





Comparing the Utility and Surgical Outcomes of Harmonic Focus Ultrasonic Scalpel with Ligasure Small Jaw Bipolar Device in Thyroidectomies: A Prospective Randomized Controlled Trial

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ABSTRACT

Background. Ultrasonic or bipolar radiofrequency energy devices are routinely used for dissection and hemostasis during thyroidectomy. We report a single-center, prospective, randomized controlled trial comparing the utility and outcomes of Harmonic Focus, an ultrasonic coagulating shear device (UCSD), versus Ligasure Small Jaw, an electrothermal bipolar vessel sealer (EBVS) in thyroidectomy (NCT01765686).

Methods. Between December 2012 to January 2016, eligible patients were randomized to undergo hemithyroidectomy using either a UCSD or an EBVS. The primary outcome was duration of surgery. Secondary outcomes included blood loss, postoperative complications, ease of device use, ease of device set-up, vocal cord

function, postoperative wound drainage, pain score, and adverse events.

Results. Of 110 patients assessed for eligibility, 100 were randomly allocated (UCSD: 49 patients; EBVS: 51 patients) and analyzed by intention-to-treat. There were no differences in specimen delivery time, total duration of surgery, wound drainage, and adverse events between the two groups. The UCSD group had a greater proportion of patients with higher postoperative pain scores in the first 72 h (8.1% vs. 2.0%, $p = 0.043$). Surgeons reported greater ease of use for the UCSD (49% vs. 27%; $p = 0.005$), while operating room staff favored the EBVS (60% vs. 33%, $p = 0.005$).

Conclusions. Energy devices are equally effective in reducing thyroidectomy operative times, with no differences in the duration of surgery, drainage, or adverse events. Use of the UCSD was associated with higher postoperative pain scores, but was favored by the surgeons, likely due to the ability to perform fine dissection with the device itself.

Shen-Han Lee and Thien Khanh Nguyen contributed equally to this work.

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Thyroidectomy is a common surgical procedure that has evolved over the ages from a high-mortality surgery (almost 50% mortality) to one with low morbidity and virtually 0% mortality.¹ This was largely achieved at the turn of the twentieth century through the work of Theodor

Kocher, who realized the importance of meticulous hemostasis and dissection and was awarded the Nobel prize for this achievement.

The thyroid gland is a highly vascular organ. Intraoperative bleeding blurs the operative field and planes, increasing the risk of injury to the recurrent laryngeal nerves and parathyroid glands. Postoperative bleeding results in hematoma (risk 0.1–2.1%^{2–4}), commonly in the first 6 h after surgery, and may cause airway compression and respiratory distress.⁵

Traditionally, hemostasis is achieved by clamping and tying the vessels, with or without electrocautery,⁶ but energy devices are now routinely used for hemostasis. Newer-generation energy devices deliver more focused thermal energy and reduce the risk of collateral tissue injury. These devices are multifunctional, capable of sealing, blunt-dissecting, grasping, and dividing tissue, and thus making surgery more efficient.

There are two types of commonly used energy devices—ultrasonic coagulation shear device (UCSD) and electrothermal bipolar vessel sealer (EBVS). An EBVS applies a precise amount of bipolar electrical energy and pressure to fuse collagen and elastin in blood vessels, sealing it permanently.⁷ A microblade cuts the tissue at the end of coagulation. Using this technology, the Ligasure Vessel Sealing System (Medtronic–Covidien) is able to seal vessels up to 7 mm in diameter.⁶ In contrast, a UCSD uses ultrasonic vibrations to cut and coagulate tissue, with the active blade of the scalpel vibrating at 55,000 Hz.⁸ The high frequency generates heat, lowers the temperature for vaporization, denatures protein, and seals vessels with minimal lateral thermal spread. The Harmonic Scalpel (Harmonic Focus; Ethicon, Johnson & Johnson) utilizes this technology and seals vessels up to 5 mm in diameter.

There is substantial level I evidence to suggest that using either device confers benefit over ‘clamp-and-tie’ hemostasis by shortening operative time.^{9–11} However, direct comparison between these two devices in recent prospective randomized controlled trials (RCTs) have shown no difference in outcomes in terms of operative time, drain output, and postoperative complications. A systemic review and meta-analysis found that compared with an EBVS, a UCSD was associated with a statistically significant reduction in blood loss and operating time (2.22 mL and 3.32 min, respectively), although its clinical significance was questionable given the small absolute difference.¹² Otherwise, this study found no difference in the rate of complications, overall morbidity, and hospital stay.¹² The available evidence to date does not suggest one instrument is better than the other, and it has been suggested that surgeon comfort with a particular instrument should take precedent.

