

and the development of resistant bacteria or increased incidence of CD diarrhea.[25,26] We did not have fatal cardiac arrhythmias, and only 2.8% patients developed prolongation of QTc interval. This result may be due to our low dose and enteral route of erythromycin.

A high dose and intravenous route of erythromycin administration increase fatal arrhythmias and QTc.[11] *Roe NA et al.* reported an incidence of 29.8% QTc prolongation in patients receiving prokinetic medications.[28] The mean duration of erythromycin in our patient population was 4.98 days, which is comparatively shorter than that described in the literature.

The effective enteral prokinetic dose of erythromycin remains controversial. *Camilleri* described that the effective prokinetic enteral dose of erythromycin is 250 mg^3 times a day for a week.[29] By contrast, *Grant and Thomas* mentioned that enteral 50 – 100 mg of erythromycin four times a day exerts better prokinetic effects.[9] Our effective prokinetic dose (125 mg twice daily) is much lower than the above described dosages. The presence of various comorbidities may lead to increased gastroparesis, but no significant difference in the prokinetic erythromycin response was found among our patients with comorbid conditions.[22]

The gastrointestinal tract is a commonly affected organ in multiorgan dysfunction syndrome (MODS), manifested by gastroparesis, regurgitation, vomiting, and bowel dysfunctions.[30] In our study, 77% patients had MODS and enteral feed intolerance, but they responded to the prokinetic effect of erythromycin significantly.

Patients in shock and on vasopressor therapy have a better outcome if they are on enteral feed than if they are not.[31] In our study, patients in shock and those not tolerating feeds responded well to the prokinetic erythromycin effects and started to tolerate the feeds.

Elderly patients have an increased risk for enteral feed intolerance because of various factors.[32] Fortunately, our patients were comparatively young, and the younger patients had a better prokinetic response than the older patients.

The GCS was higher in our patients with a better response to erythromycin than in those with a poor response to erythromycin. The high volume of feeding in the presence of GI hypomobility would be a risk for enteral feed intolerance. In our study, this group of patients showed a significantly better prokinetic response to erythromycin therapy than their counterparts.[33] The duration of erythromycin therapy was significantly shorter in our study than in other studies, and the number of patients who responded to erythromycin was greater than that of patients who did not. This result can be ascribed to our protocol, where erythromycin doses were increased in increments every 24 h.

Several studies about patients with a high severity of illness, MODS, severe trauma, or severe traumatic brain injury stated that these patients have a longer ICU stay and higher mortality when compared with their counterperts.[34] The important finding from our study was that the patients not responding to the prokinetic action of erythromycin therapy and who were unable to tolerate the enteral feeding had a significantly higher mortality than their counterparts.

Limitations of our study include that it was a single-center study and the patients were not randomized to treatment and control arms. Blinding was not done in the study. There might be some unknown confounding factors involved which can be further clarified in a larger multicenter and blinded randomized control trial.

CONCLUSION

Patients with laparotomy and brain injury had frequent feed intolerance. In combination with metoclopramide, the optimal prokinetic dose of enteral erythromycin was 125 mg twice daily and the optimal duration of therapy was 5 days in intensive care patients. Enteral erythromycin is a safe prokinetic agent with few non-fatal adverse effects. Erythromycin has a good prokinetic response in patients with organ dysfunction and shock. Patients with persistent feed intolerance even with a high dose of erythromycin had poor outcome.

Double-blind randomized controlled trials are required to validate our data and conclusion.

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