Taiwanese Journal of Obstetrics & Gynecology 58 (2019) 128–132

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Comparison of LigaSure™ tissue fusion system and a conventional bipolar device in hysterectomy via natural orifice transluminal endoscopic surgery (NOTES): A randomized controlled trial

Chyi-Long Lee [a, b, 1], Kai-Yun Wu [a, b, 1], Chen-Ying Huang [a, b, 1], Chih-Feng Yen [a, b, *]

[a] Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Branch, Taiwan
[b] Department of Obstetrics and Gynecology, Chang Gung University College of Medicine, Taiwan

ARTICLE INFO

Article history:
Accepted 7 August 2018

Keywords:
Hysterectomy
Transvaginal
Natural orifice transluminal endoscopic surgery
Ligasure
Operating time

ABSTRACT

Objective: To evaluate the efficacy and effectiveness of applying LigaSure™ Tissue Fusion System in hysterectomy via transvaginal natural orifice transluminal endoscopic surgery (NOTES) in comparison with using the conventional bipolar device.

Materials and methods: Eighty women scheduled for hysterectomy by transvaginal NOTES were prospectively randomized into applying LigaSure (study group) or conventional bipolar instrument (control group) in an intention-to-treat analysis. Primary endpoints were the device-related efficacy; secondary endpoints were surgical effectiveness measured by operative time, blood loss, postoperative pain and adverse events.

Results: In the eligibly allocated patients, three in the control group (n = 39) converted to applying LigaSure and one converted to conventional laparoscopy intraoperatively, while none in the LigaSure group (n = 38) found such conversions. Patients who completed full analysis in the LigaSure (n = 36) and control (n = 35) groups did not differ significantly in operative time, estimated blood loss, and the length of hospital stay. In the subgroup of women who underwent hysterectomy only, the LigaSure group (n = 22) showed significantly reduced operative time than the control group (76.50 ± 24.74 min versus 93.96 ± 27.10 min, $p = 0.029$). Postoperative pain scores were statistically higher in the LigaSure group within 36 h; however, the difference was not clinically significant. The incidence of postoperative adverse events between the groups was not different; nevertheless, device-related adverse events was not found in the LigaSure group.

Conclusion: LigaSure™ tissue fusion technology was feasible and efficacious without compromising surgical procedures for hysterectomy by transvaginal NOTES compared with the conventional bipolar hemostasis device.

Introduction

Vaginal hysterectomy is the least invasive approach for women requiring uterine removal with benign conditions. However, operative capabilities in vaginal hysterectomy are limited by the restricted vaginal space, enlarged uterus and high risk of infection. In addition, postoperative hemorrhage is common, and approximately one-third of patients develop post-operative febrile infection regardless of careful precautions taken [1]. In 2010, our team first performed the hysterectomy via transvaginal natural orifice transluminal endoscopic surgery (NOTES) and demonstrated that NOTES is the easier approach to the uterine vessels at the level of isthmus, in which the vessels can be quickly and safely secured before manipulation, resulting in reduced intraoperative blood loss [2,3]. Most importantly, ligation of uterine vessels is crucial for reducing blood loss during hysterectomy via transvaginal NOTES with appropriate vessel sealing devices [3–5].

To date, NOTES procedures have been extensively used in cholecystectomy, pancreatic necrosectomy, gastrectomy, nephrectomy and hernia repair in addition to the gynecology and have proven safe track records [6–9]. Most of the instruments employed in

* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou, 5, Fu-Hsin St, Kwei-Shan, Tao-Yuan 33305, Taiwan.
E-mail address: yen2158@cgmh.org.tw (C.-F. Yen).
[1] All these authors contributed equally to the work.

https://doi.org/10.1016/j.tjog.2018.11.024

NOTES are not designed to manipulate the intraabdominal organs, and do not have sufficient angulation and push force via small accessory channels [10]. Endoscope design, conduit access, assist devices, and systems for closure require reengineering and redesign for optimal function in the NOTES setting, which require industry activity, investment, and interest.

