



Metoclopramide as intermittent and continuous infusions in critically ill patients: a pilot randomized clinical trial

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Aim: Metoclopramide is commonly used as a prokinetic agent in critically ill patients with enteral feeding intolerance. In this study, noninferiority of metoclopramide as intermittent versus continuous infusion was examined in critically ill patients with enteral feeding intolerance. **Methods:** Forty critically ill adults patients were assigned to receive metoclopramide as either intermittent (10 mg every 6 h) or continuous (2 mg/h) infusion. Frequency of feeding intolerance and adverse effects of metoclopramide were assessed during 7 days of study. **Results:** Number of patients with feeding intolerance during different times of the course was not different between the groups. Although not statistically significant, diarrhea and cardiac rhythm were more common in continuous than intermittent infusion group. **Conclusion:** Continuous and intermittent infusions of metoclopramide showed equivalent effectiveness in critically ill patients.

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Nutritional support has an essential role in patient care during the acute and severe illnesses [1,2]. Decreased morbidity, mortality, length of hospital stay and cost have been shown following appropriate metabolic support in critically ill patients [1–6]. Due to the different baseline diseases, severity of acute illnesses, type of injury and stress, concomitant organ failure and basic nutritional status, critically ill patients have different nutritional requirements. Up to 50% of critically ill patients did not receive the daily nutritional needs during the hospitalization course [7–9].

Considering protection of gastrointestinal (GI) integrity, improving mucosal growth and GI motility, minimizing infectious complications, preservation of immune system function, decreasing antigens leak from gut and helping glucose control, enteral feeding is recommended as preferred route of nutritional support in critically ill patients [10–12].

Enteral feeding intolerance is common in patients during the acute and severe illnesses [13]. Impaired GI motility is known as main cause of feeding intolerance in critically ill patients [14,15]. Several strategies including prokinetic agents are recommended to resolve feeding intolerance in critically ill patients [16–19]. From these agents, metoclopramide with rapid acting effect on GI motility showed promising results in last experiences [20–27].

In controlling of chemotherapy-induced nausea and vomiting, continuous infusion of metoclopramide was more effective than intermittent infusion in cancer patients [28,29]. Up to now, only intermittent infusion of metoclopramide was examined as a prokinetic agent [30–34]. Continuous infusion of metoclopramide may be equivalent or more effective than intermittent infusion in improving feeding intolerance in critically ill patients. This idea was examined during a

pilot randomized clinical trial in critically ill patients with feeding intolerance.

Materials & methods

This open-labeled, randomized, clinical trial (ID:IRCT201601213449N20) was performed during a 12-month period from early January 2015 to February 2016 at general ICU of Imam Khomeini hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran. The institutional review board and the medical ethics committee of the university approved the study (ethical code number: IR.TUMS.REC.1394.784) and all patients or their family members signed and approved the study protocol.

Adult critically ill patients (older than 18 years old) with enteral feeding intolerance who were candidate to receive a prokinetic agent were screened. Patients with history of seizure, head trauma, elevated intracranial pressure, GI obstruction, arrhythmia, metoclopramide hypersensitivity and extrapyramidal reactions were excluded. Finally, 42 eligible patients were assigned to receive metoclopramide either 10 mg every 6 h as intermittent infusion (during 5 min) or 2 mg/h as continuous infusion. Patients in the continuous infusion group did not receive loading dose before starting the infusion. Simple randomization method was used for patients' allocation. The drug was administered through a central vein catheter using syringe pump. All patients were mechanically ventilated, had nasogastric feeding tube and received metoclopramide for 7 days. Metoclopramide was stopped if caused seizure or arrhythmia accompanied with hemodynamic instability.

Recruited patients were daily followed regarding enteral feeding intolerance. The enteral feeding protocol was constant during the study period. Based on the ICU protocol, standard enteral feeding formula was started with dose of 50 ml every 3 h as bolus feeding and was increased gradually every 6 h up to 200 ml every 3 h based on patient's tolerance. Absence of vomiting, regurgitation, abdominal distention and diarrhea was considered as feeding tolerance. Regurgitation was defined as backflow of feeding material from nasogastric tube.