The aim of this study was to compare the utility and outcomes of EBVS versus UCSD in thyroid lobectomy for benign and malignant thyroid conditions at a single Asian tertiary academic medical center. We examined operative time, postoperative drainage, ease of use of device rated by the surgeon, ease of device setup rated by operating room staff, postoperative pain, and incidence of complications.

METHODS

Patient Eligibility

All patients aged 21–75 years at Singapore General Hospital and the National Cancer Centre Singapore (NCCS) who required thyroid lobectomy (T1 differentiated thyroid carcinomas, symptomatic goiters, or thyroid nodules requiring histological analysis) were eligible. Exclusion criteria included patients with previous neck surgery or radiotherapy, advanced disease requiring neck dissection, lobes ≥ 10 cm, nodules ≥ 8 cm, connective tissue diseases, bleeding diatheses, and chronic diseases who were taking long-term medications that might interfere with wound healing. Ethics approval was granted by the SingHealth Centralized Institutional Review Board Committee, and all patients provided written informed consent before trial entry.

Study Design and Sample Size

The primary endpoint was duration of surgery, and a sample of 100 patients (50 patients per arm) would provide at least 80% power to detect a clinically important standardized mean difference of 0.6 for this endpoint between the two device arms using a two-sided *t* test with a 5% level of significance.

Randomization

Patients were assigned randomly in a 1:1 ratio to the EBVS or UCSD arm of the trial, using block randomization, stratified by surgeons (four surgeons: NGI, HKT, JCFN, and NCT). The randomization listing was prepared prior to the start of the trial, placed in sealed envelopes a priori, and opened just prior to anesthesia induction.

Study Procedures and Assessment

Surgery was performed by the attending surgeon with either a Ligasure Small Jaw (EBVS) or an Harmonic Focus (UCSD), depending on the randomized arm. The total operating time (start of surgery until skin closure), specimen delivery time (start of surgery until specimen

delivery), measured blood loss (suction fluid volume minus irrigation fluid volume and a number of surrogates, including number of gauzes utilized and the use of ligatures), ease of use of the device (rated by the surgeon), and ease of setting up the device and the availability of equipment (rated by staff supporting surgery), assessed based on an ordinal scale of 0–5 (easy to difficult), and interruption to use of the device were recorded. The decision to use a local anesthetic was based on the surgeons' preference. When utilized, 1 mL of 1:80,000 lidocaine–adrenaline mixture was infiltrated prior to skin incision. The decision to use surgical drains were based on individual surgeon preference.

Postoperatively, patients were managed routinely based on surgeon preferences. For patients with surgical drainage, the amount and nature of drainage at 12, 24, 48, and 72 h after operation, and the postoperative day (POD) on which the drain was removed, were recorded. Drains did not delay discharge as patients were discharged home with drains. Pain scores were self-reported at 12, 24, 48, and 72 h after operation using an ordinal scale of 0–5, with higher scores denoting higher levels of pain. Follow-up with fiber optic indirect laryngoscopy was performed at 2 weeks and 3 months postdischarge. Grading of adverse events (AEs) was based on the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0, and assessed during surgery, the postoperative period, and follow-up visits.

Statistical Analyses

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) according to the intention-to-treat principle. Continuous variables were compared using the Mann–Whitney *U* test, while categorical variables were compared using the Chi square test. If the expected frequency was smaller than 5, the Fisher exact test was used. The mean total operating time, specimen delivery time, and mean maximum drainage amount by device arms were compared using analysis of variance (ANOVA), with adjustment for surgeon made using analysis of covariance (ANCOVA). A univariate logistic regression model was fitted to estimate the odds ratio (OR) to assess the association of the device with the use of postoperative wound drainage and the incidence of at least one adverse event during the trial. For each of these outcomes, the OR for device comparison was also estimated using a multivariate logistic regression model, with surgeon included as a covariate.

RESULTS

Patient Cohort

A total of 100 patients (51 EBVS, 49 UCSD) were accrued and randomized between December 2012 and January 2016 (Fig. 1). All randomized patients underwent surgery, with six patients (four EBVS, two UCSD) lost to follow-up at 3 months postdischarge. The demographic and clinical characteristics for the two groups are summarized in Table 1.

