



LigaSure Small Jaw vs. Harmonic Focus and Clamp-and-Tie Technique in Total Thyroidectomy for Benign Disease: A Prospective Randomized Trial

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Abstract

Background: The Ligasure Small Jaw (LS) and the Harmonic Focus (HF) are devices designed for thyroid surgery. Aim: to assess their efficacy and safety compared with traditional dissection in a prospective randomized trial (ClinicalTrials.gov n° NCT01649154).

Methods: One hundred-twenty six patients with benign disease undergoing total thyroidectomy were randomly assigned into 3 groups: Clamp-and-Tie (CAT) group (42 patients); LS group (42 patients); HF group (42 patients). Perioperative and post-operative data were compared between groups.

Results: The three groups were homogeneous in terms of age, gender, BMI and pathology. In LS and HF groups the mean operative time was 20 min shorter than CAT group (p<0.001). The complication rates as well as the mean hospital stay were similar between the 3 groups (p=n.s).

Conclusion: The use of surgical devices is as safe and effective at vessel dissection and hemostasis as the CAT technique with a decrease in mean operative time.

Keywords: Thyroid; Total thyroidectomy; Benign thyroid disease; Surgical devices

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Introduction

Total thyroidectomy is increasingly performed for multinodular goiter because it enables definitive treatment of the disease, thus averting repeated operations and their related complications and the removal of possible occult malignancies, which have shown significant incidence [1-3]. The thyroid gland is one of the most vascularized organs in the human body and its removal requires meticulous hemostasis to preserve the parathyroid glands and recurrent nerves [4,5]. For this reason, the operation needs meticulous dissection and accurate hemostasis in order to obtain a dry field and to prevent unwitting damage of the adjacent structures.

The most time-consuming part of the operation is the ligation and division of the thyroid vessels. In regard to this, many attempts have been made to reduce the mean operative time and to suggest new methods of vessel ligation and division without increasing the risk of postoperative complications [6,7]. Conventional hemostasis is performed by the clamp-and tie technique, and monopolar or bipolar electrocautery for the small vessels [1].

During the last two decades, many improvements regarded haemostasis have been proposed for thyroid surgery. Today, the use of electric monopolar coagulation is no longer used because of the possibility of the lateral heat dispersion to the surrounding structures [6,7]. New tools based on a different method of energy transmission, including ultrasonic or electrical energy, have been proposed and implemented for thyroid surgery. The use of these devices is well known in abdominal surgery, but also they have proved suitable for thyroid surgery [8-10]. Indeed, other easy-to-use devices such as the LigaSure vessel sealing system (Valleylab, Boulder, CO) or Harmonic Focus[®] ultrasonic device (EthiconEndo-Surgery, Guaynabo, PR, USA). However, their effectiveness in achieving hemostasis remains is still limited by the vessel diameter, and the risk of damage to adjacent structures cannot be completely excluded [11-14].

Moreover, even if the reduction in operative time seems possible with their use, on the other

Table 1: Inclusion and Exclusion Criteria.

Inclusion criteria	
·	Benign disease requiring total thyroidectomy
·	Age >18 years
Exclusion criteria	
·	Parathyroid glands disease associated
·	Suspicion of malignancy
·	Previous cervical surgery
·	Patients unwilling or unable to provide informed consent
·	Age <18 years
·	Pregnancy
·	Patients having antithrombotic therapy

hand, their high cost has to be taken into account [15]. However, their effectiveness in achieving hemostasis remains is still limited by the vessel diameter, and the risk of damage to adjacent structures cannot be completely excluded [11-13]. Moreover, even if the reduction in operative time seems possible with their use, on the other hand, their high cost has to be taken into account [15,16].

Several studies have been published comparing LigaSure® or Harmonic Focus® ultrasonic to the clamp-and-tie technique, but only three [1,7,17] comparing all the three different technique, and in addition only two studies comparing all the newest commercial devices (LigaSure™ Small Jaw LF1212 and Harmonic Focus®) [18,19]. Sartori PV et al. [17] analyzed a mixed group of patients affected with benign as well as malignant diseases in controlled prospective clinical trials.

Up to date, it has not been established which device could perform better in term of reducing time for thyroid surgery and cost-effective. This is the first prospective three arms (LS vs. HF vs. CAT) randomized controlled clinical trial with a homogeneous and a large group of patients comparing postoperative outcomes in patients undergoing total thyroidectomy. The newest devices (LigaSure™ Small Jaw LF1212 or Harmonic Focus®) or the clamp-and-tie technique were used in order to assess which device could reduce the operative time can be without worsening the postoperative outcome.

