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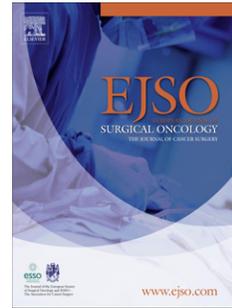
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Effect of preservation of the right gastro-epiploic artery on delayed gastric emptying

A randomized clinical trial

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Abstract

Background: Delayed gastric emptying is a main complication with unknown origin after a HIPEC procedure. The aim of this study was to investigate if preservation of the right gastro-epiploic artery (GEA) during standard omentectomy would have a positive effect on gastric emptying after a HIPEC procedure.

Methods: Forty-two patients subjected to a HIPEC procedure were randomized into two groups peroperatively before performing an omentectomy: in Group I (N=21) omentectomy was performed below the gastro-colic ligament, preserving the GEA; in Group II (N=21) omentectomy was performed above the gastro-colic ligament resecting the GEA. The primary end point was the number of days to full oral intake of solid food. Secondary end points were number of days to intended occlusion of gastric tube and total hospital admission time.

Results: No significant differences were discovered between both groups in any of the study endpoints after the HIPEC procedure. No significant differences were observed in patient or operation characteristics between the randomized groups.

Conclusions: No association was demonstrated between preservation of the gastro-epiploic artery during omentectomy and gastric emptying after a HIPEC procedure. The extensive intestinal manipulation or the heated intraperitoneal chemotherapy during surgery are more plausible causes of this phenomenon.

Keywords:

Gastro-epiploic artery, omentectomy, delayed gastric emptying, HIPEC

This clinical trial was not registered in a public trial registry, according to the ICMJE, as this was not required at the time of study onset. Retrospective registration was not possible.

This clinical trial was registered in the Netherlands at the Central Committee on Research involving Human Subjects (CCMO) under registration number **P06.0301L**.

Introduction

Peritoneal carcinomatosis (PC) is a sign of advanced progressive malignant disease with a very poor life expectancy. [1] Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC procedure) has become an important choice of treatment with intention to cure for patients with PC in the absence of visceral metastases. [2,3]

Completeness of cytoreduction is considered the main prognostic factor for survival. However, aggressive cytoreductive surgery is not without significant perioperative morbidity and mortality. Recent reviews have confirmed the mean length of Intensive Care stay to be 3 days (range 1-5 days) and the mean overall hospital stay to be 19 days (range 7-48 days). Overall treatment-related mortality varies from 0,9% to 5,8% in institutions considered to be tertiary high volume centers. Re-operations are necessary in 11,2% of the patients (range 0%-23%) and the average major morbidity incidence is 28.8% (range 0%-52%). [4,5]

Delayed gastric emptying (DGE) is considered one of the main minor complications after a HIPEC procedure. Minor complications are also defined as grade 1-2 complications. [6]

DGE has been defined as post-surgical nausea, vomiting and gastric atony in absence of gastric outlet obstruction. This phenomenon has been classified into three grades; mild, moderate and severe depending on the time to tolerance of solid oral intake of respectively 7, 14 and 21 days. [7] A wide range in the incidence of delayed gastric emptying after a HIPEC procedure has been reported, with figures varying from 0% to 86%. [3,8,9]

DGE is also frequently reported after other major upper abdominal operations. In particular, a high incidence of DGE is apparent after operations of the pancreas and duodenum. The mechanisms responsible for DGE after surgery are poorly understood. Decreased secretion of motility stimulating hormones after resection of the duodenum, disruption of the gastro-

duodenal neural connections or gastric innervation and post-operative surgical complications have all been correlated to delayed gastric emptying. [10-12]

Identification of a major contributory factor of DGE would be an important step towards improved treatment of significant patient morbidity and prolonged hospital admission after major abdominal surgery.

Unlike surgery such as a standard pancreaticoduodenectomy, cytoreductive surgery during a HIPEC procedure in our institute very rarely involves resections in the pancreas head region. Moreover, the majority of previous mentioned explanations are not likely to cause DGE in patients after a HIPEC procedure.

However, delayed gastric emptying also has a possible association with resection of the right gastric epiploic artery (GEA). [13] During cytoreductive surgery as part of a HIPEC procedure it is standard practice to remove the omentum. [14] An omentectomy is generally performed with resection above the gastro-colic ligament sacrificing the right gastroepiploic artery. This artery supplies the distal part of the stomach (the pylorus and antrum) with blood via the greater curvature of the stomach.

