

• GASTRIC CANCER •

Preventing prolonged post-operative ileus in gastric cancer patients undergoing gastrectomy and intra-peritoneal chemotherapy

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Abstract

AIM: To assess the efficacy of metoclopramide (Met) for prevention of prolonged post-operative ileus in advanced gastric cancer patients undergoing D2 gastrectomy and intra-peritoneal chemotherapy (IPC).

METHODS: Thirty-two advanced gastric cancer patients undergoing D2 gastrectomy and IPC were allocated to two groups. Sixteen patients received Met immediately after operation (group A), and 16 did not (group B). Another 16 patients who underwent D2 gastrectomy without IPC were enrolled as the control group (group C). All patients had received epidural pain control. The primary endpoints were time to first post-operative flatus and time until oral feeding with a soft diet without discomfort. Secondary endpoints were early complications during hospitalization.

RESULTS: Gender, the type of resection, operating time, blood loss, tumor status and amount of narcotics were comparable in the three groups. However, the group C patients were older than those in groups A and B (67.5 ± 17.7 vs 56.8 ± 13.2 , 57.5 ± 11.7 years, $P = 0.048$). First bowel flatus occurred after 4.35 ± 0.93 d in group A, 4.94 ± 1.37 d in group B, and 4.71 ± 1.22 d in group C ($P > 0.05$). Oral feeding of a soft diet was tolerated 7.21 ± 1.92 d after operation in group A, 10.15 ± 2.17 d in group B, and 7.53 ± 1.35 d in group C (groups A and C vs group B, $P < 0.05$). There was no significant difference in respect to the first flatus among the three groups. However, the time of tolerating oral intake with soft food in groups A and C patients was significantly

shorter than that in group B patients. Levels of C-reactive protein (CRP) were significantly lower in group C and there was a more prominent and prolonged response in CRP level in patients undergoing IPC. The incidence of post-operative complications was similar in the three groups except for prolonged post-operative ileus. There was no increased risk of anastomotic leakage in patients receiving Met.

CONCLUSION: The results suggest that a combination of intravenous Met and epidural pain control may be required to achieve a considerable decrease in time to resumption of oral soft diet in advanced gastric cancer patients who underwent gastrectomy and IPC. Furthermore, the administration of Met did not increase anastomotic leakage. Met has a role in the prevention of prolonged post-operative ileus.

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Key words: Metoclopramide; C-reactive protein; Gastric cancer; Intraperitoneal chemotherapy

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INTRODUCTION

The long-term results of treatment for resectable gastric cancer have not shown any significant improvement in recent decades^[1]. Analyses of surgical treatment failure after curative resection have indicated intra-peritoneal recurrence is the major pattern of tumor recurrence^[2]. Large randomized trials of intravenous or radiotherapy have failed to demonstrate any benefit for lowering intra-peritoneal recurrence^[3,4].

Therefore, intra-peritoneal chemotherapy (IPC) as an adjuvant to surgery, may be considered as a rational therapeutic modality.

Although the role of IPC in treating peritoneal seeding or preventing peritoneal recurrence for advanced gastric cancer is still controversial, its use in prophylactic treatment in potentially curative gastric cancer resection has shown improved survival and lower peritoneal recurrence rates in Japan and Korea^[5,6]. There are some prospective randomized trials that have shown a patient with surgery plus IPC was

1.3 more times more likely to survive 5 years than a patient with surgery alone^[6]. However, prolonged post-operative ileus (POI) is one of the most commonly reported complications of IPC^[7-9]. In the situation of an immunocompromised condition induced by surgical trauma, cancer, and chemotherapy, prolonged gastro-intestinal (GI) tract stasis can increase the potential for bacterial overgrowth and translocation, potentially leading to systemic sepsis and multiple organ failure, both of which are the most prevalent post-operative complications causing death^[10,11].

To our knowledge, there are few reports concerning aggressive treatment or prevention of POI in patients undergoing IPC. Most treatments for this problem are largely supportive, including naso-gastric (NG) decompression, intravenous hydration and parenteral nutrition.

Metoclopramide (Met) antagonizes central and peripheral dopamine receptors and sensitizes GI tract receptors to acetylcholine^[12-14]. These actions increase peristalsis in the antrum, duodenum, and jejunum and increase the lower esophageal pressure. In previous studies about the effect of Met on intestinal motility, major surgical procedures have not been combined with intensive regional chemotherapy. The incidence of prolonged POI was reported as relatively low and the prophylactic use of Met as seemingly unnecessary or ineffective^[15-19].