Materials and Methods

From April 2011 to May 2012 at the Department of General and Endocrine Surgery of Regina Apostolorum Hospital in Albano Laziale (Rome, Italy), 126 consecutive patients having thyroid benign disease were randomized to undergo total thyroidectomy using Clamp-and-Tie technique (CAT) group, Ligasure™ Small Jaw LF1212 (LS, Valleylab®, Covidien, Boulder, CO, USA) group or Harmonic Focus (HF, Ultracision®, Ethicon Endosurgery, Cincinnati, OH, USA) group. All thyroidectomies were performed by one of 3 Endocrine Surgeons with more than 10 years of experience in thyroid surgery. Inclusion and exclusion criteria of both gender patients are reported in Table 1. The study was registered on Clinicaltrial.gov (ID n°=NCT01649154).

Endpoints of the study included comparative evaluation of the following outcomes: operative time, postoperative complications (hemorrhage, post-operative hypocalcemia, surgical site infection, vocal dysphonia for permanent or temporary vocal cord palsy), need of hexogen calcium therapy because of parathyroid gland dysfunction, and length of hospital stay. Operative time was calculated from skin incision to skin closure.

Before the surgery, general surgeons visited all patients to assess the indication for surgical treatment and, specifically, Ear, Nose, and Throat physicians examined the vocal cord motility using flexible laryngoscopy. This latter was repeated after the surgery only in case of vocal dysphonia appearance to detect permanent or temporary vocal cord paralysis. We defined postoperative hypocalcemia as the need of calcium or vitamin D supplements, in according to symptoms and low serum calcium rate, usually within 24 hrs after surgery. While, we defined permanent hypocalcemia as the need of supplement therapy (calcium and/or vitamin D) at 6 months after thyroidectomy. We established, in line with the literature, a total serum calcium concentration cut-off of <8 mg/dl (2 mmol/L) as the biochemical diagnosis hypocalcemia. To test parathyroid function, serum calcium levels were determined preoperatively and 4, 12, 24, 36 hours and 7 days after surgery. Patient follow up was at postoperative day 7 and 6 months later.

In the LS and HF groups, Small Jaw and Harmonic Focus were the main devices used except when vessels were larger than 4 mm in diameter. In 3 cases in the LS group and in 2 cases in HF group such vessels were found in the upper pole and the surgeons ligated and divided them using conventional CAT technique. In CAT group we performed the technique we had crafted and used for several years which consists in clamping and tying vessels in the superior and inferior pole and the application a bipolar energy for the rest of the gland.

In all cases total thyroidectomy was performed after identification of both recurrent laryngeal nerves and at least one parathyroid gland on each side. In all the three groups and on each side dissection was started at the middle thyroid vein followed by the division of superior pole. After the identification of parathyroid gland and recurrent laryngeal nerve the inferior pole was divided and the gland was freed from its posterior vascular attachments. Thyroid bed drainage was systemically provided by a J-P tube which was removed one day after surgery.

All the patients were informed about the characteristics of these techniques and the advantages and possible complications of the procedures. All signed a consent form. The Regina Apostolorum Hospital Review Board approved the study design. Sample size was determined by taking the operative time as primary outcome. The Standard deviation (S) of the operative time found in previous published data was on average 22 min [1,7,21]. The reduction of the operative time (Δ) found in the literature for these procedures versus the conventional hemostasis was on average 20 min [1,5,7,12].

The maximum significant value (α) chosen for the study was five percent. The minimum statistical power ($1-\beta$) chosen for the study was 90%. The calculation for the minimum sample size (n) in each group was the following: $n=2 \times (S^2/\Delta^2) \times (Z_{\alpha/2} - Z_{1-\beta})^2=40$. Randomization was performed using random block size, immediately before surgery. The surgeon recorded the studied parameters. A statistician who did not know the technique used for each group performed the statistical analysis.

Data are described using number and percent for categorical variables, and mean/median \pm SD for continuous variables. Association between parametric variables were analyzed using t test or analyses of variance, and association between nonparametric variables were analyzed using the Mann-Whitney or Kruskal-Wallis test. Association between categorical data was analyzed using χ^2 or

Table 2: Demographic and clinical characteristics.

	LS [†] 42 Patients	HF [†] 42 Patients	CAT [‡] 42 Patients	p
Age, yrs [§] (mean)	54	55	59	0.356
Gender (M:F), No.	6:36	6:36	7:35	0.878
BMI, No.				0.258
<25	39	41	40	
>25	3	1	2	
Pathology, (%)				0.139
Colloid goiter	48	52	50	
Thyroiditis	26	26	27	
Hyperthyroidism	26	22	23	

[†]LS: Ligasure Small Jaw; [‡]HF: Harmonic Focus; [‡]CAT, Clamp-and-Tie; [§] yrs: years; ^{||}No: Number

Table 3: Intraoperative and postoperative outcomes.

