Gastric Cancer (2011) 14:124–129
DOI 10.1007/s10120-011-0010-z

ORIGINAL ARTICLE

# Efficacy of NiTi Hand CAC$^{TM}$ 30 for jejunojejunostomy in gastric cancer surgery: results from a multicenter prospective randomized trial

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Received: 18 July 2010 / Accepted: 31 October 2010 / Published online: 24 February 2011


**Abstract**
*Background* Although a novel technique for the performance of intestinal sutureless anastomosis using a compression device has recently been investigated, it has not yet received widespread acceptance. We performed a multicenter prospective randomized trial in order to determine the clinical efficacy of the NiTi Hand CAC$^{TM}$ 30, a type of compression anastomosis clip (CAC), for jejunojejunostomy in gastric cancer surgery.
*Methods* Forty-seven patients from 6 institutions, who were diagnosed with gastric adenocarcinoma, were enrolled; these patients were randomized to a CAC group and a hand-sewn (control) group. Three patients dropped out for various reasons, and results for 44 patients were finally analyzed. The CAC group consisted of 20 patients, and there were 24 patients in the control group.
*Results* Anastomosis time, the primary endpoint of this trial, was shorter in the CAC group than in the control group ($P < 0.001$). However, total operation times ($P = 0.055$) did not differ. All reconstructions were completed by Roux-en-Y anastomosis, and the complication rates of the two groups did not differ ($P = 0.908$); however, jejunojejunostomy leakage occurred in two patients in the CAC group.
*Conclusions* Our prospective multicenter clinical trial showed that the use of the NiTi Hand CAC$^{TM}$ 30 for jejunojejunostomy in gastric cancer surgery was feasible and could reduce anastomosis time. However, considering that there were two cases of leakage, extended use of the NiTi Hand CAC$^{TM}$ 30 should be carefully applied.

**Keywords** Roux-en-Y anastomosis · Compression anastomosis clip · Jejunojejunostomy · Sutureless

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## Introduction

Gastric cancer is one of the most common malignancies worldwide, and surgical resection is the only curative treatment [1]. For gastric cancer in the upper third of the stomach, total gastrectomy and lymph node dissection followed by Roux-en-Y reconstruction is the most common surgical method [2, 3]. Although jejunojejunostomy is not a critical procedure compared with esophagojejunostomy in Roux-en-Y reconstruction, it requires a certain amount of time, and leakage of this anastomosis may be fatal.

The first intestinal anastomosis was performed manually by Theodor Billroth at the end of the nineteenth century [4, 5]. Although various anastomosis techniques have been developed for use in the performance of gastrointestinal surgery in consideration of hemostasis and freedom from tension, the hand suture technique is still one of the most popular methods. Jejunojejunostomy in Roux-en-Y reconstruction for the treatment of gastric cancer has traditionally been performed using a hand-sewing technique. However, operation time and the rate of complications have decreased recently due to the development of several anastomotic devices [6–8]. Nevertheless, few reports have described jejunojejunostomy in Roux-en-Y reconstruction created by an anastomotic device [9].

In particular, a new anastomosis device, the compression anastomosis clip (CAC), was first introduced in 2000, and was approved for use by the Food and Drug Administration of the United States (US FDA). To date, the NiTi Hand CAC$^{TM}$ (NiTi$^{TM}$ Surgical Solution, Netanya, Israel), a compression anastomotic device, has typically been applied for colo-colonic anastomosis [10–12]. However, widespread use of this device for anastomosis of the small intestine has not yet been accepted.

Here, we report a multicenter prospective randomized trial performed in order to provide information on the clinical efficacy of the NiTi Hand CAC$^{TM}$ 30, a type of CAC, for use in the performance of jejunojejunostomy in Roux-en-Y reconstruction in total gastrectomy for the treatment of gastric cancer.

## Patients and methods

This trial was approved by the Institutional Review Board (IRB) of the six participating institutions. The six surgeons from these institutions have performed more than 100 gastric cancer surgeries per year. In order to minimize technical error, all surgeons were trained two or three times with the use of the NiTi Hand CAC$^{TM}$ 30 in an animal laboratory.

