RESEARCH ARTICLE

Comparison of Ligasure Versus Conventional Surgery for Curative Gastric Cancer Resection: a Meta-Analysis

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Abstract

Background: The LigaSure vessel sealing system has been proposed to save operation time and reduce intraoperative blood loss for various surgeries. However, its usage for gastric cancer is still controversial. The aim of the present meta-analysis was to compare the effectiveness of LigaSure with conventional surgery in gastrectomy. Materials and Methods: Sources were retrieved from the Cochrane Library, MEDLINE, EMBASE, SCOPUS and Google Scholar until February, 2015. All randomized controlled trials comparing LigaSure with conventional surgery in curative gastric cancer resection were selected. After data extraction, statistics were performed by Review Manager 5.1 software. Results: Three eligible randomized controlled trials were evaluated, with a total of 335 patients. The quality of the included trials was good, yet some methodological and clinical heterogeneity existed. There were no significant differences between the LigaSure and conventional groups in operative time (weighted mean difference [WMD], -22.95 minutes; 95% confidence interval [CI], [-59.75, 13.85]; P = 0.22), blood loss (WMD, -45.8 ml; 95% CI, [-134.5, 42.90]; P = 0.31), nor the incidence of surgical complications (odds ratio, 1.18; 95% CI, [0.68, 2.05]; P = 0.54). But there was a longer duration of hospital stay in LigaSure group (WMD, 1.41 days; 95% CI, [0.14, 2.68]; P = 0.03). Conclusions: All available randomized evidence has been summarized. LigaSure does not confer significant advantage over conventional surgery for curative gastric cancer resection. The usefulness of the device may be limited in gastrectomy. But, more trials are needed for further assessment of the LigaSure system for gastric cancer.

Keywords: Gastric cancer - LigaSure - conventional surgery - randomized controlled trials (RCTs)

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Introduction

Gastric cancer is one of the most common malignancies worldwide (Siegel et al., 2015). Currently, gastrectomy with lymph node (LN) dissection remains the mainstay of curative treatment (Songun et al., 2010). The operation involves radical total gastrectomy or distal subtotal gastrectomy and D1 lymphadenectomy for early gastric cancer or D2 lymphadenectomy for advanced gastric cancer(Society, 2004). It requires careful hemostasis with a clear operative field for high-quality LN dissection and avoidance of accidental injury. In conventional surgery, most lymphatic channels, vessels, and tissue bundles are ligated with suture material or thread to prevent bleeding and lymphatic leakage. As a result, it is often associated with a long surgical time and significant bleeding. In recent years, a new hemostatic tool, namely the LigaSure vessel sealing system, has been developed. The LigaSure system bases on mechanical pressure and the principle of bipolar electrocoagulation to seal blood vessels up to 7 mm in diameter in 2-7s (Heniford et al., 2001). The device delivers a controlled high-power current at a low voltage to melt collagen and elastin, permanently fusing the vascular layers and obliterating the vessel lumen. The collagen and elastin reform to create a "seal zone," which appears as a distinctive, translucent area with plastic resistance to deformation (Spivak et al., 1998). Experimental and clinical results of the LigaSure system have demonstrated that it is safe and effective in many surgical procedures, and can lead to shortened operating time (Palazzo et al., 2002; Lee et al., 2003; Saiura et al., 2006; Eroglu et al., 2007; Elhao et al., 2009; Silva-Filho et al., 2009; Yao et al., 2009; Yao et al., 2011). Its value in complex gastrointestinal surgery, such as extended lymphadenectomy and D2 dissection for gastric cancer, is still a matter of controversy. There were only a few randomized controlled trials (RCTs) with a limited number of patients (Lee et al., 2003; Takiguchi et al., 2010; Fujita et al., 2014).

In this study, we intended to systematically review the literature by including all published RCTs and to assess outcomes of LigaSure versus conventional surgery for curative gastric cancer resection.

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Materials and Methods

Search strategy

A systematic literature search was conducted according to the standards of the Cochrane collaboration. The following databases were searched: Cochrane Library, MEDLINE, EMBASE, SCOPUS and Google Scholar (until February, 2015). The search strategy included the terms: 'stomach' or 'gastric' or 'gastrointestinal' and 'cancer' or 'carcinoma' and 'LigaSure'. No language limitations were set. All relevant articles were scanned, and all additional studies of potential interest were also retrieved. We analyzed the studies on the basis of abstract or title at first. If the studies could not be judged from abstract or title, or relevant articles needing careful scrutiny, then full text was read.