LigaSure™ vessel sealing system manufactured by Covidien has been used in laparoscopic hysterectomy for years. Its unique combination of controlled pressure and energy causes fusion of vessels, resulting in a secured vascular seal that has high tensile strength. The use of electrothermal bipolar vessel sealer in total laparoscopic hysterectomy was shown to be less time-consuming and had lower estimated blood loss compared to ultrasonic harmonic scalpel [11]. We have applied LigaSure™ in transumbilical single-port laparoscopy for hysterectomy in difficult conditions with encouraging experiences [12]. Consistent findings where a significant reduction in operative time and shorter lengths of hospital stay during vaginal hysterectomy using LigaSure were also reported [13].

Given the safety and feasibility of LigaSure vessel sealing device in various laparoscopic surgeries, the objective of the current study was to evaluate the surgical efficacy and effectiveness of LigaSure compared with conventional bipolar instrument during hysterectomy via transvaginal NOTES.

Materials and methods

Study design

This prospective, randomized, single-blind study was conducted between July 29, 2013 and April 14, 2014, at the Chang Gung Memorial Hospital, Linkou, Taiwan, in an intention-to-treat analysis. The study was approved by the institutional review board of the Chang Gung Memorial Hospital ([102] CGMF-TP No.203). Informed consent was obtained from all patients enrolled in the study.

Patients and allocation

Our exclusion criteria for NOTES includes virginity, pregnancy, malignant disease, suspected severe pelvic adhesions from history of multiple abdominal surgeries except cesarean delivery, pelvic inflammatory disease and/or tubo-ovarian abscesses [14]. Besides, as a comparative study between hemostasis or the vessel sealing devices, patients with coagulation disorder, and/or with the diagnosis of liver or renal dysfunction within 6 months were not eligible.

A total of 80 eligible women scheduled for hysterectomy, with or without adnexal procedures, via transvaginal NOTES were then recruited and prospectively randomized in an 1:1 ratio into either the study group by using the LigaSure™ 5 mm Blunt Tip laparoscopic instrument (Covidien, Mansfield, MA); or the control group by using the conventional bipolar device (Eragon Grasping and Dissecting Forceps Maryland Dissector 5 mm; Richard Wolf, GmbH, Knittlingen, Germany) with ForceTriad™ generator (Covidien) for vessel sealing. All authors performed the operations according to our previous publication [14] and each operators had equal amount of participated patients in both groups.

Study endpoints and assessments

Primary endpoint were the device-related feasibility and efficacy for the NOTES-hysterectomy, defined as any device-related failure to accomplish any procedures of the surgery, or any necessary switching of the hemostasis device or conversion of surgical procedures. Conversion to conventional laparoscopy or open surgery was defined as a complication suggestive of incompetence of the energy device. Secondary endpoints were the device-associated efficiency and effectiveness for the NOTES-hysterectomy, which was measured by surgical outcomes including the operative time, the intraoperative blood loss, length of hospital stay and postoperative pain scores. Operative time was defined as the duration from first incision till completion of skin closure; intraoperative blood loss was estimated from the amount of blood collected in surgical waste such as drapes, gauze swabs, and cotton balls as well as in suction bottles and buckets. In addition, postoperative first day hemoglobin and hematocrit levels were subtracted from the baseline preoperative measurements to assess perioperative blood loss. Postoperative pain score of the surgical site was recorded twice per day via Visual Analog Scale (VAS) until hospital discharge.