We obtained written informed consent from all enrolled patients. Patients diagnosed with adenocarcinoma of the stomach by endoscopic biopsy were enrolled in this trial, and other eligibility criteria, exclusion criteria, and drop-out criteria are listed in Table 1. Between December 2008 and January 2010, 47 patients were finally enrolled. They were randomized into two groups, with a different jejunojejunostomy technique used in each group: (A) the CAC group, in which the NiTi Hand CAC$^{TM}$ 30 was used for jejunojejunal anastomosis in Roux-en-Y reconstruction, and (B) the control group, in which a hand-sewn anastomosis was used. Patients were randomly allocated by computer at the beginning of the operation (Fig. 1).

**Table 1** Inclusion, exclusion, and drop-out criteria for this randomized clinical trial

| |
|---|
| Inclusion criteria |
| Gastric adenocarcinoma confirmed by endoscopic biopsy |
| 20 ≤ Age (years) ≤ 85 |
| Possible curative resectability |
| ASA <3 |
| Informed consent |
| Exclusion criteria |
| Patients who simultaneously have another type of cancer |
| Patients who have undergone a prior gastric resection |
| Patients who have cancer with bleeding, perforation, or obstruction |
| Patients who are or become pregnant |
| Patients who have uncontrolled chronic disease |
| Drop-out criteria |
| Non-curative resection |
| Refusal to participate |

*ASA* American Society of Anesthesiologists

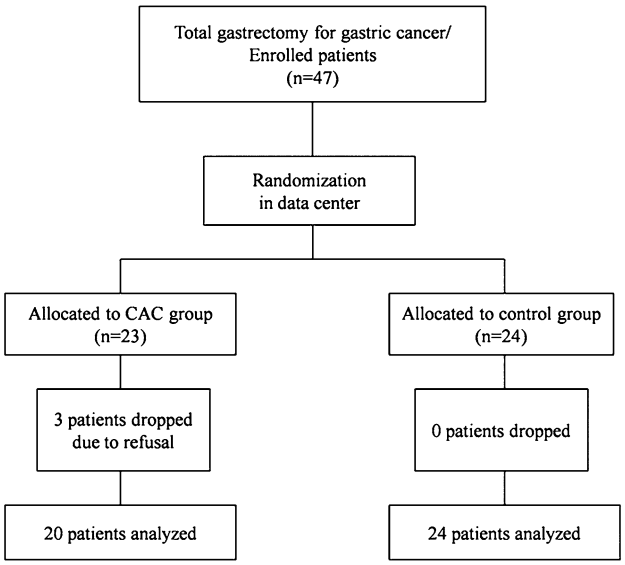


**Fig. 1** Flowchart of the trial. *CAC* Compression anastomosis clip

All patients underwent total gastrectomy for the treatment of gastric cancer. Lymph node dissection of D1 + $\beta$ or D2 was performed according to the *Japanese classification of gastric carcinoma* of the Japanese Gastric Cancer Association [13]. Patients with gastric cancer of an early stage that was not indicated for endoscopic submucocal dissection underwent surgery by a laparoscopic technique in which jejunojejunostomy was performed through a minilaparotomy. If circumstances required, cancer-involved organs, such as the spleen or distal pancreas, were simultaneously resected for curative surgery in patients with locally advanced gastric cancers.