The present study was a prospective, controlled trial in which only gastric cancer patients who underwent sub-total or total gastrectomy were enrolled. The aim of the study was to assess the effects of Met on the IPC-induced ileus.

MATERIALS AND METHODS

This study was approved by the institutional review board of Tri-Service General Hospital and informed consent was obtained from patients and family members. It was a prospective, controlled study conducted in the above hospital from March 2001 to October 2004, involving patients lesser than 70 years who had undergone R0 curative gastrectomy with D2 lymph node, i.e., N1 and N2, dissection^[20] followed by IPC for advanced gastric cancer, including T3 (serosal penetration) or T4 (invasion of adjacent organs), according to the Japanese Classification of Gastric Carcinoma^[21]. The type of resection, total or sub-total gastrectomy, depended on the location and Bormann type of primary tumor. After the potentially curative operation was performed, the peritoneal cavity was extensively washed, using seven liters of physiologic saline (1 L, seven times), followed by IPC with mitomycin-C (MMC) 10 mg in 1 L normal saline, for 60 min for all patients. The patients were allocated into two groups of 16 patients each. Patients in group A received intravenous Met 10 mg, every 8 h, commencing immediately after completion of the operation and continued until oral feeding with soft diet was resumed or abdominal cramping pain developed. Patients in group B received an equivalent volume of 5% dextrose in water, and did not receive Met. A control group (group C) of further 16 patients did not receive IPC and Met. All patients had received epidural pain control for the first three post-operative days, and then pain control was changed to intramuscular meperidine

on post-operative day (POD) four in three groups.

Epidural pain control

Before surgery, a thoracic epidural catheter was inserted at T₈-T₁₀ and advanced 5 cm into the epidural space. A test dose of 3 mL of 2% lidocaine containing epinephrine (5 µg/mL) was administered to rule out intra-thecal or intravascular misplacement. After pre-operative assessment of the epidural block, general anesthesia was induced with fentanyl (2 µg/kg), cisatracurium (2 mg), thiamylal (3-5 mg/kg), and lidocaine (1.5 mg/mg) by intravenous (IV) administration, and tracheal intubation was facilitated with succinylcholine (1.5 mg/mg). General anesthesia was maintained with desflurane in oxygen (300 mL/min) in a totally closed circuit system where the end-tidal desflurane concentration was maintained at 7.5±0.5%. Cisatracurium was used for muscle relaxation. No additional intravenous opioid was given during operation. Standard monitors included pulse oximetry, electrocardiography, central venous pressure measurement, and intra-arterial pressure measurement via a radial artery catheter. At the end of surgery, the residual neuromuscular block was antagonized with edrophonium (4 mg) and atropine (0.6 mg); the endotracheal tube was removed when the patient breathed spontaneously. After surgery, all patients received a uniform epidural pain control regimen consisting of morphine (1 mg) in 10 mL of 0.095% bupivacaine every 8 h until 72 h. If pain relief was insufficient, meperidine (50 mg every 6 h) was given. Acetaminophen tablets or meperidine were administered after termination of epidural pain control.

Postoperative care

Serum electrolytes were monitored and corrected in the first seven post-operative days for all patients. Serum C-reactive protein (CRP) levels and abdominal drainage fluid amylase levels were determined post-operatively in all patients. Pancreatic leakage was suspected if the amylase levels of abdominal drainage fluid rose to more than 4 000 U/L^[22]. NG tubes were removed immediately after operation in patients receiving a total gastrectomy and maintained for one day in patients receiving a sub-total gastrectomy. Indication of NG tube reinsertion was biliary vomiting or abdominal distension. Oral intake with 5% glucose solution resumed immediately after the first bowel flatus, and then progressed to a soft diet two days later, if no abdominal discomfort developed. Patients who could not resume oral intake of a soft diet beyond the seventh POD and have generalized ileus shown in plain abdominal x-ray film (KUB) (Figure 1), were defined as having prolonged POI. The epidural catheter was removed routinely on the third POD (approximately 72 h after surgery). The main aim of the study was to compare the length of time of IPC-induced ileus. Therefore, data collected included time to the first post-operative bowel flatus, and number of days required for patients to tolerate a soft oral diet. Narcotic use was recorded for comparison among the three groups. Other information analyzed included operation time, type of resection, blood loss, and complications.