Surgical Characteristics

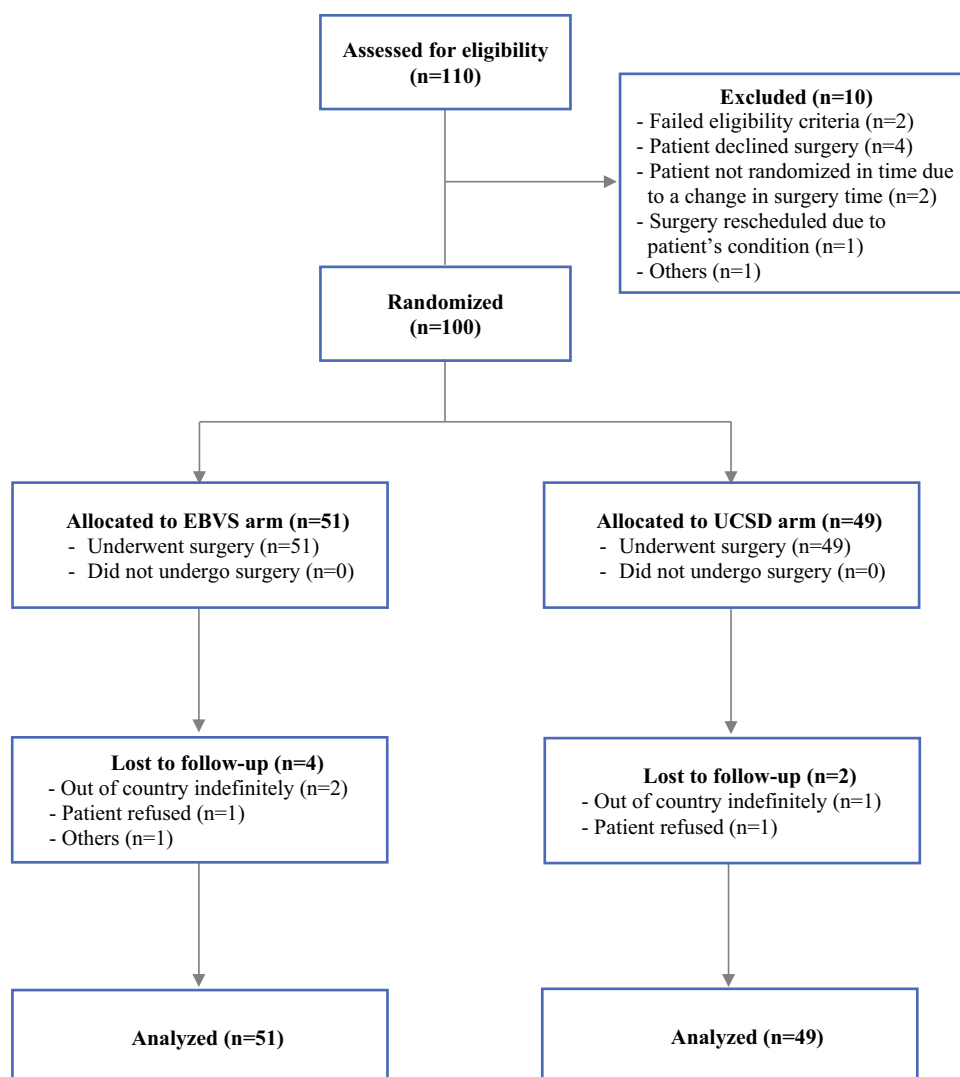
The majority of surgeries were performed by JCFN (39%), followed by NGI (27%), HKT and NCT (17% each) (Table 2). Half of the patients had two parathyroid glands identified, and of these, about 13% had their glands accidentally resected. No central compartment node was encountered in any case. There were no significant differences in these or in bleeding characteristics (suction amount, irrigation fluid amount, and number of gauzes used during surgery) between the two arms. On average, the time taken for specimen delivery was 34.2 min for EBVS and 34.7 min for UCSD (Table 3). The average total operating time of each device arm was also similar at 60.2 min for EBVS and 60.3 min for UCSD. Three surgeries (two EBVS, one UCSD) experienced interruptions with the use of the device (Table 4), but none resulted in an absolute device failure. A quarter of all patients required ties (27% EBVS, 24% UCSD). No surgery required conversion to total thyroidectomy in the operating theater.

A higher proportion of surgeons gave 'easy to use' ratings to the UCSD (rating of 0: 49% UCSD vs. 27% EBVS; $p = 0.005$), while a higher proportion of operating room staff gave 'easy to set up' ratings for the EBVS (rating of 0: 60% EBVS vs. 33% UCSD; $p = 0.005$). Comments on the use and setup of the devices are listed in electronic supplementary Appendices 1 and 2.