Primary end point of the study was improving in enteral feeding intolerance. During the survey, gastric residual volume was measured every 6 h for each patient. At these times, feeding tube was aspirated and yielded volume was recorded as residual volume. Enteral feeding intolerance was defined as gastric residual volume equal to or greater than 250 ml concomitant with symptoms of nausea, vomiting and regurgitation or gastric residual volume more than 500 ml during the tube feeding.

Daily calorie and protein intake and time to reach the calorie and protein goals were evaluated for all patients. Mean daily calorie and protein intake of each patient was calculated considering total volume of daily enteral feeding and ingredients of the used formula (Standard EnteraMeal®). Mean calorie and protein requirements of each patient were calculated according the American Society for Parenteral and Enteral Nutrition recommendations [3].

Secondary end point of study was evaluating safety of metoclopramide through different routes of administration. During the study course (7 days), patients were monitored regarding metoclopramide related adverse effects including hemodynamic instability and cardiac rhythm disturbances, extrapyramidal reactions, seizure and diarrhea. Naranjo adverse drug reactions probability scale was used for causality assessment of the adverse effects [35]. Recruited patients also were followed for ICU outcome; discharge or death.

Metoclopramide significantly reduced residual volume from 268.7 ± 112.3 ml to 57.0 ± 23.1 ml in critically ill patients with feeding intolerance [31]. Considering mean $\pm$ standard deviation of change in residual volume after metoclopramide administration, sample size of the study was calculated by including $\alpha = 0.05$ and 80% power ($1 - \beta = 0.8$).

All statistical evaluations were done using SPSS version 17 software. The distribution of continuous variables was evaluated using the Kolmogorov Smirnov test. Independent t-test and Mann–Whitney test were used for comparing mean $\pm$ standard deviation of normally and non-normally distributed continuous variables, respectively. Chi square or Fisher's exact test was used to evaluate probable associations between categorical variables. Repeated measure ANOVA was used for assessment of within and between groups' differences in frequency values of feeding intolerance during the course. p-value < 0.05 was considered significant.

Results

At first, 42 patients with the inclusion criteria of study were recruited. However, two patients were excluded during the course and finally 40 patients completed the study protocol (Figure 1).

Patient characteristics, reasons for ICU admission (surgical or medical and primary underlying disease), medications and outcome (discharge vs death) in each group are shown in Table 1. Hemodynamic and laboratory parameters of the patients are shown in Table 2. These characteristics were comparable between the groups.

Mean values of daily calorie intake in the continuous and intermittent infusion groups was 1108.96 ± 429.79 and 1176.53 ± 401.40 Kcal, respectively ($p = 0.64$). Patients in the continuous infusion group received