Statistical analyses

Quantitative variables were compared using analysis of variance. Comparisons between groups were performed using Student's *t*-test. All data are expressed as the mean ± standard deviation (SD). $p < 0.05$ was considered to represent statistical significance. Cochran–Mantel–Haenszel test and Chi-square test or Fisher's exact test were employed to compare qualitative data between the two groups, as appropriate. The intention to treat population comprised all patients randomized to undergo surgery using any of the two study devices and was used to determine the rate of conversion from transvaginal NOTES to conventional laparoscopic hysterectomy. The full analysis set (FAS), a subset of the intention to treat population, was used for effectiveness analyses and comprised patients who underwent surgery using the designated study device. Patients undergoing surgery with a device other than the designated study device were excluded from the evaluation.

Results

In the study period, 86 patients scheduled for NOTES hysterectomy were evaluated initially for the eligibility of the trial, and finally 80 patients were recruited and signed the consent to participate the randomized allocation (Fig. 1). However, in the 40 patients allocated to use the LigaSure tissue fusion system, one withdrew the consent before operation and one experienced randomization error, therefore the final eligible patients in the study group was 38. In the 40 patients allocated to use the conventional bipolar device, one withdrew the consent before operation, and the final eligible patients in the control group was 39 (Fig. 1). These population sets were used for the evaluation of the device efficacy for NOTES.

Device-related feasibility and efficacy for the surgery

A total of three patients in the conventional device group (Subjects P056, P078 and P084) were converted to LigaSure as decided by the PI as uncontrolled bleeding occurred during the operation which was considered as serious adverse event. Switching of the energy system successfully prevented further blood loss. The causality of the event was assessed and concluded that it was likely to be caused by the difficult situations of the surgery rather than by the device. One patient in control group by using the conventional bipolar device (Subject P077) converted to conventional laparoscopy due to the intraoperative uretero-vesical injury given the situation of myoma adherence to bladder extensively. Incidence was considered a device-related serious adverse event and needed double-J-stent insertion. The causality of the event was assessed and concluded to be probable/likely device related.

