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Metoclopramide Improves Gastric but not Gallbladder Emptying in Cardiac Surgery Patients with Early Intragastric Enteral Feeding: Randomized Controlled Trial

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Aim To evaluate the effect of metoclopramide on gastric emptying in coronary artery bypass graft (CABG) surgery patients with early enteral nutrition and to evaluate the effect of metoclopramide on motility of the gallbladder in these patients.

Methods A prospective, randomized, placebo-controlled, double-blind study of 40 patients treated at cardiosurgical intensive care unit after CABG surgery. The patients were divided into two groups: metoclopramide group (20 patients; age 60 ± 9 years; 85% male), and control group (20 patients; age 59 ± 8 years; 70% male). In both groups, enteral feeding with isoosmotic enteral formula was initiated by nasogastric tube 18 hours after surgery. After 6 hours, feeding was stopped, and paracetamol solution (1,000 mg) and 10 mg of metoclopramide IV or 2 ml of saline IV were concurrently administered. Blood samples were obtained 15 (t_{+15}), 30 (t_{+30}), 60 (t_{+60}), and 120 (t_{+120}) minutes after the administration of paracetamol. Paracetamol absorption was assessed from the plasma paracetamol concentration and the area under the curve (AUC) from 0 to 120 minutes. Sonographic measurement of gallbladder ejection fraction was also performed 15 (t_{+15}), 30 (t_{+30}), 60 (t_{+60}), and 120 (t_{+120}) minutes after the administration of paracetamol.

Results The plasma paracetamol concentrations 15, 30, 60, and 120 minutes after the administration of paracetamol were significantly higher in metoclopramide group than in control group: (t_{+15}) 5.4 ± 2.7 vs 3.3 ± 2.5 (Mann-Whitney *U* test; $P = 0.017$); (t_{+30}) 6.7 ± 2.4 vs 3.7 ± 2.0 ($P = 0.006$); (t_{+60}) 7.7 ± 2.5 vs 5.1 ± 3.2 ($P = 0.008$); (t_{+120}) 8.5 ± 2.2 vs 5.2 ± 2.8 ($P = 0.005$). The AUC value was 34% larger in the metoclopramide group vs control group (574 ± 296 vs 429 ± 309; $P = 0.027$). There were no significant differences in gallbladder ejection fraction between groups (group metoclopramide vs control group: (t_0-t_{+15}) −2% vs −2%; (t_{+15}-t_{+30}) 1% vs 4%; (t_{+30}-t_{+60}) 0% vs −1%; (t_{+60}-t_{+120}) 1% vs 3%; P = NS).

Conclusions In CABG surgery patients with early enteral feeding, a single dose of intravenous metoclopramide effectively improves gastric emptying, but does not have any prokinetic effect on gallbladder motility.

In the past several years, it has been clearly recognized that early enteral feeding has certain crucial advantages over delayed enteral feeding and also over conventional total parenteral nutrition: it preserves the integrity of the gut mucosa, reduces bacterial translocation, stimulates the host's defense mechanism, decreases the costs, and improves the outcome (1-4).

Early postoperative intragastric enteral feeding in cardiac surgery patients is frequently complicated by delayed gastric emptying and subsequent intolerance of enteral formula (5,6). Dopamine antagonist metoclopramide, a safe and inexpensive prokinetic agent, has previously been shown to significantly accelerate gastric emptying in a heterogeneous group of mechanically venti-

lated, critically ill patients (7-9). The primary aim of this study was to evaluate the effect of a single dose of intravenous metoclopramide on gastric emptying in coronary artery by-pass graft (CABG) surgery patients with early postoperative intragastric enteral feeding.

Large gallbladder volume and gallbladder hypomotility are predictors of biliary stasis and the formation of biliary sludge (10). Biliary stasis and sludge have been recognized as precursors of acute acalculous cholecystitis and idiopathic pancreatitis, rare but very serious complications after cardiac surgery (11). Previously, we demonstrated that early postoperative gastric supply of nutrients after cardiac and noncardiac surgery diminishes the volume and stimulates the motility of the gallbladder (12). However, in the same study we found that the gallbladder volume was significantly higher in cardiac than in noncardiac surgery patients, e.g. the stimulation of the motility of the gallbladder with nutrients was smaller in cardiac than in noncardiac surgery patients (12). The second aim of this study was to confirm that metoclopramide further stimulates gallbladder motility in CABG surgery patients with early postoperative intragastric enteral feeding.

Subjects and Methods

The investigation was designed as prospective, randomized, placebo-controlled, double-blind clinical study. The study was performed in a sixteen-bed medical-surgical intensive care unit (ICU) in a tertiary care university hospital during the four month period. All patients were preoperatively informed about the research and they accepted to participate. The protocol was approved by the University Research Board.