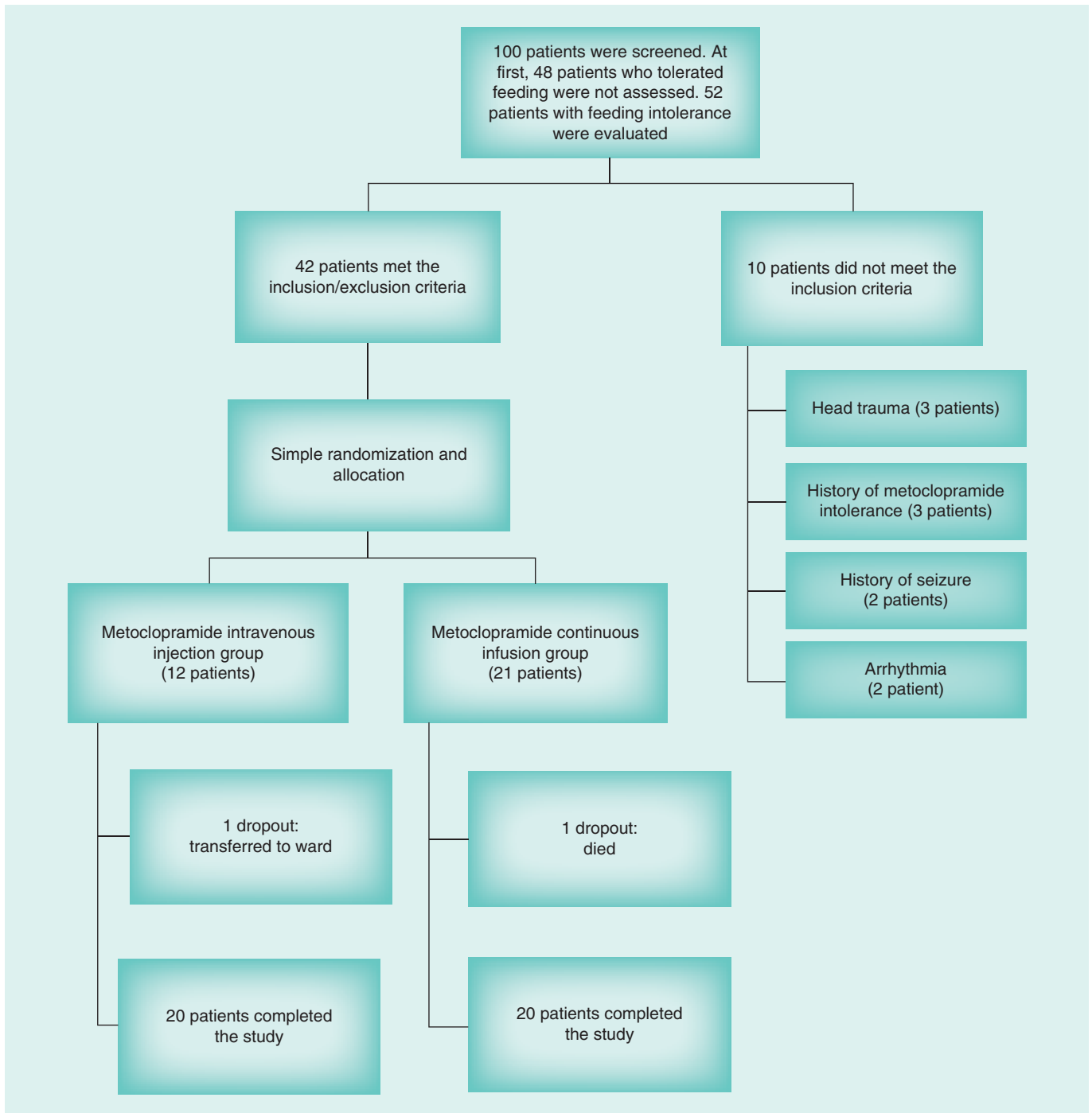


Figure 1. Consolidated Standards for Reporting Trials flowchart of the study.

39.96 ± 16.20 g/day protein, whereas this was 43.24 ± 15.49 g/day in the intermittent infusion group ($p = 0.55$). In the continuous and intermittent infusion groups, one (5%) and four (20%) patients reached to the calorie goal in first 12 h of the study course ($p = 0.04$). However, 10 (50%) and 8 (40%) patients in the continuous and intermittent infusion groups did not reach to the calorie goal during 7 days ($p = 0.38$).

Time to reach the protein goal was comparable between the groups. In each group of continuous and intermittent infusion, nine (45%) patients did not reach the protein goal during the follow-up period ($p = 0.12$).

Median ± IQR (25–75) of days with enteral feeding intolerance were 1 (0–2.75) and 0.00 (0.00–0.00) in the continuous and intermittent infusion groups, respectively ($p = 0.13$). In most days, number of

Parameter	Continuous infusion group (n = 20)	Intermittent infusion group (n = 20)	p-value
Age (years); mean $\pm$ standard deviation	60.95 $\pm$ 20.23	61.10 $\pm$ 19.37	0.98
Gender (n):			
– Female	8	6	0.26
– Male	12	14	
Weight (kg); mean $\pm$ standard deviation	69.55 $\pm$ 17.19	65 $\pm$ 11.35	0.33
ICU admission (n):			
– Surgical	14	11	0.25
– Medical	6	9	
APACHE score; median (IQR 25–75)	18 (14–22)	18 (16–20)	0.37
Duration of ICU stay before recruitment to the study (days); mean $\pm$ standard deviation	3.02 $\pm$ 1.18	2.48 $\pm$ 1.39	0.34
Baseline diseases (n):			
– CV diseases	6	6	0.63
– DM	2	1	0.50
Neuropsychiatric disease (n):	3	1	0.53
– CV diseases and DM	2	2	0.69
– CV and neuropsychiatric diseases	1	1	0.75
– DM and neuropsychiatric disease	0	3	0.11
– Respiratory diseases	1	0	0.50
– CV and respiratory diseases	1	0	0.50
– None	5	7	0.22
Medications (n):			
– Opioid analgesics	5	5	0.64
– Vasopressors	8	7	0.61
– Nitrates	4	5	0.50
– Sedative	12	8	0.17
– Nonopioid analgesic	5	5	0.30
– Calcium channel blocker	1	1	0.75
– Laxatives	9	10	0.50
– Anticonvulsants	6	4	0.35
Outcome (n):			
– Discharge	17	18	0.50
– Death	3	2	