It is possible that temporary impairment of the blood flow to the distal stomach after resection of the GEA could contribute to delayed gastric emptying. This claim has been countered by Murakami et al., who observed no differences in the incidence of DGE after sacrifice of the GEA during pylorus-preserving pancreaticoduodenectomy in comparison to the literature. [15]

To date, all performed studies upon which these statements were made were observational or retrospective studies. No randomized clinical trials have been performed to investigate if an impaired blood flow to the stomach has any influence on gastric emptying.

We hypothesized that preservation of the right gastric epiploic artery (GEA) during omentectomy would have a positive effect on gastric emptying, reducing the grade of DGE by 50% from moderate to mild. Thus it would have a positive effect on the postoperative recovery. To investigate our hypothesis we performed a randomized clinical trial with patients undergoing HIPEC procedure for peritoneal carcinomatosis of colorectal cancer.

Methods

Study design

This study was designed as a randomized clinical trial. The main objective was to investigate the influence of preservation of the right gastro-epiploic artery on gastric emptying. The study was performed in a clinical setting as part of the HIPEC procedure between January 2006 and October 2009.

Delayed gastric emptying was defined as the inability to tolerate solid oral intake before postoperative day 14, which is classified as moderate DGE according to the consensus by Wente et al. [7]

The primary endpoint was the time to unlimited oral intake of solid food. Secondary endpoints were the time to intended occlusion of the gastric tube and total hospital admission time.

The study protocol was approved by the ethical committee of the Netherlands Cancer Institute; NKI-AvL, Amsterdam. Written informed consent was obtained from all patients before operation.

Inclusion criteria

All patients with peritoneal carcinomatosis from intestinal type adenocarcinoma, for whom a HIPEC procedure was indicated. An omentectomy had to be performed on all patients.

Exclusion criteria

Before randomization: all patients with previous gastric surgery or omentectomy and patients with macroscopic tumor in the greater omentum proximal to the gastric-epiploic artery requiring any type of gastric resection were not eligible.

After randomization: included patients with either post-operative complications of the digestive tract for which re-intervention was required (e.g. suture leakage, perforation, fistula, haemorrhage, abscess) or with a prolonged Intensive Care stay of more than two days were excluded from the evaluation of the endpoints. This decision was determined based on studies that have significantly correlated these complications to influence the incidence of delayed gastric emptying. [16,17]

Randomization and Blinding

Randomization was performed by the independent trial bureau within our institution, through a specialized computer program. If the patient met all inclusion criteria, the trial bureau was contacted by telephone during the operation before omentectomy and subsequent randomization was performed.

Only the surgeon and authors were informed on the results of the randomization. Patient and hospital personnel responsible for the post-operative treatment remained blinded for this information during hospital admission.

Surgical treatment

Omentectomy was performed as part of the cytoreductive surgical treatment. Depending on the result of randomization the greater omentum was either resected immediately under the gastro-epiploic artery, preserving the right gastro-epiploic artery (group I or GEA_{PRE}) or it was resected along the greater curvature of the stomach including a resection of the right gastro-epiploic artery (group II or GEA_{RES}). Ligation of the GEA was performed near the pylorus and splenic hilum. No resections of stomach, duodenum or pancreas head were performed as part of the cytoreductive surgery in any of these patients.

After cytoreduction, all patients were treated with heated intra-peritoneal chemotherapy perfusion (Mitomycin-C; 35mg/m²) for 90 minutes as described previously. [3] Maximum temperature of the chemotherapy perfusion fluid is 41°C for all patients. At the end of the operation all patients received a gastric and a jejunal tube trans-cutaneously via the stomach for respective evacuation of gastric fluid surplus and early enteral post-operative feeding. Three drains used for the chemotherapy perfusion were left in-situ postoperatively.

Postoperative management

All patients were managed according to a standard post-operative protocol for the HIPEC procedure at our institute. Post-operative pain was managed in all patients via an epidural catheter with a mixture of morphine and bupivacaine for at least five days. This was combined with oral analgesics, Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), for at least ten days post-operatively. No systemic morphine was administered. All patients were treated with H₂-receptor antagonists for as long as NSAIDs were administered. Nausea was treated symptomatically with Serotonin receptor antagonists. No patients were treated with prokinetic drugs during hospital admission.