Patients

Forty patients, treated at the cardiac surgery ICU after CABG surgery, were included in the study. Exclusion criteria were: off-pump cardiac surgery, anamnestic data about diseases of gastroduodenal part of the digestive tract, endoscopic findings confirming gastric or duodenal ulcer in the last five years, preoperative ultrasonographic findings confirming cholelithiasis, loss of weight over 10% in the last three months, extreme obesity (body mass index (BMI) >35), diabetes mellitus, elevated preoperative biochemical parameters of liver (aspartate aminotransferases, alanine aminotransferase, gamma-glutamyltransferase, and bilirubin) or kidney function (urea and creatinine), preoperative intake of drugs which could influence paracetamol absorption test (e.g. nonsteroidal antiinflammatory agents, NSAD), and gastric motility (cisapride, metoclopramide, and erythromycin), including dopamine in doses >2 μg/kg/min. The patients with serious concomitant valvular disease, recent infarction (<3 weeks), preoperative ejection fraction $<40\%$ and intraoperative use of intra-aortal balloon pump were also excluded due to the possible influence of hemodynamic instability on gastric motility (5). Using software for generating random numbers, were allocated patients either to the metoclopramide group (20 patients) or control group (20 patients). All 40 patients underwent the same preoperative procedure: intestinal enema day before the operation, overnight fasting, and night premedication with diazepam. The surgery started in all patients after 8 hours of fasting. Anesthesia with etomidate as the induction agent was maintained with midazolam and fentanyl, using rocuronium for relaxation. Cephalosporin 3rd generation (ceftriaxone or cefotaxime) was used as intraoperative antimicrobic prophylaxis. All patients received a two-lumen nasogastric tube; the exact intragastric position was verified by X-ray immediately after entering ICU. All patients were monitored hemodynamically with Swan-Ganz catheter (Arrow, Reading, PA, USA) as a part of protocol guided perioperative care in our institution and operated with technique of intermittent ischemia (occlusion). Postoperative mechanical ventilation lasted at least 6 hours postoperatively under continuous sedation with propofol. The infusion of propofol was terminated after 6 hours and the patients were taken off mechanical ventilation and extubated according to the decision of a senior anesthesiologist. All patients included in the study were extubated within twelve hours after the end of surgery and all were normothermic at the beginning of the study. Postoperative analgesia, when required, was maintained with morphine chloride (maximum one bolus of 0.01 mg/kg IV during the study). The age, severity of illness (Simplified Acute Physiology Score II – SAPS II, ref. 13), gender, body mass index (BMI), duration of cardiopulmonal by-pass and surgery, and overall quantity of the used fentanyl during the surgical procedure, are presented in Table 1.

Table 1. Age, gender, Simplified Acute Physiology Score II (SAPS II), body mass index (BMI), duration of cardiopulmonal bypass and surgery, and overall quantity of used fentanyl (mean±standard deviation) during the surgical procedure in the patients given metoclopramide and the control group

Parameter	Control	Metoclopramide	*P*†
Age (years)	59±8	60±9	0.591
Gender (male; %)	14 (70)	17 (85)	0.683
SAPS II*	20±9	22±10	0.338
BMI	28.8±2.4	29.6±4.5	0.382
Duration of cardiopulmonary bypass (min)	98±18	91±21	0.709
Duration of surgical procedure (min)	177±45	171±52	0.470
Overall quantity of used fentanyl during the surgical procedure (mg)	2.4±0.5	2.2±0.6	0.511

*According to ref. 23.
†χ^2 test and Mann-Whitney *U* test.

Enteral Feeding Protocol

In both groups early intragastric enteral feeding started with isoosmolar enteral formula (Osmolite®, Ross, IL, USA) through nasogastric tube 18 hours after CABG surgery according to the scheme: first 3 hours – 30 mL/h and next 3 hours – 50 mL/h, ie total 240 mL in 6 hours (12). After 6 hours of feeding the enteral feeding was stopped, paracetamol solution (1,000 mg/50 mL) was administered by a nasogastric tube, and the patients received 10 mg of metoclopramide IV or 2 mL of saline IV, depending on the group in which they where randomized.