APACHE: Acute Physiology And Chronic Health Evaluation; CV: Cardiovascular; DM: Diabetes mellitus; IQR: Interquartile range; SD: Standard deviation.

patients with feeding intolerance was comparable between the groups. However in days 2 and 3, number of patients with feeding intolerance in the intermittent infusion group was significantly less than the continuous infusion group ($p = 0.03$).

Change in frequency of feeding intolerance during the study course was not significant for both within ($p = 0.23$) and between ($p = 0.11$) groups comparisons.

GI adverse effect of metoclopramide occurred more frequently in the continuous than intermittent infusion group. Diarrhea occurred in three (15%) and one (5%) patients in the continuous and intermittent infusion groups, respectively ($p = 0.05$).

Cardiac rhythm disturbances were detected in five (25%) and two (10%) patients in the continuous and intermittent infusion groups respectively ($p = 0.54$).

Sinus tachycardia and atrial fibrillation were detected in two (10%) and three (15%) patients in the continuous infusion and one (5%) and one (5%) patients in the intermittent infusion group, respectively. Hemodynamic parameters were stable in patients with cardiac rhythm disturbances. No episode of seizure or extrapyramidal reactions was detected in the patients. Based on the Naranjo scale, all metoclopramide adverse effects were categorized as possible.

Discussion

The results of the present study showed equivalent effectiveness of metoclopramide when given in critically ill patients as prokinetic to improve intolerance to the enteral feeding. Metoclopramide works with different mechanisms in improving feeding intolerance. It has potent central and peripheral dopamine (D2) and weak 5-HT₃ antagonistic effects. Other effects of metoclopramide are 5-HT₄ agonistic activity and acetylcholine release from gut neurons. These effects improve transmission of acetylcholine at muscarinic receptors and consequently facilitate GI motility [24–26].

The recommended metoclopramide dose as a prokinetic agent is 10 mg four-times per day through slow intravenous injection [22]. Effectiveness and safety of metoclopramide were compared with other prokinet-

ics in critically ill patients. In these studies, metoclopramide was used as 10 mg every 6–8 h as intravenous injections for adults [30–34].

In a randomized, placebo-controlled, crossover study prokinetic effect of metoclopramide was compared with erythromycin, cisapride and placebo. Considering gastric residual volume, there was no significant difference between the compounds. However, prokinetic effect of metoclopramide started faster and its gastric emptying rate was more than others [30]. In another study, onset of action of metoclopramide was faster than cisapride and gastric residual volume significantly decreased after third dose [31].

Both intravenous metoclopramide and erythromycin significantly reduced mean gastric residual volume 24 h after administration. Treatment with erythromycin was more effective than metoclopramide, but the effect of both agents rapidly reduced over time. Combination therapy was effective in most patients who did not response to monotherapy [30].

In another study both erythromycin 250 mg and metoclopramide 10 mg intravenously every 6 h significantly decreased gastric residual volume and increased feeding rate. However, erythromycin increased GI motility more than metoclopramide [33].

Table 2. Hemodynamic and laboratory parameters of the patients.