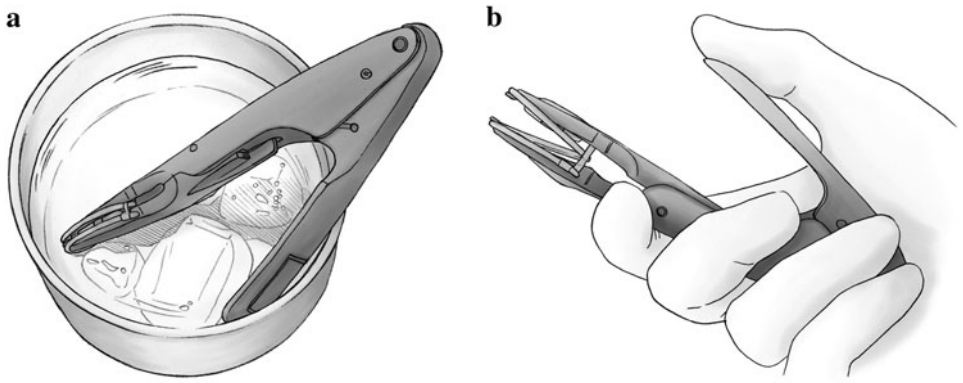


**Fig. 2** Preparation for anastomosis with the NiTi Hand CAC™ 30 (NiTi™ Surgical Solution, Netanya, Israel). (**a**) The NiTi Hand CAC™ 30 with holder was soaked in low-temperature saline. (**b**) Grip to insert the NiTi Hand CAC™ 30 into the small bowel. These schematic figures were provided by MEDIFINE (Seoul, Korea)

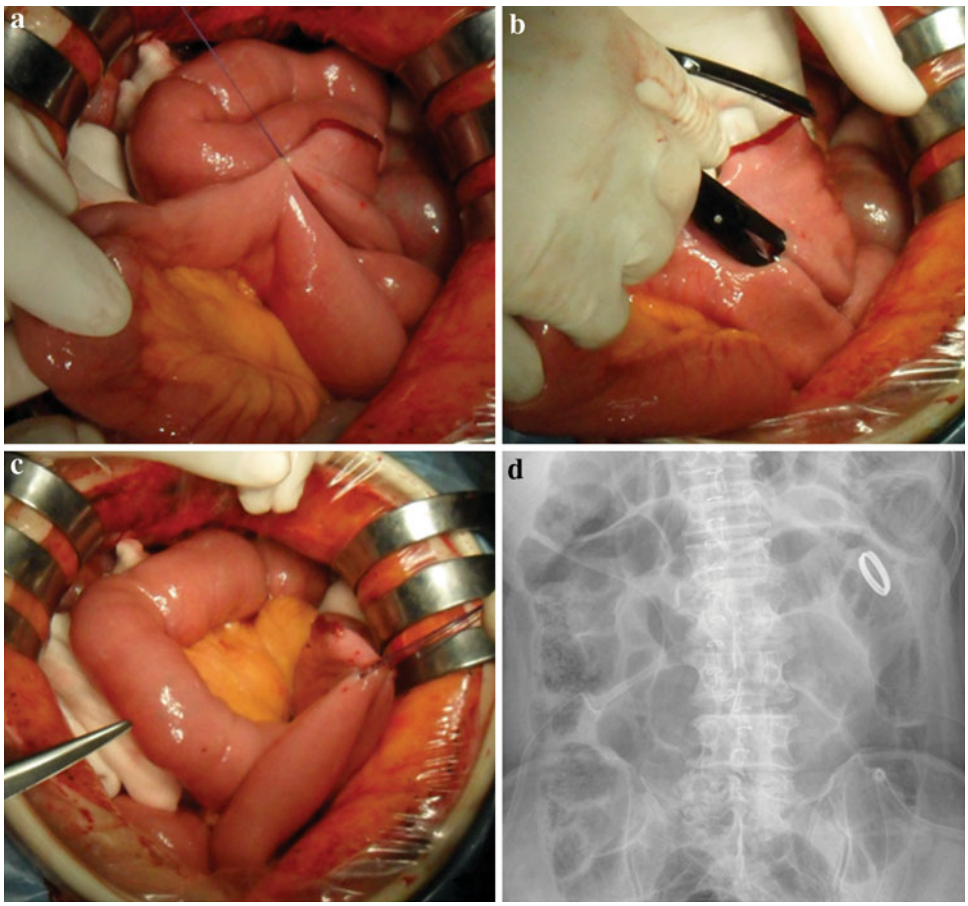


**Fig. 3** Anastomosis using the NiTi Hand CAC™ 30. (**a**) The stay suture was performed at the anastomosis site; (**b**) insertion of the device into small holes made in two portions of the jejunum; (**c**) closure of the insertion site; (**d**) plain X-ray of the abdomen on postoperative day 1