Enteral feeding of liquid food via the jejunal tube was started on day one postoperatively.

The gastric tube was occluded in absence of nausea as well as a daily production of gastric fluid less than 1000ml. When the gastric tube was occluded, increasing intake of food orally was stimulated and subsequent administration of liquid food was decreased.

Occluded gastric and jejunum tubes were not removed before day 10 after the operation.

Other abdominal drains were removed when drainage was less than 50ml per day.

Statistical analysis

To detect the hypothesized decrease in time to normal enteral feeding from 14 to 8 days, a sample size of 15 patients in each study arm was calculated based on a significant level of 0.05 and a power of at least 0.80.

Patient characteristics were compared between the two treatment arms and between evaluable and non-evaluable patients using Fischer exact or Two Sample T-test. Primary and secondary endpoints were compared with the two sample t-test with a two-sided significance level of 0.05.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA.) and R version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria) with the exact rank tests package.

Results

A total of 42 patients (22 males and 20 females) were randomized and divided equally over two groups; in group I omentectomy was performed with preservation of the gastro-epiploic artery (GEA_{PRE}), in group II the gastro-epiploic artery was resected along with the greater omentum (GEA_{RES}).

In total 11 patients were excluded from the evaluation after randomization; 6 patients in group I and 5 patients in group II. (figure 1). All exclusions were due to surgical complications within the first week after surgery.

In group I, a total of five patients were subjected to a second laparotomy; two due to bowel leakage caused by serosal damage, two due to intra-peritoneal leakage of gastric fluid along the gastrostomy and 1 patient suffered intestinal suture failure. The sixth patient was subjected to percutaneous drainage of a subphrenic abscess and remained in the intensive care unit for 5 days.

Four patients in group II needed re-operation; two patients had bowel leakage caused by serosal damage, one patient suffered intra-peritoneal leakage of gastric fluid along the gastrostomy and the last patient required a re-operation due to a necrotic stoma. The fifth patient required percutaneous drainage of a pelvic abscess.

No significant differences were observed in patient or operation characteristics. Age, gender, bowel resection during the CRS and co-morbidity in terms of diabetes mellitus were comparable between both groups. (Table 1) Although not significant, the differences in bowel resection must be noted. A bowel resection was performed for 75% of the patients in the GEA_{RES} group and only performed for 47% of the patients in the GEA_{PRE} group.

A significant difference was detected in median age between the evaluated patients compared to the group of patients who were excluded from the evaluation. The group of patients who were excluded from the evaluation was significantly older to those who remained in study: 66 years versus 57 years respectively ($P < 0.01$). No other differences were identified between the excluded and included groups of patients. (Table 2)

The days to normal oral intake of solid foods, days to occlusion of the gastric tube and the total hospital admission are illustrated in table 3. No significant differences were demonstrated in any of these study endpoints between the randomized groups.

Discussion

We hypothesized that preservation of the right gastric-epiploic artery (GEA) during omentectomy would contribute to a 50% reduction of delayed gastric emptying after a HIPEC procedure and therefore to a shortening of hospital admission time in the early post-operative period.

In our study, no significant differences in any of the study endpoints were observed between patients randomized between resection and preservation of the GEA during omentectomy.

If resection of the GEA does not influence delayed gastric emptying, what could be the possible cause for DGE in our specific patient population?

Delayed gastric emptying is a complex disorder. An estimated 4% of the adult population experiences symptomatic manifestations of this condition. It is associated with many diseases and post-surgical conditions. It is considered to have multifactorial aetiology and is responsible for severe morbidity, prolonged hospitalisation and increased medical costs. [18]

DGE without mechanical obstruction in the post-operative period has mainly been reported after upper intestinal tract surgery, such as gastric surgery with vagotomy, oesophageal surgery and pancreatic surgery. It is generally a self-limiting phenomenon which can occur in the postoperative period as long as three to six weeks and incidentally longer. [19,20]

The incidence of this phenomenon varies within different studies, arguably due to differences in the definition used for DGE.

Several factors influencing DGE after other major abdominal surgical procedures have been suggested as mentioned earlier. Most of these factors are not thought to be of any relevance after a HIPEC procedure, simply due to the fact that these factors are dependent on the operative procedure and resected viscera. As part of a HIPEC procedure, resections of the

distal stomach, duodenum and pancreas head are seldom necessary. [21] Moreover, none of the included patients in this study had resections performed in this abdominal region.