Parameter	Continuous infusion group (n = 20)	Intermittent infusion (n = 20)	p-value
BS (mg/dl)	166.85 ± 32.43	158.07 ± 33.95	0.40
Scr (mg/dl)	1.16 ± 0.63	1.40 ± 1.06	0.39
MAP (mmhg)	92.90 ± 12.70	88.80 ± 9.09	0.24
Na (meq/l)	138.89 ± 5.57	138.99 ± 8.24	0.96
K (meq/l)	3.99 ± 0.33	4.01 ± 0.27	0.86
Mg (meq/l)	2.12 ± 0.31	2.13 ± 0.39	0.92
P (meq/l)	3.31 ± 0.57	3.53 ± 0.95	0.37
Ca (meq/l)	8 ± 60	8.38 ± 1.15	0.20
HR (beat/min)	97.80 ± 14.44	87.80 ± 22.49	0.10
WBC (×10 ³ mm ³)	10.37 ± 4.22	10.25 ± 4.24	0.91
Hb (g/dl)	9.44 ± 1.26	9.56 ± 1.33	0.69
HCT (%)	28.68 ± 5.13	29.07 ± 3.73	0.25
Plt (number/mm ³)	165300 ± 75.30	215600 ± 109.36	0.27
PT (s)	13.50 ± 2.29	13.87 ± 2.79	0.53
PTT (s)	30.07 ± 5.41	30.83 ± 5.09	0.79
INR	1.30 ± 35	1.36 ± .50	0.30

Data presented as mean ± standard deviation.

BS: Blood sugar; Hb: Hemoglobin; HCT: Hematocrit; HR: Heart rate; INR: International normalized ratio; MAP: Mean arterial pressure; Plt: Platelets; PT: Prothrombin time; PTT: Partial thromboplastin time; Scr: Serum creatinine; WBC: White blood cell.

As an effective prokinetic regimen, combination of intermittent infusion of metoclopramide and continuous infusion of low-dose erythromycin was recommended in critically ill patients [34].

Evidences regarding effectiveness and safety of metoclopramide as continuous infusion came from cancer populations. In two studies, effectiveness and safety of different routes of administration of metoclopramide for control of chemotherapy-induced nausea and vomiting were compared. In first study by Joss *et al.*, effectiveness and safety of high-dose metoclopramide as continuous infusion was evaluated in subjects with chemotherapy-induced nausea and vomiting. Patients received intravenous metoclopramide; 2 mg/kg during 15 min as a loading dose followed by 5 mg/kg over 13 h as continuous infusion. In this study, continuous infusion of metoclopramide was effective and safe for controlling chemotherapy-induced nausea and vomiting [28]. However, in this study control group was missed.

Among first randomized study in 1991, Kiyoshi Mori *et al.*, compared effectiveness and safety of metoclopramide as continuous and intermittent infusions in patients receiving cisplatin for 5 days. In this study, 24 patients received metoclopramide either as intermittent infusion (1 mg/kg during 30 min, every 8 h, days 1–5) or continuous infusion (3 mg/kg/24 h, days 1–5) during a randomized cross over study. Nausea and vomiting were controlled in ten and six patients in the continuous and intermittent infusion group, respectively. Adverse effects attributed to metoclopramide were comparable between the groups [29].

Although these limited evidences support effectiveness and safety of continuous infusion of metoclopramide in chemotherapy-induced nausea and vomiting but considering design, sample size, measuring tools and end points, the results seem not conclusive.

Table 3. Nutritional parameters of the patients.

Parameter	Continuous infusion group (n = 20)	Intermittent infusion group (n = 20)	p-value
Volume of enteral nutrition (ml/day)	1108.96 ± 429.79	1176.53 ± 401.40	0.65
Calorie intake (kcal/day)	1110.39 ± 430.46	1182.28 ± 403.11	0.63
Protein intake (g/day)	39.96 ± 16.20	43.24 ± 15.49	0.55
Time (h) to reach the calorie goal:			0.38
– 12	1	4	
– 24	4	3	
– 48	5	1	
– 72	0	4	
– None	10	8	
Time (h) to reach the protein goal:			0.12
– 12	3	1	
– 24	4	2	
– 48	1	7	
– 72	3	1	
– None	9	9	
Number of days with feeding intolerance	1 (1–2.75)	0 (0–0)	0.14
Number (%) of patients with feeding intolerance:			
– Day 1	3 (15)	2 (10)	0.70
– Day 2	4 (20)	1 (5)	0.03
– Day 3	4 (20)	1 (5)	0.03
– Day 4	2 (10)	1 (5)	0.59
– Day 5	2 (10)	2 (10)	0.93
– Day 6	1 (5)	0 (0)	0.31
– Day 7	2 (10)	1 (5)	0.59

Data are presented as mean ± standard deviation or median (interquartile range: 25–75).