Postoperative Course

Twenty patients (8 EBVS, 12 UCSD) had surgical drains—three (two EBVS, one UCSD) had sanguineous drainage and the remaining were serosanguineous. There was a trend towards a higher probability of UCSD patients having surgical drainage than EBVS patients (OR 1.74, 95% confidence interval [CI] 0.64–4.72), although this did not reach statistical significance (electronic supplementary Table 1). There were also no significant differences in the mean maximum drainage amount within 72 h after operation between the two device arms (32.8 mL EBVS vs. 34.3 mL UCSD; $p = 0.907$). Adjustment for surgeon did

FIG. 1 CONSORT diagram.
EBVS electrothermal bipolar vessel sealer, *UCSD* ultrasonic coagulating shear device



not change these conclusions. Among patients with postoperative wound drainage, all except three had their drainage removed by POD3. Drains were removed when the daily output was down-trending and minimal (< 10 mL). Patients with delayed drain removal had high drainage in the immediate postoperative period. The median time to removal of drainage was POD1 for UCSD patients and POD3 for EBVS patients ($p = 0.097$) [electronic supplementary Fig. 1].

A larger proportion of UCSD patients reported a pain score of ≥ 3 within 72 h after operation (UCSD 8.1% vs. EBVS 2.0%; $p = 0.043$) (Table 2). Fifteen EBVS patients and 18 UCSD patients had one or more AEs (electronic supplementary Table 2). The odds of AEs did not differ significantly between the two arms (OR 1.39, 95% CI 0.60–3.22), and adjustment for surgeon made no appreciable difference. The majority of reported AEs were grade 1–2, most commonly voice hoarseness (18% EBVS, 16% UCSD) [electronic supplementary Table 3]. Three AEs

were graded ≥ 3 , involving nerve injury and hypocalcemia (electronic supplementary Table 4). The reason for nerve injury may be due to thermal injury, but we were unable to ascertain the reason for hypocalcemia. There was one serious AE of postoperative hemorrhage in the EBVS arm 10 days after discharge from an uneventful surgery (electronic supplementary Table 5). Five patients (three EBVS, two UCSD) had reduced vocal cord mobility or immobility 2 weeks postdischarge (electronic supplementary Table 6), all of which resolved 3 months postdischarge (except for one patient who defaulted follow-up and left the country indefinitely).

DISCUSSION

In this single-center RCT, we found no statistically significant difference between operative time, postoperative wound drainage volume, time to drain removal, and postoperative complications in hemithyroidectomies with

TABLE 1 Demographics and clinical characteristics by device arm

	EBVS		UCSD		<i>p</i> value ^a
	<i>N</i>	%	<i>N</i>	%	
Total	51	100.0	49	100.0	
Age at surgery, years					
Median age at surgery, years (range)	53 (28–75)	49 (21–73)	0.216		
Sex					
Female	37	72.5	37	75.5	0.736
Male	14	27.4	12	24.5	
Race					
Chinese	41	80.4	37	75.5	0.048
Malay	0	–	6	12.2	
Indian	5	9.8	2	4.1	
Others	5	9.8	4	8.2	
Final diagnosis					
Multinodular goitre	36	70.6	29	59.2	0.871
Lymphocytic thyroiditis	1	2.0	1	2.0	
Follicular adenoma	8	15.7	10	20.4	
Thyroid carcinoma					
Follicular carcinoma	1	2.0	1	2.0	
Papillary carcinoma	4	7.8	7	14.3	
Oncocytic carcinoma	1	2.0	1	2.0	

^aBased on either the Chi square or Fisher's exact test, unless otherwise specified

EBVS electrothermal bipolar vessel sealer, UCSD ultrasonic coagulating shear device

EBVS versus UCSD. However, the mean total operative time for both techniques (EBVS 60.2 min and UCSD 60.3 min) were shorter compared with historical controls at our institution (mean operative time 100 min, median 75 min). The overall nerve injury rate in our study was 1%, and is comparable to that reported in the literature.⁵ Our findings concur with previously published RCTs comparing the EBVS with the UCSD, which found no significant difference in operative times, length of stay, postoperative wound drainage, or complications.^{13–17} Of note, most of these RCTs used an earlier generation of EBVS (Ligasure Precise), which only dissects and ligates. This may explain the slightly shorter operative time seen with the UCSD since an additional step to cut is needed for Ligasure Precise. The newer generation Ligasure Small Jaw has an integrated cutting mechanism, and more recent studies,^{16–18} including this study, have only used Ligasure Small Jaw to allow for better comparison.