Student's *t*-test, Fisher exact test or the Mann-Whitney *U*-test were used in the statistical analysis. Probabilities of less than 0.05 were accepted as significant.

RESULTS

There were no major differences among the three groups with regard to clinico-pathological characteristics (Table 1). However, patients receiving IPC were younger than those not receiving IPC (56.8 ± 13.2 , 57.5 ± 11.7 years *vs* 67.5 ± 17.7 years, $P = 0.048$). All three groups had an increase of serum CRP post-operatively (Figure 2). Group A and B patients, however, had much higher levels of CRP, which were significantly raised at the first day post IPC, compared with the group C patients ($P < 0.05$). There was a more prominent and prolonged response in patients undergoing IPC.

The mean time of first flatus and resumption of glucose solution was not different among the three groups (Table 2). Regarding a soft oral diet, however, there was a significantly shorter mean time in group A patients compared with group

B patients (7.21 ± 1.92 d *vs* 10.15 ± 2.17 d, $P < 0.05$) and no difference between group A and group C (7.21 ± 1.92 d *vs* 7.53 ± 1.35 d, $P > 0.05$). There was one death (6.25%) secondary to aspiration pneumonia and sepsis in group B. Several complications (prolonged POI, wound infection, pneumonia, anastomotic leakage, pancreatic leakage) are shown in Table 3. The patients in group B have a higher incidence of prolonged POI. All complications were successfully treated with medical therapy, except for one case of aspiration pneumonia leading to the only death.

DISCUSSION

Prolonged POI is a significant problem after abdominal surgery, especially when accompanied by IPC. This study indicates that intravenous Met, combined with thoracic epidural pain

Table 1 Clinicopathological characteristics of patients in three groups

	Group A (n = 16)	Group B (n = 16)	Group C (n = 16)	P
Sex (M/F)	11/5	12/4	10/6	NS
Age (yr)	56.8 ± 13.2	57.5 ± 11.7	67.5 ± 17.7	0.048
Sub-total/total gastrectomy	11/5	10/6	10/6	NS
Operation time (min)	272 ± 60	312 ± 69	259 ± 43	NS
Blood loss (mL)	216 ± 106	235 ± 92	196 ± 137	NS
Meperidine use (mg/d)	83.3 ± 21.6	91.4 ± 31.2	79.3 ± 15.9	NS
Primary tumor ¹				NS
pT3	14	13	14	
pT4	2	3	2	
Stage ²				NS
II	4	4	3	
IIIa	4	3	4	
IIIb	5	6	6	
IV	3	3	3	

Gender was assessed by χ^2 test, others were assessed by *t*-test. Significant difference in age ($P = 0.048$) between group C and groups A and B. ¹T classification according to the Japanese Classification of Gastric Carcinoma (22). ²Staging classification according to the 1997 TNM staging system. NS: not significant. All patients had received R0 gastrectomy with D2 lymph node dissection.

Table 2 Bowel motility recovery (mean days and standard deviation)

	Group A ^a (n = 16)	Group B ^a (n = 16)	Group C ^a (n = 16)	P
First bowel flatus	4.35 ± 0.93	4.94 ± 1.37	4.71 ± 1.22	NS
Time elapsed to glucose solution	5.43 ± 1.15	6.67 ± 2.71	5.81 ± 1.35	NS
Time elapsed to soft diet	7.21 ± 1.92	10.15 ± 2.17	7.53 ± 1.35	<0.05
NG tube reinsertion (%)	1 (6.25)	9 (56.25)	1 (6.25)	<0.01

Significant difference in days to soft diet (^a $P < 0.05$) between group B and groups A and C. NG tube: nasogastric tube. NS: not significant.

Table 3 Postoperative complications and mortality

	Group A ^b (n = 16)	Group B ^b (n = 16)	Group C ^b (n = 16)	P
Death	0	1 ¹	0	NS
Prolonged POI	1 (6.25)	9 (56.26)	1 (6.25)	<0.01
Wound infection	2	1	2	NS
Pneumonia	2	3	2	NS
Anastomotic leak	0	0	1	NS
Pancreatic leak	3	3	2	NS

¹The patient died of aspiration pneumonia and sepsis. Significant difference in prolonged POI (^b $P < 0.01$) between group B and groups A and C. Prolonged POI was defined as intolerance to oral soft diet more than 7 d and generalized ileus shown in KUB. Pancreatic leakage was defined as amylase level of abdominal fluid more than 4 000 U/L. POI: post-operative ileus. NS: not significant.