After the total gastrectomy, an esophagojejunostomy was created with a circular stapler. In the CAC group, jejunojejunostomy was performed at the jejunum 40 cm distal from the esophagojejunostomy site, using the CAC. The CAC device with holder was soaked in low-temperature saline for 30 s (Fig. 2). Two jejunal loops were placed side by side with two stay sutures. Small holes were made for insertion of the CAC. The cooled CAC with the holder was inserted into the jejunum, and the holder was suitably clamped in order to achieve compression considering the thickness of the small bowel. The holder was removed, leaving the compressed CAC, and the small holes were then closed with interrupted sutures (Fig. 3). After additional reinforcement was made with several sero-muscular sutures, we confirmed the tightness of the anastomosis without air leakage. In the control group, end-to-side jejunojejunostomy was performed with a continuous interlocking suture with a sero-muscular reinforced suture. Patients were started on sips of water on the second or third postoperative day, and were discharged once they did not

have specific complaints and had normal clinical status after the sixth postoperative day.

The primary endpoint in this trial was the anastomosis time in the performance of the jejunojejunostomy. Secondary endpoints included the length of hospital stay and the complication rate. The sample size of the enrolled patients was calculated on the presumption that the anastomosis time for the patients in the CAC group would be shorter than that in the control group. A drop-out rate of 10% was assumed. To obtain a power of 80% and a significance level of 0.05, the required sample size was calculated as 50 patients. Although the participating institutions did not achieve the expected number for enrollment, this trial was terminated because the anastomosis time was significantly reduced when the study period permitted by the IRB had ended.

Results of continuous variables are presented as medians and ranges. The Mann–Whitney *U*-test was adopted for the analysis of differences between the two groups in anastomosis and operation times, length of hospital stay, and the day of postoperative flatus. Complication rates were analyzed by the $\chi^2$ test. All analyses were performed with the statistical software Statistical Package for the Social Sciences (SPSS), version 13.0 for Windows (SPSS, Chicago, IL, USA). $P < 0.05$ was regarded as significant.

**Table 2** Comparison of clinical and surgical variables between the two groups

| Variables | Control group 24 patients (%) | CAC group 20 patients (%) | *P* value[a] |
|---|---|---|---|
| Age (years) | | | |
| <65 | 17 (70.8) | 15 (75.0) | 0.757 |
| ≥65 | 7 (29.2) | 5 (25.0) | |
| Gender | | | |
| Male | 20 (83.3) | 13 (65.0) | 0.162 |
| Female | 4 (16.7) | 7 (35.0) | |
| Comorbidity | | | |
| Yes | 8 (33.3) | 4 (20.0) | 0.323 |
| No | 16 (66.7) | 16 (80.0) | |
| Approach | | | |
| Laparoscopy | 14 (58.3) | 13 (65.0) | 0.651 |
| Open | 10 (41.7) | 7 (35.0) | |
| LN dissection | | | |
| D1 + α or β | 11 (45.9) | 12 (60.0) | 0.643 |
| D2 | 13 (54.2) | 8 (40.0) | |
| Co-resection of other organs | | | |
| Yes | 7 (29.2) | 2 (10.0) | 0.339 |
| No | 17 (70.8) | 18 (90.0) | |
| Roux-en-Y Limb | | | |
| Antecolic | 21 (87.5) | 16 (80.0) | 0.580 |
| Retrocolic | 3 (12.5) | 4 (20.0) | |

[a] *P* value by $\chi^2$ test *CAC* compression anastomosis clip, *LN* lymph node

## Results

Of 47 patients, 23 patients were recruited into the CAC group and 24 into the control group. However, three patients who refused to participate in this trial after enrollment were dropped, and results for 44 patients (20 in the CAC group and 24 in the control group) were then analyzed (Fig. 1). The median age of the participating patients was 53 years (range 25–82 years) and 11 patients (25%) were female. There were no significant differences between the two groups with regard to clinicopathologic factors, including age, gender, comorbidity, and operative methods (Table 2).