A mechanism that is considered plausible contributing to DGE is the manipulation of intestines by the surgeon. This has been demonstrated to stimulate an innate inflammatory response, which triggers inhibitory mechanisms of the enterogastric neural pathway. [22,23] During cytoreductive surgery manipulation of stomach, small and large intestine must be considered substantial and unavoidable. Thus, a major inflammatory response in the postoperative period it is to be expected.

Furthermore, the intraperitoneal administration of heated chemotherapy could also contribute to DGE after a HIPEC procedure. It has been confirmed that administered chemotherapy has a penetration depth of up to 3 mm in the intraperitoneal tissue. Moreover, the hyperthermia has an additional cytotoxic effect. [24,25] The hyperthermic chemotherapy perfusion could cause temporal impairment of the gastric phasic contractions by disturbing the rhythmic depolarization potential due to the intramural penetration of Mitomycin-C during the operation or due to the inflammatory response to the cytotoxic effect postoperatively.

If either of these mechanisms could be proven to be major contributors to delayed gastric emptying, main treatment for this phenomenon would arguably mainly be symptomatic, due to respective unavoidability and standard procedure.

A debatable limitation to this study could be included number of patients. However, authors hypothesized a 50% reduction of DGE by preserving the GEA as clinically relevant prior to the

study and taking this clinical relevance into account, sample size calculation resulted in the minimal inclusion of at least 15 patients per study arm.

Comparison of the patients characteristics of the included patients revealed no significant differences. Yet, a discrepancy in numbers of bowel resections was noted between the groups, 47% in the GEA_{PRE} group vs. 75% in the GEA_{RES} group. These differences could be of influence on gastric emptying. Moreover, with the inclusion of larger number of patients, similar figures could be significantly different. However, it is arguable that more bowel resections in the GEA_{RES} group would contribute to an additional negative impact to the time to unlimited oral intake of solid food. Our results show no differences in the endpoints between both groups, there is even a slight advantage in all endpoints towards the GEA_{RES} group. These results support the conclusion that the preservation of the GEA has no positive affect on gastric emptying.

The patients that were excluded from evaluation did not differ between the two randomized groups. Reasons for exclusion were surgical complications in all patients. However, comparison between the excluded patients and study patients revealed unexpected significant differences in the median ages between the two groups: the excluded patients were significantly older. As demonstrated earlier, all patient specific and operative characteristics between the two groups were comparable and reasons for exclusion were due to severe surgical complications; nine patients required a re-operation and two additional patients required percutaneous drainage of an abscess. These figures of re-operations and occurrences are equivalent to those in major reviews on CRS-HIPEC. [4,26] Moreover, to our knowledge age has not been demonstrated as a significant risk factor for re-operations or development of a post-operative abscess. Age has only been correlated to

be an independent prognostic indicator for survival after CRS-HIPEC. [27] Therefore, no feasible explanation can be given for this age difference between included and excluded patients. Due to the overall comparability of the included patients, the authors do not consider this difference in median age to be of influence on the overall study results.

In conclusion, to authors knowledge this is the first randomized clinical trial towards the effect on post-operative gastric emptying comparing preservation and resection of the right gastro-epiploic artery. No association was demonstrated between preservation of the gastro-epiploic artery during omentectomy and gastric emptying after a HIPEC procedure. Delayed gastric emptying could be an effect of the extensive intestinal manipulation during cytoreductive surgery as well as the hyperthermic intraperitoneal chemotherapy administration.

Conflict of interest

No sources of funding were required for research or publication. No financial and personal relationships with other people or organisations that could inappropriately influence work on this manuscript can be declared.

Role of the funding source

No funding was required for this clinical trial.