Figure 1 One patient in group B developed biliary vomiting on the 7th post-operative d. The supine abdominal plain x-ray film showed generalized ileus. (Arrow: dilated colonic air; arrow head: water-soluble contrast media retention in proximal jejunum).

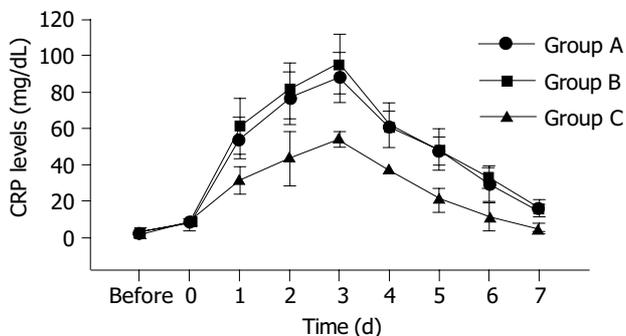


Figure 2 Serial measurement of CRP levels in three groups of patients (group A, with IPC and Met treatment; group B, with IPC but without Met treatment; group C, without IPC and Met) at eight different time points. The change of serum CRP were found to be prominent and prolonged in groups A and B. The data are expressed as mean \pm SD.

control, could effectively prevent prolonged IPC-induced ileus in gastric cancer patients. Further it is indicated that the administration of intravenous Met in patients receiving GI resection does not increase the risk of leakage of the newly constructed GI anastomosis.

IPC, with or without hyperthermia, has been used successfully for a variety of intra-abdominal malignancies, especially ovarian and GI tract cancer^[23,24]. Although it has many advantages, such as a high cytotoxic level of intra-peritoneal drug and less systemic toxicity, it is associated with morbidity. Prolonged POI is one of the most consistent and common side effect^[7,8,25,26]. Prolonged POI was also observed in our study in which intra-peritoneal infusion of MMC was performed in 32 patients. Of these patients, 10 (31.2%) developed prolonged POI, especially in group B (56.25%). This is a higher incidence compared with a previous report that indicated an incidence of 42%. The reason of the higher incidence might partly be due to us giving a more clear definition of prolonged POI in our study.

POI is a poorly understood complication in post-surgical patients. The autonomic nervous system, inflammatory mediators, neurotransmitters, and opioid receptors have all been implicated in the pathophysiology of POI^[27-32]. With

respect to the inflammatory response to surgery, Cannon and Murphy demonstrated in 1906 that opening the peritoneum in dogs and surgical manipulation of the bowel resulted in decreased peristalsis^[33]. More recently Kalfff *et al.*^[31], showed an association between bowel manipulation and impaired contractile activity, noting increased neutrophil infiltration of the muscularis. Surgical manipulation of the bowel and subsequent ileus has been linked to the release of inflammatory mediators from WBC. The inflammatory mediators released as part of a stress response contributes to the development of POI. In general, it is characterized as a temporary impairment of intestinal motility after surgery. Usually different areas of the GI tract resume function at different times. The stomach can take 24-48 h to recover, whereas the colon requires 72-120 h to resume normal motility patterns. Thus, uncomplicated POI resolves spontaneously after approximately 3-5 d^[34,35]. Moreover, some studies indicated that after 7 d of fasting, the intestinal mass decreased by nearly 50%, which might increase the risk of bacterial translocation and septic complications^[36-38]. Therefore, we made a definition of prolonged POI as intolerance of soft diet exceeding 7 d after operation and generalized ileus in KUB. Abdominal surgical procedures may be responsible for the uncomplicated POI. However, extensive surgical procedures, IPC, or a combination of both, may be responsible for prolonged ileus. Stimulation in the small intestine, such as mechanical inflammation after surgical manipulation, may be enhanced by chemical inflammation after IPC, and thus prolong reasonably predictable uncomplicated POI. This was clearly observed in our study which indicated that more patients receiving IPC developed prolonged POI than patients not receiving IPC. Indeed, the concentration of acute phase protein (CRP) in the blood samples of the patients receiving IPC exceeded the level in patients not receiving IPC, suggesting IPC may worsen POI by increasing an inflammatory response.