	LS [†] 42 Patients	HF [†] 42 Patients	CAT [‡] 42 Patients	p
Mortality	---	---	---	---
Overall morbidity (%)	25%	32%	33%	0.922
Post-operative calcemia (ml/dl, mean)				0.818
4h				
12h	8.44	8.5	8.3	
24h	8.3	9.7	8.2	
36h	8.5	8.5	8.5	
7 days	8.5	8.5	8.5	
Permanent hypocalcemia, No.	9.3	9.3	9.3	---

[†]LS: Ligasure Small Jaw; [‡]HF: Harmonic Focus; [‡]CAT: Clamp-and-Tie; ^{||}No: Number

Fisher Exact test when appropriate.

Results

The demographic and clinical characteristics for the three groups are shown in Table 2. The three groups were similar in terms of age, gender, BMI and pathology. Table 3 summarizes intraoperative and post-operative data. No mortality was observed. Overall morbidity, defined as any modification from the normal postoperative course with or without the need for medical or surgical treatment, was as high as 25% in the LS group, 32% in the CT group and 33% in CAT group (p=0.922). Permanent complications (permanent hypocalcemia and permanent recurrent nerve lesion) were not encountered. Transient recurrent nerve lesion, demonstrated after appearance of post-operative dysphonia, was registered in 7 patients (16%) in LS group, in 5 patients (12%) in HF group and in 8 patients (19%) in CAT group (p=0.658) as reported in Table 3.

Cervical neck hematoma was encountered in 1 patient, who required reoperation (1 in the LS group) to stop a bleeding from a left sternocleidomastoid muscle vein. The mean length of hospital stay was 3.1 days for LS and CAT groups and 3.03 days for HF group. No significant difference was found between the 3 groups when mean hospitalization time was studied (Table 3).

There was no significant difference between the 3 groups at 4, 12, 24, 36 hours and at postoperative day 7. Estimates postoperative calcemia were 2.1 ± 0.125 mmol/liter, 2.07 ± 0.15 mmol/liter, 2.12 ± 0.15 mmol/liter, 2.15 ± 0.15 mmol/liter and 2.32 ± 0.125 mmol/liter at 4, 12, 24, 36 hours and at postoperative day 7, respectively (p=0.818). Summarizes the outcomes in terms of postoperative serum calcium,

showing a higher frequency of transient hypocalcemia in patients CAT group. Overall mean serum volume of drainage in postoperative day 1 was 68.9 ± 19.4 ml. Specifically, as reported, patients in CAT group had mean volume of 74.1 ± 22.7 ml; those in LS group had mean volume of 67.9 ± 16.8 ml; and in LS group measured mean volume amounted to 63.9 ± 22.7ml (p=0.542). No patient required a prolonged J-P drain placement more than 24 hr. No patients require a prolonged J-P drain placement more than 24 hrs.

The operative time was the only parameter that significantly differed between the 3 groups. LS and HF groups allowed a shorter operative time (59.5 min and 60.3 min, respectively) compared to Clamp and Tie technique (77.8 min) (p<0.001). Moreover, a sub-group analysis comparing LS and HF was included (Table 4).

Discussion

Literature demonstrates that there are significant differences in clinical outcomes between the hemostatic modalities in modern thyroid surgery. Several studies have been published, comparing clinical outcomes of energy-based devices to standard clamp-and-tie technique [22-24]. The two most widely used hemostatic tools are the ultrasound-based Harmonic scalpel (Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, OH) and Ligasure system (Valleylab, Covidien, Boulder, CO). These devices have received acceptance worldwide in several surgical fields. They are claimed to be safe and effective because they allow vessel sealing and division without dispersion of electric power and with little or no production of heat.

In thyroid surgery, there is an additional reason to use it. Partial or total thyroidectomy requires microsurgical techniques because a

Table 4: Sub-group analysis comparing LS[‡] vs. HF[†]

	LS [‡] (42 pts)	HF [†] (42 pts)	p
P.O.# complications, No.¶	19	24	0.196
Vocal dysphonia, No.¶	1	2	0.137
Bleeding, No.¶	1	0	1
Transient hypocalcemia, No.¶	17	22	0.453

*LS: Ligasure Small Jaw; †HF: Harmonic Focus; #P.O: Post-operative; ¶No: Number

number of minute vessels must be divided. Use of the energy-based devices technique is likely not only to shorten operative time but also to enable surgeons to feel comfortable with them [18]. The majority of the published trials compared HF or LS to CAT technique (two arms randomized controlled trials, RCT), and the results of these comparisons demonstrated that LS and HF presented the best profile in terms of the majority of clinical outcomes (operative time, hypoparathyroidism, blood loss, drain output, and cost), compared to clamp-and-tie technique [25-27].