Study selection and data extraction

We used the name of the first author and the year of publication for article identification. Studies were included for analysis if they met the following criteria: 1) RCT without language restriction; 2) the study compared the LigaSure vessel sealing system versus conventional vessel ligation in gastrectomy for gastric cancer; 3) it was possible to extract or calculate the appropriate data from the published results.

From each eligible trial, we compiled the following data in the database: study name, publication year, journal reference, country, study design (treatment arms, study duration, randomization, allocation concealment, blinding), participants (main inclusion and exclusion criteria, sample size, baseline data such as age and gender), interventions (intervention groups, type of surgery, surgical experience).

The primary outcomes were total operation time and intraoperative blood loss. The secondary outcomes included duration of postoperative hospital stay and postoperative complications.

Quality assessment

The risk of bias and quality in each eligible study were assessed by Cochrane's risk of bias tool, including the following 7 areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Risk of bias graph was drawn, and risk of bias summary was compiled.

Statistical analysis

For total operation time, amount of intraoperative blood loss, and duration of postoperative hospital stay, the effective size of each trial was reckoned by the mean difference (MD) between treatment groups and pooled as the weighted mean difference (WMD) with 95 % confidence interval (CI) by using the inverse variance method. If estimates for mean and standard deviation (SD) were not provided, we used the methods from Hozo et al. (Hozo et al., 2005) to convert median and range estimates into mean and SD. For the postoperative complication, incidence was counted and odds ratio (OR) was analyzed. Data were analyzed using Review Manager 5.1 meta-analysis software, as previously reported (Yao et al., 2008; Song et al., 2015). Statistical heterogeneity was tested by using χ^2 and I^2 tests. If heterogeneity was high ($I^2 > 50\%$), we used the random effect model; otherwise, the fixed effect model was applied. Statistical significance was set at $P < 0.05$.

Results

Our search yielded 44 literature results, 39 were excluded on the basis of abstract or title. After further careful scrutiny, 2 were excluded because they did not match the criteria. Three were considered eligible according to the inclusion criteria (Figure 1) (Lee et al., 2003; Takiguchi et al., 2010; Fujita et al., 2014). Baseline characteristics of the included trials and patients were presented in Tables 1 and 2. There were a total of 335 patients: 160 participants were in the LigaSure group and 175 participants in the conventional surgery group. In Fujita 2014's trial (Fujita et al., 2014), 1 patient allocated to the LigaSure group underwent gastrojejunostomy without gastric resection based on the intraoperative findings, and 1 patient allocated to the conventional group was diagnosed with esophageal cancer after randomization and underwent subtotal esophagectomy. These 2 patients were excluded from our analysis, making a final number of 335 patients.

The quality of the included studies was good in terms of sample size, allocation concealment, blinding, as well as of other sources of bias (Figure 2). All of the studies applied randomization and provided adequate data for

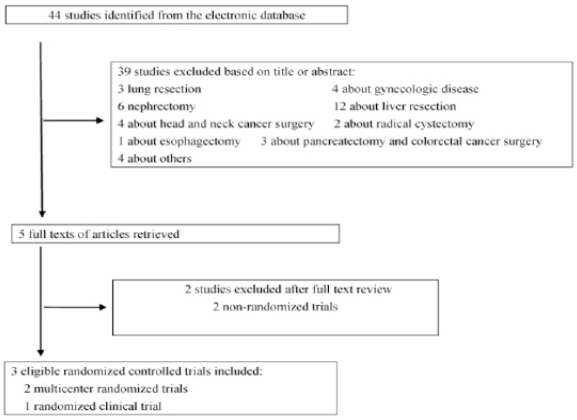

Figure 1. Flow Chart Diagram of the Study Selection

Table 1. Clinical Characteristics of the Included Trials

Study	Recruitment	County	Surgical experience
Fujita 2014	2009.1---2010.5	Japan	Expert and experienced surgeons
Lee 2003	1999.3—2001.5	Taiwan	Trained and experienced surgeons
Takiguchi 2010	2007.7—2008.8	Japan	Unclear