We found a significantly higher proportion of patients with greater postoperative pain within 72 h in the UCSD group, compared with the EBVS group. The impact of energy devices on postoperative pain has had mixed results in previous RCTs. Some studies have reported no difference in postoperative pain between the UCSD and the

EBVS, measured in terms of pain score^{13,18,19} and/or analgesia requirements,^{16,18,19} although there were higher subjective levels of discomfort and pain in the UCSD group while swallowing ($p < 0.00$).^{18,19} It has been suggested that the greater postoperative pain in the UCSD arm may be due to the device producing a higher amount of lateral thermal energy spread compared with the EBVS, as evidenced by preclinical models.^{20,21}

We found that there was a significant difference between the surgeons' rating on the ease of use of the device, with the UCSD preferred over the EBVS. This is likely because the Harmonic Focus has a finer and curved tip, which mimics the usual dissection instruments used during thyroid surgery. In contrast, even with the addition of the scalpel element in the Ligasure system, the bulk of the instrument tip makes this more cumbersome for fine dissection. Conversely, a higher proportion of operating room staff rated EBVS as being easier to set up as it is a single-step 'plug and play' system. Since the two instruments are equivalent in their safety and efficiency profile, surgeon preference plays an important role in deciding which instrument to use. This is certainly the case in our institution, where surgeons were more likely to bias their preference towards using the UCSD.

TABLE 2 Surgical characteristics and pain score by device arm

	EBVS		UCSD		<i>p</i> value ^a
	<i>N</i>	%	<i>N</i>	%	
Total	51	100.0	49	100.0	
Surgeon					
NGI	14	27.5	13	26.5	0.987
HKT	9	17.6	8	16.3	
JCFN	20	39.2	19	38.8	
NCT	8	15.7	9	18.4	
Tracheoesophageal groove clearance					
Yes	3	5.9	2	4.1	1.000
No	48	94.1	47	95.9	
Had frozen section performed					
Yes	23	45.1	19	38.8	0.522
No	28	54.9	30	61.2	
No. of laryngeal nerves identified and preserved					
1	50	98.0	49	100.0	1.000
2	1	2.0	0	–	
No. of parathyroid glands identified					
0	1	2.0	1	2.0	1.000
1	6	11.8	7	14.3	
2	42	82.4	41	83.7	
3	1	2.0	0	–	
4	1	2.0	0	–	
Median (range)	2 (0–4)		2 (0–2)		0.444 ^b
<i>Parathyroid gland accidentally resected</i>					
Among patients with parathyroid glands identified	50	100.0	48	100.0	
Yes	7	14.0	6	12.5	0.827
Suction amount, mL					
0 ^c	44	86.3	43	87.8	0.826
> 0	7	13.7	6	12.2	
Among patients with suction amount > 0 mL	7		6		
Median (range)	60 (10–100)		55 (20–100)		0.881 ^b
Irrigation fluid amount, mL					
0 ^c	43	84.3	42	85.7	0.845
> 0	8	15.7	7	14.3	
Among patients with irrigation fluid amount > 0 mL	8		7		
Median (range)	50 (10–100)		50 (20–100)		0.855 ^b
<i>Number of gauzes used</i>					
Among patients with non-missing data ^d	51	100.0	48	100.0	
0 ^e	1	2.0	1	2.1	1.000
> 0	50	98.0	47	97.9	
Among patients with > 0 gauzes used	50		47		
Median (range)	4 (1–22)		4 (1–25)		0.907 ^b
Transfusion required					
No	51	100.0	48	100.0	NA
Yes	0	–	0	–	
Worst pain score within 72 h postoperatively					
0	42	82.4	42	85.7	0.043
1	0	–	1	2.0	

TABLE 2 continued

	EBVS		UCSD		<i>p</i> value ^a
	<i>N</i>	%	<i>N</i>	%	
2	8	15.7	2	4.1	
3	1	2.0	1	2.0	
4	0	–	0	–	
5	0	–	3	6.1	

NA not applicable, EBVS electrothermal bipolar vessel sealer, UCSD ultrasonic coagulating shear device

^aBased on either the Chi square or Fisher's exact test, unless otherwise specified

^bBased on the Mann–Whitney *U* test

^cIncluded eight patients with an 'unknown (minimal)' or 'minimal' suction amount, three patients with an 'unknown (minimal)' or 'minimal' irrigation fluid amount, and two patients with 'minimal' number of gauzes used