Gastric Motility (Emptying) Measurement

Paracetamol absorption model was used as an indirect measure of gastric motility and emptying. Paracetamol is not absorbed from the stomach, but is rapidly absorbed from the small intestine. Consequently, the rate of gastric emptying determines the rate of intestinal absorption of paracetamol (14-16). Venous blood samples were obtained from an indwelling peripheral cannula immediately before (calibration sample) and 15 (t_{+15}), 30 (t_{+30}), 60 (t_{+60}), and 120 (t_{+120}) minutes after the administration of paracetamol. Plasma concentration of paracetamol was determined by an immunologic method including fluorescence polarization (TDx® acetaminophen, Abbott Laboratories, North Chicago, IL, USA). Paracetamol absorption was assessed from the plasma paracetamol concentration, peak paracetamol plasma levels (C_{max}), and the area under the paracetamol concentration curve from 0 to 120 min (AUC_{120}) calculated by means of the trapezoidal model (15,16).

Gallbladder Motility (Emptying) Measurement

In all patients sonographic evaluation of gallbladder volume was performed immediately after the enteral feeding was stopped (t_0) and after 15 (t_{+15}), 30 (t_{+30}), 60 (t_{+60}), and 120 (t_{+120}) minutes. The patients' gallbladder volume was estimated by real-time ultrasound scan using a 3.5-5 MHz curved transducer (Hitachi 515 EUB; Tokyo, Japan). All examinations were performed by the same investigator (A. S.). Standard subcostal cross-section was used, and for the calculation of gallbladder volume, as earlier described, ellipsoid formula was used (17). The gallbladder ejection fraction (GBEF) was used as a measure of gallbladder motility (GB) and gallbladder emptying using standard formula for ejection fraction as follows (17): GBEF t_x/t_y (%) = (GB volume t_x-GB volume t_y)/GB volume $t_x \times 100$; e.g. GBEF t_0/t_{15} = (GB volume t_0-GB volume t_{15})/GB volume $t_0 \times 100$; GBEF t_{15}/t_{30} = (GB volume t_{15}-GB volume t_{30})/GB volume $t_{15} \times 100$; GBEF t_{30}/t_{60} = (GB volume t_{30}-GB volume t_{60})/GB volume $t_{30} \times 100$; GBEF t_{60}/t_{120} = (GB volume t_{60}-GB volume t_{120})/GB volume $t_{120} \times 100$.

Statistical Analysis

All values were presented as mean ± standard deviation. Statistical analysis was done with the Statistica 6.0 software (StatSoft. Inc., Tulsa, OK, USA), using χ^2 test for comparing qualitative baseline variables between the groups and Mann-Whitney *U* test for comparisons of quantitative variables of unpaired samples.

Results

The patients from both groups did not differ in age, gender, severity of illness (SAPS II), body mass index (BMI), duration of cardiopulmonal by-pass and surgery, and overall quantity of used fentanyl during the surgical procedure (Table 1). Values of plasma paracetamol concentration 15, 30, 60 and 120 minutes after the administration of paracetamol and saline or metoclopramide were significantly higher in patients in the metoclopramide group (Table 2). Also, the value of

Table 2. Plasma paracetamol concentration (mg/L) at 15 (t_{+15}), 30 (t_{+30}), 60 (t_{+60}), and 120 (t_{+120}) minutes after administration of paracetamol and saline or metoclopramide in patients in control group and metoclopramide group

	Plasma paracetamol concentration (mean±standard deviation) after administration of paracetamol and saline or metoclopramide			
Group	t_{+15}	t_{+30}	t_{+60}	t_{+120}
Control	3.3±2.5	3.7±2.0	5.1±3.2	5.1±2.8
Metoclopramide	5.4±2.7	6.7±2.4	7.7±2.5	8.5±2.2
*P**	0.017	0.006	0.008	0.005

*Mann-Whitney *U* test.

Table 3. Peak paracetamol plasma levels (C_{max}, mg/L) and the area under the paracetamol concentration curve from 0 to 120 minutes (AUC_{120}) (mean±standard deviation) in the control group and metoclopramide group

Group	C_{max}	AUC_{120}
Control	5.15±2.8	429±309
Metoclopramide	8.51±2.2	574±296
*P**	0.007	0.027

*Mann-Whitney *U* test.

Table 4. Gallbladder ejection fraction 0-15 (t_0/t_{+15}), 15-30 (t_{+15}/t_{+30}), 30-60 (t_{+30}/t_{+60}) and 60-120 (t_{+60}/t_{+120}) minutes after the administration of paracetamol and saline or metoclopramide in control group and metoclopramide group

	Gallbladder ejection fraction (%) after administration of paracetamol and saline or metoclopramide			
Group	t_0/t_{+15}	t_{+15}/t_{+30}	t_{+30}/t_{+60}	t_{+60}/t_{+120}
Control	-2	1	0	1
Metoclopramide	-2	4	-1	3
*P**	0.72	0.24	0.41	0.39

*Mann-Whitney *U* test.

peak paracetamol plasma level (C_{max}), and the value of the area under the paracetamol concentration curve from 0 to 120 min (AUC_{120}) were significantly higher in patients in the metoclopramide group (Table 3). There were no significant differences in the values of the gallbladder ejection fraction (GBEF) between the control group and metoclopramide group (Table 4).