Table 3 shows the surgical outcomes for both groups. The anastomosis time (median 10 min, range 5.0–33.0 min) in the CAC group was significantly shorter than that (median 17 min, range 8.5–38.0 min) in the control group ($P < 0.001$). However, no significant difference was observed in total operation time (240 vs. 190 min, $P = 0.055$). The complication rate, day of postoperative flatus, length of hospital stay, and mortality rate were also not significantly different between the two groups (Table 3).

The total complication rate was 34.1%, and five patients underwent reoperation. Unfortunately, leakage of the

**Table 3** Surgical outcomes for the two groups

| Variables | Hand-sewn group (24 patients) | CAC group (20 patients) | *P* value[a] |
|---|---|---|---|
| Anastomosis time (median, range) (min) | 17, 8.5–38.0 | 10, 5.0–33.0 | **<0.001** |
| Operation time (median, range) (min) | 240, 165–350 | 190, 116–273 | 0.055 |
| Complications (*n*, %) | 8, 33.3 | 7, 35.0 | 0.908 |
| Jejunojejunostomy-related | 0 | 2 | |
| Others | 8 | 7 | |
| Day of postoperative flatus (median, range) (day) | 4, 2–8 | 4, 2–6 | 0.671 |
| Length of hospital stay (median, range) (days) | 9, 3–90 | 7, 4–21 | 0.247 |
| Mortality (*n*, %) | 0 (0.0%) | 1 (5.0%) | 0.268 |

[a] *P* value by Mann–Whitney *U*-test for continuous variables, $\chi^2$ test for categorical variables *P* value in bold is significant

**Table 4** Complications that occurred in the two groups and their management

| |
|---|
| Hand-sewn group; 8 patients |
| EJ leakage (2); conservative care |
| Pancreas leakage (2); conservative care |
| Colon perforation (1); reoperation |
| Wound infection (1); evacuation |
| Fluid collection (2); percutaneous drainage |
| CAC group; 7 patients |
| EJ leakage (1); conservative care |
| EJ bleeding (1); reoperation[a] |
| Fluid collection (2); percutaneous drainage |
| CAC leakage (2); reoperation |
| Foreign body (1); reoperation |

*EJ* esophagojejunostomy

[a] Death due to multiple organ failure

jejunojejunostomy occurred in two patients in the CAC group, and reoperation, including re-anastomosis with the hand-sewing technique, was performed. These cases of leakage occurred in the early period of this trial. Other complications and their management are listed in Table 4. There was one death in the CAC group; the patient died of multiple organ failure after reoperation, performed because of bleeding at the esophagojejunostomy site.

## Discussion

This multicenter randomized controlled clinical trial was designed to evaluate the efficacy of a novel compression anastomosis device, the NiTi Hand CAC$^{TM}$ 30, in performing anastomosis of the small intestine in gastric cancer surgery. The concept of compression sutureless anastomosis was first established by Murphy in 1892 [14]. His device, known as Murphy's button, consisted of two metallic rings, which were placed in the bowel lumen for anastomosis. Following compression of the bowel lumen by the two rings, necrosis was induced, and a new lumen was created; this foreign metallic body was spontaneously discharged from the body along with the necrotic tissues several days later. After that, other compression devices, such as the AKA-2 (Seidel Medipool, Munich, Germany) and the biofragmentable anastomosis ring were developed [15, 16]. A new compression anastomotic device, the NiTi Hand CAC$^{TM}$ 30, has recently been applied in anastomosis of the large intestine, and we decided to perform a clinical trial to determine its efficacy in anastomosis of the small intestine. Although the concept of this device, which is composed of nickel and titanium, is similar to that of other compression devices, it has additional important characteristics that include reversibility, temperature-dependence, and memory-shaped metal. When this device is cooled, it becomes flexible. After it is applied to the intestines, it returns to the austenite state for compression of the intestinal wall [17]. Therefore, its insertion into narrow holes in the small intestine is possible. In addition, assurance of necrotic process is effectively possible in spite of various bowel thicknesses.