Table 2. Baseline Characteristics of the Included Patients

Study	Groups	Patients numbers	Age (years)	Men	Women
Fujita2014*	LigaSure surgery	81	72 ± 7.5**	55	26
	Conventional surgery	79	69 ± 8.8**	57	22
Lee 2003	LigaSure surgery	40	68 ± 15	26	14
	Conventional surgery	40	64 ± 13	29	11
Takiguchi 2010	LigaSure surgery	55	68.8 ± 9.7	40	15
	Conventional surgery	42	65.8 ± 9.2	28	14

* 1 patient allocated to the LigaSure group underwent gastrojejunostomy without gastric resection based on the intraoperative findings, and 1 patient allocated to the conventional group was diagnosed with esophageal cancer after randomization and underwent subtotal esophagectomy, these 2 patients were excluded from our analysis; ** Converted from median by the method from Hozo 16, as presented in the statistical analysis section.

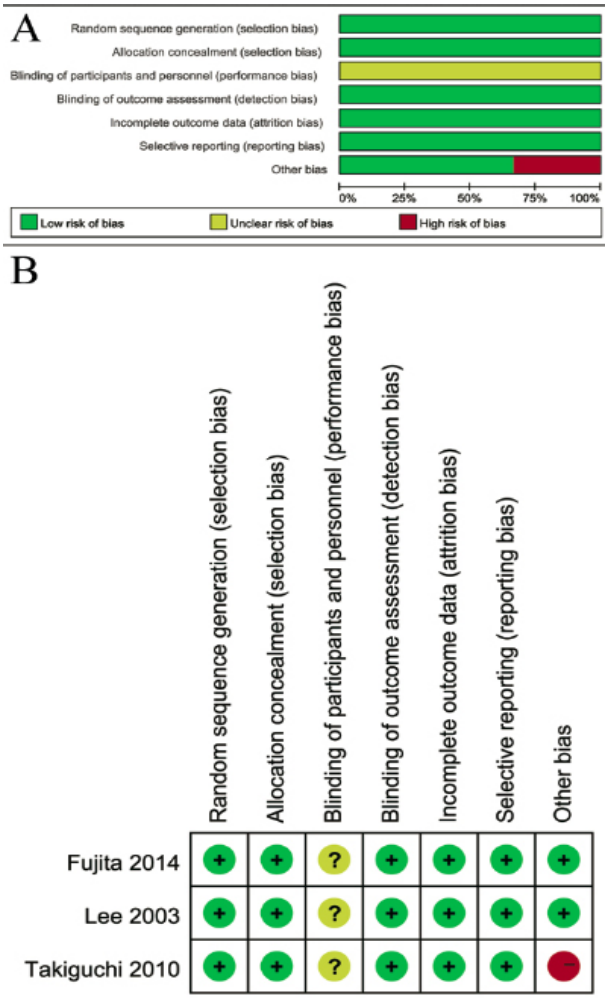

Figure 2. Quality assessment using the Cochrane risk of bias tool. (A) Risk of bias graph. (B) Risk of bias summary. Explanation: green circle means low risk of bias, yellow circle means unclear risk of bias, red circle means high risk of bias.

analysis. Surgical experience was described in 2 of the 3 studies. Only 1 trial didn't provide any information about surgical experience, indicating bias could be possible from this point.

Operation time was a major outcome of our analysis (Figure 3). Lee2003 (Lee et al., 2003) reported that using the LigaSure system in radical gastric cancer surgery reduced the operating time by 23.9 % when compared with the conventional method (169 ± 25 minutes versus 222 ± 28 minutes; P=0.001). However, Takiguchi2010 (Takiguchi et al., 2010) and Fujita2014 (Fujita et al., 2014) did not find significantly differences. Meta-analysis showed that operation time between LigaSure surgery and conventional surgery was not significantly different (WMD, -22.95 minutes; 95% CI, [-59.75, 13.85]; P = 0.22), and the random effect model was used.

Our results demonstrated that there were no differences in intraoperative blood loss between LigaSure and conventional surgery. The pooled estimate was -45.8 ml in intraoperative blood loss (95 % CI, [-134.50, 42.90]; P = 0.31) by using the random effect model (Figure 4). However, Figure 5 displayed that length of hospitalization was longer following operations in LigaSure surgery than in conventional surgery (WMD, 1.41 days; 95% CI, [0.14, 2.68]; P = 0.03), and the fixed effect model was applied.