Discussion

The prokinetic role of metoclopramide in patients receiving early postoperative enteral feeding after open-heart surgery has not been investigated up to now. In this study we were focused on two questions: 1) does metoclopramide improve gastric emptying in CABG surgery patients receiving early postoperative intragastric enteral feeding? and 2) does metoclopramide improve gallbladder motility and gallbladder emptying in these patients?

In our study, patients who received 10 mg of metoclopramide IV (metoclopramide group) had significantly higher plasma concentration of paracetamol in the next 120 minutes after the administration of metoclopramide compared with the patients who received 2 mL of saline IV (control group). As groups of patients were reciprocally comparable, and due to the fact that metoclopramide group had significantly higher plasma paracetamol concentration, C_{max} and AUC_{120}, we can conclude that metoclopramide stimulated gastric emptying in CABG surgery patients receiving early postoperative intragastric enteral feeding. Gastric hypomotility and gastric paresis with subsequent intolerance of enteral formula are frequent phenomena in patients after open-heart surgery (5,6). Postoperative intolerance of enteral food in cardiac surgery patients is caused by various factors such as the use of certain anesthetics, opiates, vasoactive drugs, and postoperative mechanical ventilation (5,6). It may also be the consequence of perioperative splanchnic hypoperfusion and/or the use of extracorporal circulation (5). It has been demonstrated recently that metoclopramide stimulates gastric emptying in critically ill patients who tolerate enteral feeding, as well as in those who do not (7-9). The results of this study confirmed that the effect of metoclopramide was equal even after CABG surgery. It significantly stimulated gastric emptying and thus probably enabled better tolerance of enteral formula. This information could be very important in the prevention and treatment of gastric intolerance of liquid enteral formula in early postoperative care of patients after open-heart surgery.

Postoperative hypomotility of the gallbladder, with subsequent biliary stasis, is a well-known mechanism in the formation of biliary sludge (10). Biliary sludge is a precursor of two relatively rare (< 2%), but extremely serious intra-abdominal complications after cardiac surgery, acute acalculous cholecystitis and "idiopathic" pancreatitis (10,11,18,19). Moreover, it has been proved that biliary sludge has an important impact on the later development of cholelithiasis and chronic cholecystitis (20). The best prevention of postoperative hypomotility of the gallbladder and forming of biliary sludge is early enteral feeding because the installation of nutrients in the upper part of the digestive tract stimulates contractions of the gallbladder (12,21). However, in our previous study, we found that open-heart surgery with extracorporal circulation suppresses the motility of gall-

bladder, because the stimulation of the motility of gallbladder with nutrients is significantly smaller in cardiac than in noncardiac surgery patients (12). Nevertheless, in the present research we could not conclude that metoclopramide additionaly stimulates the motitlity, thus improving the emptying of the gallbladder in those patients. Obtained results are similar to the results of some previous clinical studies where the effect of metoclopramide on the gallbladder contractility could not be found either in the healthy volunteers or in diabetic patients (22,23). This, together with investigations of other authors (7-9), confirms that metoclopramide, with a direct effect on lower esophageal smooth muscle and as selective dopamine-2 receptor antagonist, significantly enhance peristaltic contractility of the esophagus, gastric antrum and duodenum. Due to the fact that the motility and emptying of the gallbladder is in the greater part mediated by cholecystokinin, the impact of metoclopramide on the gallbladder motility, in this case as pure cholinergic stimulator, is much less expressed and probably not clinically relevant (21). The results of our study show that metoclopramide does not stimulate gallbladder motility, thus it is not indicated for the prevention or treatment of acute acalculous cholecystitis or "idiopatic" pancreatitis in patients after open-heart surgery.

However, this study has important limitations because of the exclusion of all cases with perioperative circulatory failure, as well as seriously ill cardiac patients, ie those with increased risk for the development of gastric paresis and gastric intolerance (6). In our opinion, before determining the definitive role of metoclopramide in enteral feeding guidelines for patients after open-heart surgery, a similar study should be done on cardiosurgical patients with significant hemodynamic instability or/and with verified (subsequent) splanchnic hypoperfusion.

In conclusion, we showed that a single dose of intravenous metoclopramide (10 mg IV) effectively improved gastric emptying in patients with early postoperative intragastric enteral nutrition with liquid isoosmolar enteral formula after uncomplicated open-heart surgery. Moreover, we showed that metoclopramide did not have any additional prokinetic effects on gallbladder motility in these patients.

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