^dThere was one patient (GI16) whose data were not documented in the source

TABLE 3 Duration of surgery by device arm

	<i>N</i>	Median (range)	Mean (SD)	<i>p</i> value ^a	
				Without adjustment for other covariates	With adjustment for surgeon (stratification variable)
Total operating time, mins					
EBVS	51	55 (36–105)	60.2 (15.5)	0.969	0.985
UCSD	49	60 (35–135)	60.3 (18.2)		
Specimen delivery time, mins					
EBVS	51	35 (17–65)	34.2 (10.5)	0.831	0.838
UCSD	48 ^b	35 (15–105)	34.7 (14.0)		

SD standard deviation, EBVS electrothermal bipolar vessel sealer, UCSD ultrasonic coagulating shear device

^aTo compare differences in mean duration of surgery between device arms

^bOne patient (NC07) had an unknown specimen delivery time

Our study is not without limitations. It was conducted in a single Asian center, with a relatively small sample size of predominantly Chinese ethnicity. Therefore, our results may not be generalizable across other populations. With only four surgeons during randomization, it may be difficult with a small sample size to know whether there is user bias in outcomes. The broad spread of thyroid pathologies may influence the overall outcomes independent of the energy device used; however, there was no statistically significant difference in the distribution of pathologies between the two groups. We limited our study to only thyroid lobectomies because our primary objective was operative time. Compared with total thyroidectomies, lobectomies are less prone to variability as they are usually performed for more limited thyroid disease. In addition, as an academic center, we reserved total thyroidectomies for the training of residents. While residents participated in hemithyroidectomies, their role was limited to assisting, to

minimize confounding the operative time. Therefore, our findings may not be directly extrapolated to total thyroidectomies.

The decision to use drains was based on surgeon preference, although we acknowledge that the majority of thyroid surgeries today are performed without drains. In our study, only 20% of cases were performed using drains. Our considerations for placing a drain include large tumor requiring extensive dissection, extremely vascularized thyroid tissue, or a short, slender neck in which a postoperative seroma can be unsightly. With regard to postoperative pain, we recognize that ordinal self-reported pain scales may be subjected to social, cognitive, and contextual influences, and may not be as robust as other validated pain measures. With regard to the surgeon and operating room staff ratings of ease of use and setup, these are subjective measures and therefore the results may differ between different institutions.

TABLE 4 Ease of use of device

	EBVS		UCSD		<i>p</i> value ^a
	<i>N</i>	%	<i>N</i>	%	
Total	51	100.0	49	100.0	
Interruption during use of the device					
Yes	2	3.9	1	2.0	1.000
No	49	96.1	48	98.0	
Absolute device failure requiring change of equipment					
Yes	0	–	0	–	NA
No	51	100.0	49	100.0	
Number of ties used					
0	37	72.5	37	75.5	1.000
1	11	21.6	11	22.4	
2	2	3.9	1	2.0	
3	1	2.0	0	–	
Median (range)	0 (0–3)		0 (0–2)		0.665 ^b
<i>Surgeon's rating on ease of use of the device</i>					
Among patients with non-missing data ^c	48	100.0	49	100.0	
0	13	27.1	24	49.0	0.005
1	27	56.3	25	51.0	
2	6	12.5	0	–	
3	2	4.2	0	–	
4	0	–	0	–	
5	0	–	0	–	
<i>Staff's rating on ease of setting up, equipment availability, and challenges encountered with use of the device</i>					
Among patients with non-missing data ^c	48	100.0	49	100.0	
0	29	60.4	16	32.7	0.005
1	15	31.3	22	44.9	
2	2	4.2	6	12.2	
3	0	–	5	10.2	
4	1	2.1	0	–	
5	1	2.1	0	–	

NA not applicable, EBVS electrothermal bipolar vessel sealer, UCSD ultrasonic coagulating shear device

^aBased on either the Chi square or Fisher's exact test, unless otherwise specified

^bBased on the Mann–Whitney *U* test

^cRatings had not yet been implemented when the first three patients in the trial underwent their surgery; comments by both the surgeon and staff on the ease of use and setting up of the device for these three patients are reported in electronic supplementary Appendices 1 and 2, respectively

CONCLUSIONS

We found no difference in the duration of surgery, postoperative wound drainage, and adverse events between the two devices. However, we found that use of the UCSD was associated with higher postoperative pain scores. The UCSD was rated by surgeons to have greater ease of use, but was rated by the operating room staff as less easy to set up.

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