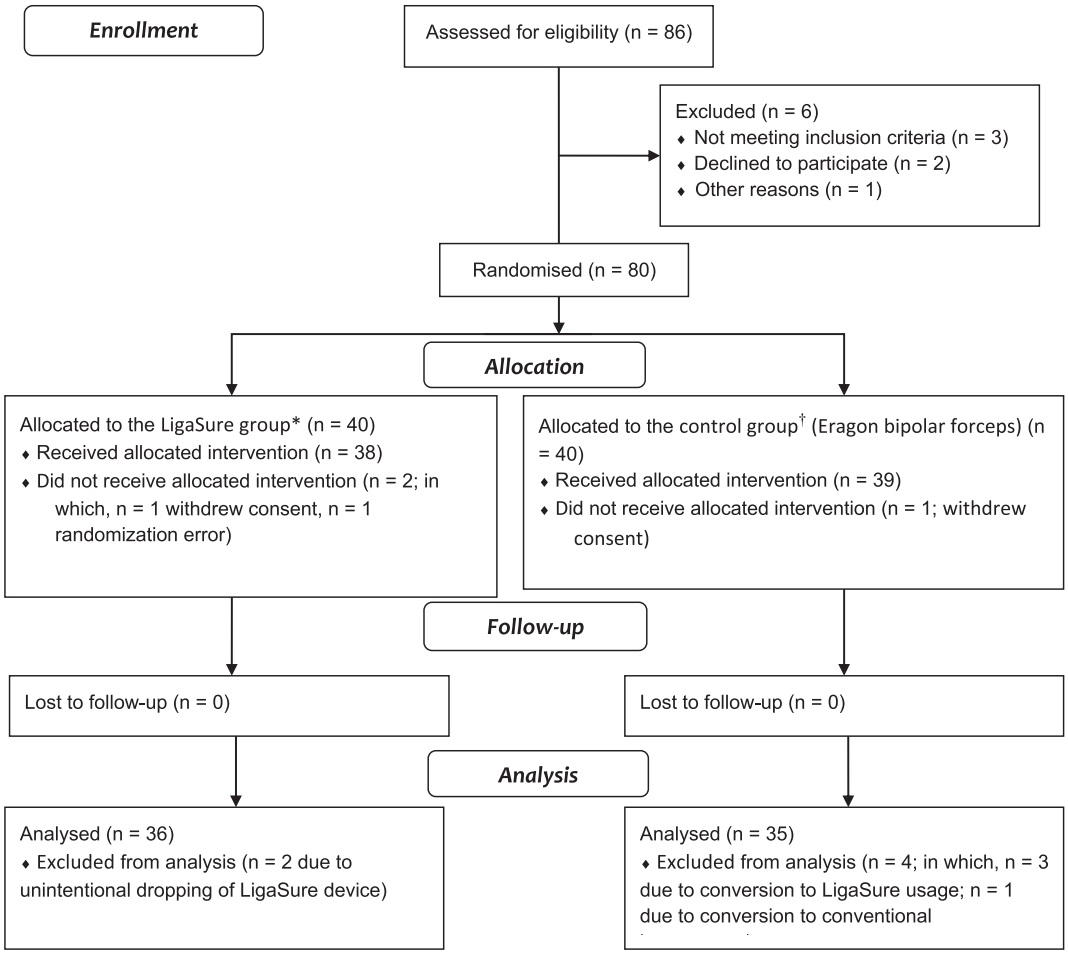

Fig. 1. Flow of patients. * using LigaSure tissue fusion system. † using conventional bipolar vessel sealing device with ForceTriad™ generator (Covidien).

None of the patients in the LigaSure group required switching to other hemostasis device nor converting to conventional laparoscopy.

Device-specific surgical effectiveness

To evaluate the device-specific surgical effectiveness and efficiency, only the patients who underwent surgery using the designated study device, or the FAS populations, were used to compare the surgical outcomes between the LigaSure (n = 36) and the conventional bipolar (n = 35) groups (Fig. 1). Their demographics and baseline characteristics are summarized in Table 1. Both groups were well matched and shared similar baseline characteristics including age, weight and American Society of Anesthesiologists physical status classification (ASA) score. No statistically significant differences were found between the two groups, including clinical features and the mean uterine weights ($p > 0.05$).

Surgical outcomes

Mean operative time, and estimated blood loss did not differ between LigaSure and the conventional bipolar instruments in the total group or in the Hysterectomy via Transvaginal NOTES with additional Surgery subgroup (Table 2). The reduction in hemoglobin level postoperatively was similar in both study groups. In the subgroup comparison, LigaSure group who received hysterectomy via transvaginal NOTES only, had significantly reduced operative

Table 1
Demographics and baseline characteristics (FAS population).

	LigaSure (n = 36)	Control[b] (n = 35)
Age, years	46.3 ± 4.0	46.3 ± 5.0
Height, cm	157.3 ± 5.5	159.2 ± 5.6
Weight, kg	60.7 ± 8.6	62.5 ± 10.5
Body mass index, kg/m^2	24.5 ± 3.4	24.7 ± 4.4
ASA score, n (%)		
Normal healthy	2 (5.6)	1 (2.9)
With mild systemic disease	34 (94.4)	32 (91.4)
With severe systemic disease	0 (0.0)	2 (5.7)
Surgical type, n (%)		
Hysterectomy only	22 (61.1)	23 (65.7)
Combined with additional surgery[a]	14 (38.9)	12 (34.3)
Uterine weight, g	465.09 ± 296.38	444.29 ± 202.73
Active medical conditions (≥ 5%), n (%)	18 (50.0)	21 (60.0)
Anemia	6 (16.7)	11 (31.4)
Diabetes mellitus	2 (5.6)	1 (2.9)
Dizziness	1 (2.8)	3 (8.6)
Fatigue	1 (2.8)	2 (5.7)
Hypertension	3 (8.3)	3 (8.6)
Pollakiuria	2 (5.6)	6 (17.1)
Viral hepatitis carrier	0 (0.0)	2 (5.7)

Values are mean ± standard deviation unless otherwise specified.
ASA, American Society of Anesthesiologists' physical status; FAS, full analysis set.
[a] Including adhesiolysis, bilateral salpingectomy, ovarian cyst enucleation, and/or salpingo-oophorectomy.
[b] Control: using conventional bipolar vessel sealing device with ForceTriad™ generator (Covidien).