A recent meta-analysis [28] demonstrated a superiority of Harmonic Focus in terms of operative time compared to CAT technique and Ligasure, but conversely, for this energy-based ultrasonic device demonstrated the highest risk for RLN paralysis. This phenomenon can be explained by the fact that the use of ultrasonic dissection produces a higher maximum temperature (179.12°C vs. 96.52.C, $p \leq 0.001$) during thyroid parenchyma sealing, and the temperature remained above 60°C for a longer period ($p \leq 0.001$) than during electronic vessel sealing [28,29].

According to the Campbell study, LigaSure delivers less energy because of the presence of active feedback control over the power output, limiting thermal spread to adjacent tissues [30]. This phenomenon may translate into greater thermal injury to the thyroid and the surrounding tissues, such as the parathyroid glands, during their division, or the laryngeal recurrent nerve. Only three studies in literature, compared, in a three arms RCT, all the 3 different techniques [1,7,17]; unfortunately, the study of Di Rienzo et al. [7] is a paper published only in Italian, and the study of Sartori et al. [17] presented a heterogeneous population, considering both malignant and benign disease.

In addition, the results of these studies are difficult to interpret because the energy-based devices used are not comparable instruments [1,7,17]. For example, the ability of the FOCUS to reduce the operative time by several minutes compared to the LigaSure Precise has been demonstrated [2,31,32]. The surgeon must cut the tissue after sealing the vessel/tissue after using the LigaSure Precise, but not after using the FOCUS. The documented differences in operative time favouring the FOCUS can be explained by differences in the surgical steps. Thus, the comparison is illegitimate because more surgical steps must be performed using the LigaSure Precise. The only justified comparison is between the new LigaSure™ LF1212, which has an integrated cutting capability, and the FOCUS. In our study, we found no significant differences in the operative time between the two groups (LS and HF). We assume that a similar operative time was achieved because both devices allow not only the coagulation and cutting of the vessels but also the dissection of planes without requiring any additional tools.

To our knowledge, only two other RCT comparing the use of the LigaSure™ LF1212 with the FOCUS in open thyroidectomy have been published [18,19]. Dionigi and Hwang demonstrated a similar operative time for both technique (Harmonic[‡] FOCUS group 76 and

104 minutes vs. LigaSure™ LF1212 group 73 and 106 min, $p=n.s$), and no significant difference in the rates of postoperative morbidity associated with these two different devices used.

Aim of the present study was to present an ultimate comparison of these techniques, comparing all the new generation devices to the standard technique of thyroidectomy for benign disease. The Authors found that in terms of operative time, both energy-based devices allowed a faster surgical procedure compared to CAT, guaranteeing a 17 min to 20 min reduction for each thyroidectomy. LS and HF do not differ from CAT technique when overall morbidity, blood loss, cervical neck hematoma, hypocalcemia, RLN paralysis and length of stay, were analyzed, and this is in accordance to the majority of literature data.

Hypocalcemia

Postoperative hypocalcemia is one of the most common complications after total thyroidectomy (1-4) with estimated prevalence, according to a recent review and meta-analysis (6), variables between 19% to 38%. As reported in literature, the main cause of hypocalcemia is an acute parathyroid insufficiency due to a reduction of functioning of gland parenchyma (1, 20). This reduction of functioning is secondary to an intraoperative damage to parathyroid glands because of multiple factors as mechanical trauma, lateral heat dispersion, glands devascularisation or obstruction venous outflow, parathyroidectomy.

The main argument concerning the systematic use of these devices, particularly in “spending review time”, is the increase in the average cost of consumables; however, the reduction of operative time through the use of LS or HF could produce the resulting compensatory effect of a related reduction in operating room and staff costs. As a result, performing total thyroidectomies with the LS or the HF could lead to an overall average operative cost reduction and make the use of the LG Small Jaw and the Harmonic Focus cost-effective. This was in accordance with the previous published data [18,19]. However, though operative time was longer with CAT, on the other hand because this technique showed no complications as well as no difference length of hospital stay, its use might not be totally discourage in thyroid surgery. These results might carry significant clinical implications and contribute to healthcare decisions and policy to revise guidelines for thyroid surgery.

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