These studies reported postoperative complications in 36 patients (20.6 %) after LigaSure gastrectomy, including 11 patients with wound infection, 8 with pancreatic fistula, 2 with abdominal abscess, 5 with ileus and 10 other complications. After conventional gastrectomy, 29 patients (18.1 %) experienced postoperative complications, including 4 patients with wound infection, 2 with pancreatic fistula, 3 with abdominal abscess, 3 with ileus and 17 other complications. There was 1 death in LigaSure gastrectomy and 3 deaths in conventional gastrectomy, respectively. Figure 6 showed that postoperative

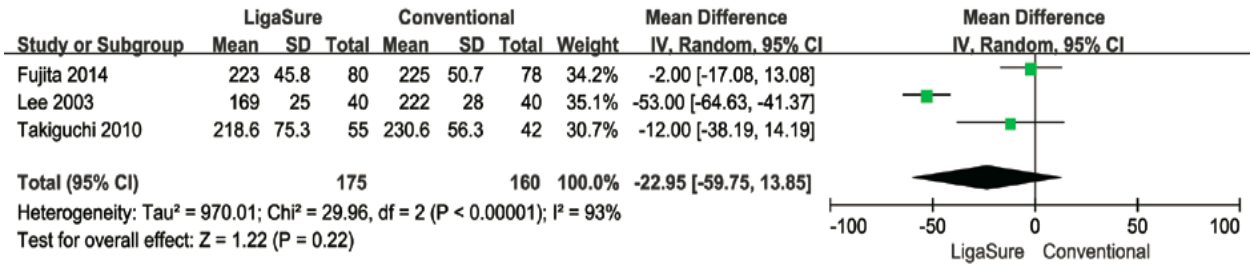

Figure 3. Comparison of Operation Time between LigaSure and Conventional Surgery

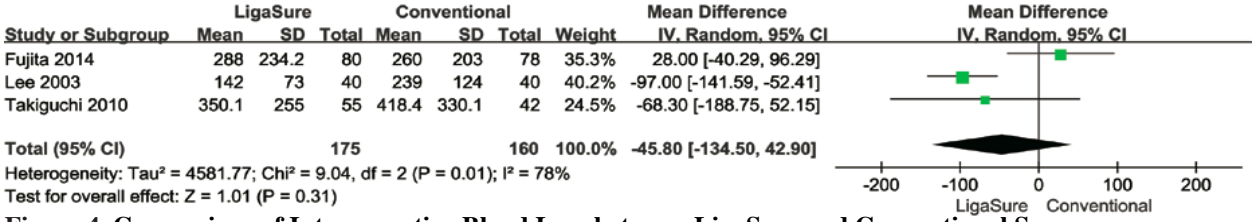

Figure 4. Comparison of Intraoperative Blood Loss between LigaSure and Conventional Surgery

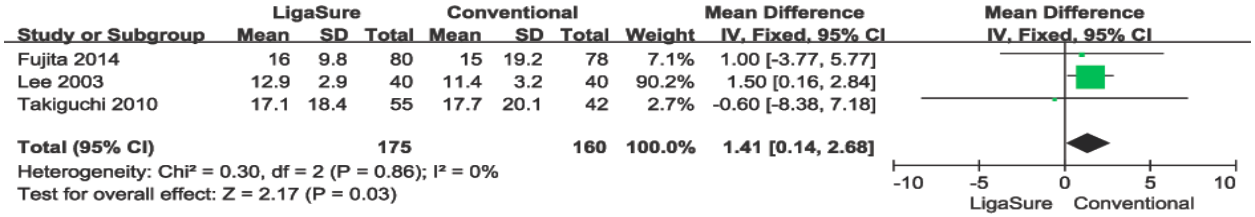

Figure 5. Comparison of Length of Hospitalization between LigaSure and conventional surgery

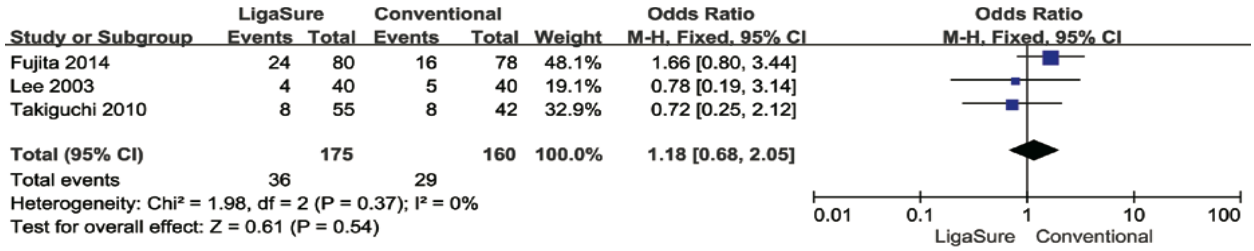

Figure 6. Comparison of Postoperative Complications between LigaSure and Conventional Surgery

complications was similar between the LigaSure and conventional groups (OR, 1.18; 95 % CI, [0.68, 2.05]; P = 0.54). There were no differences in operative, cancer-related and other complications between the groups. No heterogeneity was found between different studies (I^2 = 0%), and the fixed effect model was used.