Table 2
Perioperative outcomes.

Total hysterectomy group via Transvaginal NOTES			
	LigaSure (n = 36)	Control[a] (n = 35)	*p*
Operative time (min)	85.58 ± 30.21	99.54 ± 31.96	0.063
Total estimated blood loss (mL)	269.23 ± 232.47	310.60 ± 220.60	0.445
Reduction in hemoglobin (g/L)	0.61 ± 1.18	0.83 ± 1.07	NA
Divided per subgroup via Transvaginal NOTES			
Hysterectomy only:	LigaSure (n = 22)	Control[a] (n = 23)	*p*
Operative time (min)	76.50 ± 24.74	93.96 ± 27.10	0.029*
Total estimated blood loss (mL)	245.39 ± 195.51	290.00 ± 217.56	0.474
Hysterectomy with additional surgery:	LigaSure (n = 14)	Control[a] (n = 12)	*p*
Operative time (min)	99.86 ± 33.30	110.25 ± 38.72	0.469
Total estimated blood loss (mL)	306.69 ± 285.10	350.08 ± 230.57	0.677

Values shown are mean ± standard deviation.
* $p < 0.05$.
[a] Control: using conventional bipolar vessel sealing device with ForceTriad™ generator (Covidien).

time compared to the control group (76.50 ± 24.74 min versus 93.96 ± 27.10 min, $p = 0.029$).

Mean duration of hospital stay was similar (approximately 3.3 days), and not significantly different between device groups (Table 3). Both groups exhibited a similar reduction trend in postoperative VAS pain scores between 8 and 72 h. Compared to the LigaSure group, significantly lower VAS pain scores were observed in the conventional device group at 24 h ($p = 0.006$) and 36 h postoperatively ($p = 0.002$), but not thereafter.

Adverse events reported postoperatively

Of the FAS population, five subjects (13.9%) in the LigaSure group reported a total of eight adverse events (AEs), and two subjects (5.7%) in the control group reported a total of two AEs. Among the 10 AEs, all except two were mild to moderate, such as transient mild fever, nausea, vomiting, dysuria, and/or constipation. There was one case in each groups, respectively, presented with fever, leukocytosis, delayed passage of flatus, prolonged abdominal distention and pelvic inflammatory reaction. Both were graded as serious adverse events, in addition to the above-mentioned complication. No statistically significant difference ($p = 0.429$) in the incidence of AEs between the groups was observed, and, LigaSure use, however, was not assessed as device-related AEs.

Table 3
Length of hospital stay and postoperative pain scores (FAS population).

Parameter	LigaSure (n = 36)	Control[a] (n = 35)	*p*
Length of hospital stay			
Mean ± SD	3.34 ± 0.54	3.37 ± 0.77	0.858
Postoperative pain scores			
PO 24 h			
N	35	35	
Mean ± SD	3.9 ± 2.3	2.5 ± 1.9	0.006
PO 36 h			
N	35	34	
Mean ± SD	2.8 ± 1.9	1.4 ± 1.4	0.002
PO 48 h			
N	34	33	
Mean ± SD	1.3 ± 1.2	1.0 ± 1.4	0.313

SD, standard deviation; PO, postoperation; FAS, full analysis set.
[a] Control: using conventional bipolar vessel sealing device with ForceTriad™ generator (Covidien).