Effectiveness and safety of continuous intravenous infusion of metoclopramide as a prokinetic agent have not been evaluated in critically ill patients yet. For the first time we examined this hypothesis in critically ill patients with enteral feeding intolerance. Considering the end points of study, continuous and intermittent infusions of metoclopramide showed equivalent effectiveness. However, considering safety parameters, intermittent infusion of metoclopramide was more favorable.

Most available evidences support use of metoclopramide as an effective prokinetic agent in critically ill patients with enteral feeding intolerance [26–49]. However, its adverse effects especially cardiac complications should be considered. Metoclopramide may prolong QT interval and consequently causes cardiac arrhythmia. Advanced age, female gender, history of QT interval prolongation, baseline cardiac rhythms disturbances, structural heart diseases and poor left ventricular function are known as predisposing conditions for this event [48–51].

Compared to other agents such as cisapride and erythromycin, metoclopramide showed less cardiac complications [50]. Somnolence, nervousness, extrapyramidal reactions, dyskinesia, dizziness, restlessness, galactorrhea and menstrual dysregulation were reported following long-term use of metoclopramide in 20% of noncritically ill patients. However, metoclopramide has not significant drug interaction with other agents [51,52].

In our study, patients with enteral feeding intolerance were recruited. Considering number of patients with feeding intolerance after starting metoclopramide, both continuous and intermittent infusions improved enteral feeding tolerance in most patients among the course of study.

Metoclopramide is a lipid soluble, basic drug that rapidly distributed through the body. It has high volume of distribution at steady state. The elimination half-life and clearance of metoclopramide are dose-dependent. It is metabolized by liver and excretes in urine and feces as parent drug and metabolites. Gastric emptying effect of metoclopramide last for at least 3 h following intravenous bolus injection. This effect may be related to metoclopramide plasma concentration. Considering the pharmacokinetic behaviors, it seems that intermittent bolus injections of higher doses of metoclopramide may show more favorable prokinetic effect than continuous infusion. Also due to rapid and extensive distribution of metoclopramide, administration of a loading dose may accelerate its prokinetic effect [53–55].

This is first study that compared effectiveness of continuous and intermittent infusions of metoclo-

pramide on enteral feeding intolerance in critically ill patients. A randomized clinical trial was designed for this goal. Also safety of metoclopramide was assessed and included patients were followed for ICU outcome. However, some points should be considered when interpreting the results. Small sample size and heterogeneity in patients' baseline diseases were main limitations of the study. Different daily doses of metoclopramide (40 vs 48 mg) were examined in this trial. More frequent adverse effects in the continuous infusion group, may be related to dose of metoclopramide. Designing multicenter studies in homogenous surgical or medical patients with sufficient sample size is recommended for future.

Conclusion

Continuous and intermittent infusions of metoclopramide had equivalent prokinetic effect in critically ill patients with enteral feeding intolerance. Although not statistically significant, patients in the continuous infusion group experienced more cardiac and GI adverse effects than the intermittent infusion group.

Future perspective

Optimizing dose and method of administration are important keys to maximize effectiveness and safety of metoclopramide as a prokinetic agent in critically ill patients (Table 3).

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- In this trial, effectiveness of continuous and intermittent infusions of metoclopramide was compared in critically ill patients with enteral feeding intolerance.

Method

- Adult critically ill patients with enteral feeding intolerance were assigned to receive metoclopramide either 10 mg every 6 h as intermittent infusion (during 5 min) or 2 mg/h as continuous infusion.
- During the survey, patients were followed for enteral feeding intolerance as primary end point.
- Secondary point was detecting metoclopramide related adverse effects.

Results

- Number of patients with feeding intolerance during the course of study were comparable between the groups.
- Diarrhea significantly and cardiac rhythm disturbances nonsignificantly were more common in continuous than intermittent infusion group.

Conclusion

- Continuous and intermittent infusions of metoclopramide showed same prokinetic property in critically ill patients with enteral feeding intolerance.

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