Discussion

Since its commercial launch, the LigaSure device has been increasingly used in a variety of surgical procedures, with mixed results. Many clinical and experimental studies have proved that the LigaSure vessel sealing system could reduce both the operative time and the blood loss related with hysterectomy (Elhao et al., 2009; Silva-Filho et al., 2009), splenectomy (Yao et al., 2011), hemorrhoidectomy (Palazzo et al., 2002) , thyroidectomy (Yao et al., 2009), hepatectomy (Saiura et al., 2006), and etc. LigaSure is a rapid, safe and reliable technique without increasing postoperative complications. The main advantage of this device is that it simplifies the procedure and eliminates the need for clips and suture ligations while also achieving efficient hemostasis (Yao et al., 2011). However, there were several investigations that did not demonstrate such superioriy. For example, Hagen et al. (Hagen et al., 2005) compared the use of LigaSure with conventional suture ligature in abdominal hysterectomy. They did not uncover a time sparing effect from the use of LigaSure or any difference in the occurrence of blood loss and complications. Uzunoglu et al. (Uzunoglu et al., 2013) compared the use of LigaSure with conventional dissection techniques in pancreatic surgery. There were no differences in overall operation time, intraoperative blood loss, number of units of packed red blood cells, postoperative morbidity, length of hospital stay and mortality between the two groups.

The current investigation is the first meta-analysis comparing the use of the LigaSure technique with conventional method in gastric cancer resection. Superiority of the LigaSure was not demonstrated either. It is believed that LigaSure is often not suitable for the precise surgical maneuvers required for operations in the vicinity of extremely delicate structures such as the lymphadenectomy and bursectomy in the radical gastrectomy for gastric cancer (Fujita et al., 2014), or the recurrent laryngeal nerves and parathyroid glands during the total thyroidectomy (Kiriakopoulos et al., 2004; Cipolla et al., 2008). Conventional vessel knotting ligation still remained important when meticulous manipulation is performed. Furthermore, LigaSure has almost no role in reconstruction and anastomosis, which are as time-consuming as resection of the stomach. These may be the reasons that the effectiveness of the LigaSure is limited in radical gastrectomy (Fujita et al., 2014).

It is important to mention the heterogeneity among studies when interpreting the meta-analysis results, because some differences in methodologies might influence the results. This meta-analysis included 3 investigations, 2 were multicenter randomized controlled trials. Differences in the experience of surgeons and surgical procedures might have affected the operative outcomes of gastric surgery. Firstly, there were some differences in surgical procedures performed in the studies. In the LigaSure group of Lee 2003's RCT (Lee et al., 2003), LigaSure was used to seal all of the lymphatic ducts and blood vessels without any suture. But in Fujita 2014's RCT (Fujita et al., 2014), hand ligation was used for minor arteries and vessels while LigaSure was used to occlude major arteries and vessels.

In the meticulous manipulation of lymphadenectomy, hand ligation also was used, even in the LigaSure group. Secondly, the surgeon's experience also was an important element affecting the outcome. In Takiguchi 2010's RCT (Takiguchi et al., 2010), it was reported LigaSure could significantly reduce operative time and intraoperative blood loss at the institution that performed the most procedures. It was suggested that LigaSure could show its superiority much better in the hands of experienced surgeons. In multicenter randomized controlled trials, it was very difficult to require all doctors to have the same experience. Finally, the finding of a longer hospital stay following LigaSure operation was rather surprising. We considered that this could be related with the skewed age distribution between the two groups, than a difference in outcome between the two operation techniques.

In conclusion, application of LigaSure depends on the type of surgery. Until now, RCTs, which compared LigaSure with conventional surgery in radical gastrectomy, have not shown any significant advantages yet. More trials are needed for further assessment of the LigaSure system for gastric cancer.

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