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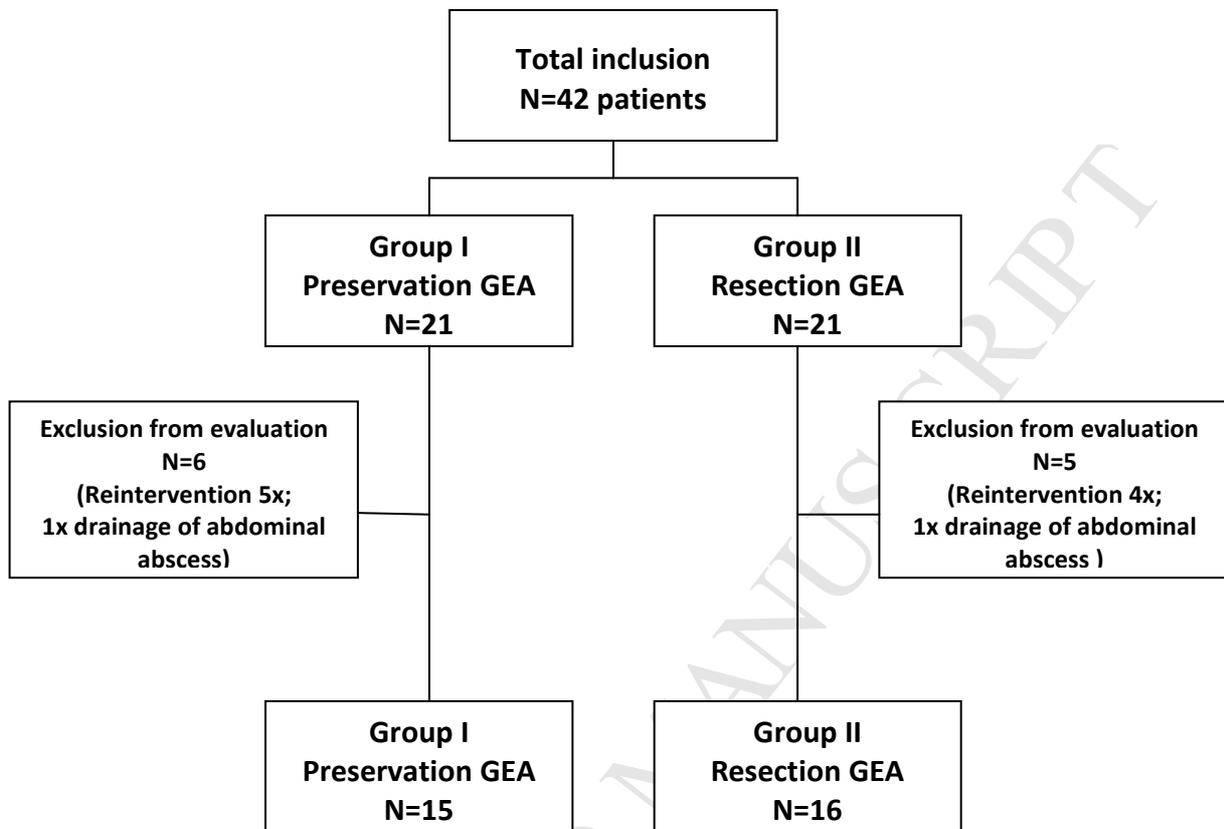
Table 1: Patient characteristics

Characteristics		GEA _{PRE} N=15	GEA _{RES} N=16	Total N=31	P Value
Mean age	Years (SD)	56 (9.9)	57 (9.5)	56 (9.5)	0.849 ¹
Gender	Male	6	9	15	0.479 ²
	Female	9	7	16	
Peroperative Bowel resection	No	8	4	12	0.149 ²
	Yes	7	12	19	
Diabetes		2	1	3	0.599 ²
		GEA _{PRE} : preservation of gastro-epiploic artery; GEA _{RES} : resection of gastro-epiploic artery; SD: standard deviation 1. Two Sample T-test. 2. Fischer exact test			

Table 2. Study endpoints

Evaluated patients		GEA_{PRE} N=15	GEA_{RES} N=16	Total N=31	P Value
Time to unlimited oral intake of solid food (days)	Mean (SD)	11.9 (9.73)	9.8 (4.37)	10.8 (7.41)	0.436¹
Time to occlusion of gastric tube (days)	Mean (SD)	7.7 (5.80)	6.4 (4.19)	7.0 (4.99)	0.481¹
Total hospital admission (days)	Mean (SD)	14.1 (5.54)	14.4 (7.38)	14.3 (6.45)	0.876¹
		GEA _{PRE} : preservation of gastro-epiploic artery, GEA _{RES} : resection of gastro-epiploic artery. 1. Two group T-test			

Figure 1: Overview of total inclusion and randomization.



GEA: Gastro-epiploic artery