Prolonged POI and GI tract stasis, in the situation of an immuno-compromised condition induced by cancer, surgical trauma and chemotherapy, will increase the potential for bacterial overgrowth and translocation, which could lead to systemic sepsis and multiple organ failure. Both these post-operative complications are the most prevalent causes of death^[9,10]. Clearly, it is important to find a strategy for preventing or treating these problems.

Met has been used as a prokinetic agent for many years and may potentially influence motility throughout the GI tract^[11-13]. It has both a central and peripheral anti-dopamine effect as well as a direct and indirect stimulatory effect on cholinergic receptors. Dopaminergic receptors have been identified throughout the GI tract. It has also been suggested that the prokinetic effect of Met may be due to the stimulatory effect on cholinergic receptors and the blockade of dopamine receptors that inhibit the release of acetylcholine. This inhibition of dopamine and augmentation of acetylcholine release are thought to sensitize the muscarinic receptors of the GI smooth muscle, allowing for coordinated intestinal motor function. However, results of several studies on the effect of Met on POI have been varied. Some studies have supported the hypothesis that Met reduces the length of POI^[39,40], whereas others refute it^[14-19]. In this study, the effect of Met on preventing prolonged POI was obvious. There

were some differences in our study compared to previous studies about the effect of Met on POI. Firstly, our study focused on prolonged POI, not uncomplicated POI. Moreover, we have a more clear definition of prolonged POI. Met may not change the course of uncomplicated POI, however, it could prevent IPC-induced prolonged POI. Theoretically, prolonged POI has more important and deleterious effect on clinical outcome than uncomplicated POI. However, there was no obvious effect of Met on clinical outcome. Small sample of this study might be the reason. Secondly, all our patients received thoracic epidural pain control. Thoracic epidural analgesia shortens POI via this mechanism by not only blocking pain and lessening stress, but also by inhibiting sympathetic efferent nerve transmission to the gut while preserving motility-promoting parasympathetic stimulation in the sacral region. Parasympathetic innervation via both the vagus nerve and sacral nerve roots can be spared, while sympathetic innervations to the gut (T5-L2) can be selectively blocked when local anesthetics are delivered through a mid-thoracic epidural catheter^[41-43]. In our study, however, most of the patients in group B who received IPC without Met administration developed prolonged ileus, even though they all had epidural pain control. This might be due to epidural anesthesia could not completely abolish IPC-induced inflammatory inhibition of intestinal motility. In contrast, additional administration of Met in group A patients can sensitize the muscarinic receptors of the GI smooth muscle, allowing for coordinated intestinal motor function even though these patients had undergone IPC and vagotomy. Therefore, the time to resumption of soft diet was significantly reduced by Met when compared without Met (Table 3). It is believed that the combination of Met and epidural pain control has a synergic effect on the motility of the GI tract.

An important consideration is whether it is safe to promote intestinal motility by epidural anesthesia or intravenous Met immediately after operation. Some authors have questioned whether Met or epidural anesthesia might be harmful to healing of GI anastomoses because of the increased bowel motility^[44,45]. In the present study, however, no patient developed anastomotic leakages after administration of Met and epidural anesthesia. Our findings do not support the common fear that disturbance to healing of GI anastomoses and an increased risk of anastomotic leakages are linked with early increase of GI motility. Similar results to ours have been reported by some authors^[46,47]. Moreover, early removal or no use of an NG tube after operation is safe in patients receiving Met, only one patient needed reinsertion of the tube in our patients. The concept has been speculated by some investigators^[48,49].

Prolonged POI occurs frequently in patients undergoing extended gastrectomy and IPC, increasing the time needed to achieve nutritional goals, and limiting the benefit of early enteral feedings. This study was the first to examine the role of Met in a group of advanced gastric cancer patients undergoing extended gastrectomy and IPC. Our results demonstrated a clear improvement in the resumption of oral soft diet in the Met-treatment group during the 1st wk post-operatively compared with the no-treatment group (7.21 ± 1.92 d *vs* 10.15 ± 2.17 d, $P < 0.05$). There is a theoretical

possibility that improvement in nutritional intake might improve outcome. We found no significant differences among three groups in infectious risk, or mortality. This study, however, was not powered to detect small differences in outcome. Further studies with more patients are needed to determine whether patient outcomes can be improved by the administration of Met in clinical outcome.

In conclusion, Met with epidural pain control prevents prolonged POI at an early post-operative stage in advanced gastric cancer patients undergoing gastrectomy and IPC. We conclude that Met can be used as a safe prokinetic drug for post-operative intestinal dysmotility worsened by IPC.

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