Discussion

To our knowledge, this study is the first prospective, randomized clinical trial designed to compare the efficacy and safety of two hemostatic instruments during hysterectomy via transvaginal NOTES. With the advantages of controlled pressure, efficacious energy delivery, and a combining cutting device on the instrument, our study demonstrated that LigaSure is an efficient device to shorten operating time and avoid the occurrence of complications in the types of difficult surgery like NOTES, which has constrained operating space.

Compared with NOTES, laparoscopic hysterectomy provides better anatomical views and performance of concomitant procedures; however, it still needs to create several incisions through the abdomen. . Shorter operative time with the use of LigaSure™ tissue fusion system was also reported in the case of lobectomy, hemorrhoidectomy, and total thyroidectomy [15,16]. Although the reduction in blood loss associated with the use of LigaSure was not statistically significant, our findings were lower than the reported study [3] and compatible with single-port laparoscopic-assisted vaginal hysterectomy [17]. Furthermore, the technique of hysterectomy is characterized by limited blood loss and many patients in both groups had additional procedures performed, thus influencing total blood loss during the surgery. Limiting the study to patients who require hysterectomy via transvaginal NOTES only without any additional procedures would probably demonstrate the difference in blood loss but would also extend the study period to an unacceptable length of time.

AEs were reported for both LigaSure and control groups, however, none of the events were associated with LigaSure use, thus, highlighting the efficacy of LigaSure in achieving hemostasis without complicating the procedures. The use of LigaSure had a lower incidence of conversion to laparoscopic procedure compared with the use of conventional bipolar vessel sealing device. Throughout the study, there was no situation where it was not possible to apply the LigaSure device on hysterectomy, even though the uterine weight in the LigaSure group was on average, heavier than that in the conventional group. There were no surgery-related deaths in this study. Intraoperative or post-operative observation of bleeding was not attributed to incomplete vascular lumen closure because of energy-based device use. Comparison between the LigaSure and comparative groups revealed no significant difference in complication rates and the types of complications were

consistent with laparoscopic hysterectomy procedure [18]. Based on these findings, LigaSure use in transvaginal NOTES was substantiated in terms of fewer adverse events.

Although the current study is a prospective randomized clinical trial, it has a number of limitations, including small sample size and the fact that it was conducted at a single hospital. All patients were not subcategorized by clinical stages, due to which the difference in symptoms at baseline was underestimated, and longer operation time might be required for complicated procedures. This study required cooperation from surgeons, and it would be difficult to run a study with a single surgeon. This imparts differences in the surgical procedure and method of using the energy-based devices. While the safety and feasibility of transvaginal access to NOTES has been proven, NOTES is still not a standard surgical technique in gynecologic surgery and difficulties associated with poor visibility, maintenance of spatial orientation, maneuverability and grasping of operating instruments are evident [17,19]. Moreover, perioperative surgical outcomes can be affected by the sealing mechanism of the energy-based devices. The bipolar devices used in this study produces permanent seal zone by denaturing collagen and elastin in the walls of vessels and this process is operator independent. Further study is required to understand the hemostatic effect and protein denaturing with the use of different vessel sealing devices such as electrothermal ultrasonic devices or laser instruments.

In conclusion, LigaSure™ tissue fusion system is a safe and efficient energy-based device for hysterectomy via transvaginal NOTES. LigaSure use reduced operative time compared with the conventional bipolar vessel sealing device without increasing the incidence of surgical complications and adverse events. The results of this small pilot study are promising, and should be pursued in larger samples, and ideally these data should be incorporated into a wider meta-analysis.

Disclosure statement

The authors have no conflicts of interest to declare.

Conflict of interest statement

Drs. CL Lee, KY Wu, CY Huang, and CF Yen report no conflict of interest.

Acknowledgments

This study was supported by the Industry-supported grant XMRPG3C0511 to Dr. C.L. Lee. Editorial support, in the form of medical writing, and assembling tables based on authors' detailed directions, collating author comments, copyediting, fact-checking, and referencing, was provided by Cactus Communications, and funded by Medtronic.

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