A compression anastomotic instrument such as the NiTi Hand CAC$^{TM}$ 30 is a type of mechanical device. The main benefits of using a mechanical device for reliable performance of intestinal anastomosis and reduction of operation time have been well established [18]. However, the use of the hand-sewing technique in the performance of intestinal anastomosis is still the standard procedure due to its cost effectiveness and safety record. In Roux-en-Y reconstruction after total gastrectomy for the treatment of gastric cancer, esophagojejunostomy is performed primarily with the use of a circular stapling device, owing to the inconvenience of creating a hand-sewn suture in the deep and narrow space. Meanwhile, in spite of the availability of mechanical devices, which may provide a time-saving advantage, jejunojejunostomy is usually performed using a hand-suture procedure, owing to easy exposure of the anastomotic site. However, the development of surgical site infections, as well as other systemic complications, is related to the duration of the procedure [19]. Therefore, to reduce the operation time, mechanical devices are usually used for jejunojejunostomy instead of hand suture. In our trial, use of the CAC for jejunojejunostomy resulted in reduced anastomotic time, with no increase in overall complications.

Since the introduction of the mechanical stapler designed by Ravitch and Steichen [20], the most popular mechanical device for use in the performance of intestinal anastomosis has been the linear stapler or circular stapler [20, 21]. However, Nudelman et al. have reported that in the field of colorectal surgery, the CAC device has several advantages over the use of the stapler devices [10–12]. First, the raw surface of the resected margin made by a stapler can lead to stricture during healing and intraluminal bleeding. However, the cut surface of the anastomosis created by the CAC device is already covered by the mucosa, and a smooth wall is left. Second, the caliber of anastomosis by the CAC is wider than that by other technique, because the size of the outer circumference is established by the anastomosis. In addition, staples left in the anastomotic wall may interfere with radiologic images, whereas CAC devices do not leave a foreign body, because it is expelled after a few days along with feces. With regard to use of a stapler for the small intestine, the lumen is too narrow for the insertion of the existing linear stapler, the abdominal cavity can be contaminated by the intestinal contents from the large holes of the bowel which are made to insert the bigger frame of linear stapler into the small bowel lumen. However, the CAC requires only small holes

for the introduction of the device. Furthermore, the flexibility of the CAC device at low temperature can allow the adjustment of the degree of pressure according to the thickness of the small bowel before the CAC device hardens. Based on these advantages, the use of the CAC for jejunojejunostomy could become a reliable procedure and reduce anastomotic operative time.

In the present trial, anastomosis using the CAC was found to be superior to hand-sewn anastomosis with regard only to the anastomotic time. Findings from other clinical studies in which a compressive anastomotic device was used for lower gastrointestinal surgery showed advantages in terms of overall operation time, postoperative complications, and recovery of bowel function, as well as anastomotic time [16, 22, 23]. Jejunojejunostomy in total gastrectomy for the treatment of gastric cancer is basically a small part of the entire operation. Therefore, shortening of the anastomotic time for jejunojejunostomy would not have an effect on the total operation time or postoperative recovery. However, for other types of small-intestinal surgery, such as segmental resection, it would be expected to obtain better postoperative outcomes when anastomosis is performed with a CAC.

Although the overall complication rate did not differ between the CAC group and the control group in the present study, two patients from the CAC group developed leakage at the jejunojejunostomy site. Reanastomosis followed by revision of the leakage site was performed in these patients. We assumed that serious complications, such as disruption of the anastomosis by the CAC, were caused by the unskilled use of the devices, in spite of the training in the animal laboratory. In the early period of the trial, insufficient compression and over-tightness might have led to the failure of the anastomosis, in spite of the training in the animal laboratory. The advice of supervisors can help to overcome the learning curve, and easily achieve the reliability of anastomosis using the NiTi Hand CAC™ 30.

In conclusion, our prospective multicenter clinical trial showed that the use of the NiTi Hand CAC™ 30 for jejunojejunostomy in gastric cancer surgery could reduce the anastomosis time without increasing overall morbidity. However, the occurrence of two cases of leakage suggests that the extended use of the device should be carefully applied.

**Conflict of interest** The authors have no conflict of interest in this study.

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