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Study on the use of focus harmonic scalpel in thyroidectomies: is it useful also in preserving voice function?

A. MINNI[1], D. ROSATI[1], C. CAVALIERE[1], A. DE CARLO[1], G. ILLUMINATI[2], V. SCARANO CATANZARO[2], M. BONONI[3]

[1]Department of Sensory Organs, "Sapienza" University of Rome, Azienda Policlinico Umberto I, Rome, Italy
[2]"F. Durante" Department of Surgical Science, "Sapienza" University of Rome, Azienda Policlinico Umberto I, Rome, Italy
[3]Department of Surgery "P. Valdoni", "Sapienza" University of Rome, Azienda Policlinico Umberto I, Rome, Italy

Abstract. – OBJECTIVE: The aim of this randomized study is to evaluate the real benefits of the FOCUS Harmonic Scalpel in total thyroidectomies compared with conventional ligation, regarding operative time, postoperative blood loss, length of stay and complications. Furthermore, as never seen in other studies, we studied the effects of using the FOCUS during thyroidectomy analyzing the vocal production of patients before and after surgery.

PATIENTS AND METHODS: We enrolled 361 patients who underwent total thyroidectomy from 2008 to 2014. It was a randomized clinical trial in which all the surgical procedures were performed by the same surgeon. Patients were randomized into two groups according to the haemostatic technique: 187 patients were included in a "conventional" group (C) in whom dissection and haemostasis were performed using conventional materials (Vicryl, stitches, V titanium hemostatic clips and monopolar or bipolar electrocautery); 174 patients were included in a group in which the FOCUS was used (F group).

RESULTS: Our data show that the FOCUS allows a one-third time-saving vs. classic haemostasis. Moreover, the use of the FOCUS would allow reduced traction and reduced manipulation of the thyroid during surgery. Our data demonstrate that the rate of complications in the Focus group might not be significantly reduced. In our series, we noticed that the quantitative acoustic assessment of voice quality show important alterations in several parameters (Shim, Jitt, sPPQ, sAPQ studied with the Multi Dimensional Voice Program evaluation) between the C group and F group.

CONCLUSIONS: The FOCUS Harmonic Scalpel reduces the operative time, post-operative blood loss and length of hospital stay in thyroidectomy. Besides, important vocal alterations after thyroidectomy seem more severe using the conventional technique instead of FOCUS.

Key Words:
Thyroid surgery, Focus Harmonic Scalpel, Voice function.

Introduction

During the past decades, the techniques of thyroid surgery have undergone small changes only. On the other hand, the last twenty years have seen dynamic development of new instruments that has had a significant impact on this kind of surgery[1-3].

Even if effective vessel haemostasis can be achieved by using the conventional clamp-and-tie technique, newer techniques of vessel haemostasis were performed to be more rapid while achieving the same effectiveness[4].

Actually, during thyroidectomy, classic manual suture ligation and electrocoagulation are the two main options to have a good haemostasis. The first one is a time-consuming procedure and implicates the risk of knot slipping, the second one is a fast procedure but implicates the potential risk to damage surrounding tissues (i.e. laryngeal nerve) by dispersion of heat[5].

In the last years, several papers have reported the utility of bipolar vessel sealing systems[6] or the Harmonic Scalpel[7] in shortening the length of thyroid surgery and reducing blood loss, while maintaining a good safety and low rate of complications for patients.

The FOCUS Harmonic Scalpel has been developed for precise and simultaneous cutting as well as hemostasis with minimal damage to surrounding tissues; it uses high-frequency mechan-

Corresponding Author: Antonio Minni, MD; e-mail: antonio.minni@uniroma1.it

ical energy to cut and coagulate at the same time tissues and vessels without the need for knot-tying[8].

The aim of this randomized study is to evaluate the real benefits of the FOCUS Harmonic Scalpel in total thyroidectomies when compared with conventional ligation, concerning operative time, postoperative blood loss, length of stay and complications. Besides, as never seen in other studies, we analyzed the effects of using the FOCUS Harmonic Scalpel during thyroidectomy on vocal production of patients after surgery.

Patients and Methods

We enrolled 361 patients (152 men and 209 women) who underwent total thyroidectomy from January 2008 to May 2014. It was a randomized clinical trial in which all the surgical procedures were performed under general anesthesia by the same surgeon (to eliminate every kind of surgical technique bias).

Patients were randomized into two groups according to the haemostatic technique: 187 patients (79 men and 108 women) were included in the first group (Conventional group or C group), in whom haemostasis and other surgical passages were performed using only conventional materials (Vicryl, stitches, haemostatic clips made of titanium and monopolar or bipolar electrocoagulation); 174 patients (73 men and 101 women) were included in FOCUS Harmonic scalpel group (Focus group or F group), in which the FOCUS was used: the application of ultrasound to tissues was performed during the entire procedure, to obtain three purposes synergistically: coagulation, cutting, and cavitation.

The patients were divided according to age, preoperative diagnosis, and thyroid size to generate homogeneous groups.

The inclusion criteria were

1. Age > 18 years;
2. Acceptance to participate in the study (signed informed consent form);
3. Scheduled total thyroidectomy for multinodular goiters or low risk differentiated carcinoma (T1N0M0).

The exclusion criteria were:

1. Preoperative medication including analgesics, corticosteroids or nonsteroidal antiinflammatory drugs;
2. Coagulation disorders;
3. Pregnancy;
4. Cervicomediastinal goiters;
5. Total thyroidectomy with need of lymph node dissection as in patients with invasive malignant cancer;
6. Concomitant parathyroid disorders;
7. History of neck irradiation.

In all cases, total thyroidectomy was performed under general anesthesia with endotracheal intubation. In both groups, the surgical incision was always a 4 to 6 cm low collar incision; after performing subplatysmal flap with high frequency electric knife, the superficial muscles were isolated at the midline. As the gland was exposed, we separated the two groups performing haemostasis of thyroid vessels in one of the following ways: (1) in the conventional group: main thyroid vessels (inferior, middle and superior) were ligated using 3/0 silk sutures while in all other vessels we used absorbable 4/0 sutures and/or electrocauterization; (2) in the FOCUS group: the haemostasis of all thyroid vessels was performed with the FOCUS Harmonic Scalpel. For a better patient safety, we used a double ligation technique on superior and inferior thyroid vessels. Synthetically, the device was used two times in 2 succeeding areas of the same vessel: just to coagulate the vessel in the distal part, and cutting the tissue after coagulation in the proximal part. In this way, no suture ligation was used.

Other surgical steps were the same for C group and F group. We identified and isolated recurrent laryngeal nerves and parathyroid glands every time and a closed suction drain was always positioned below the superficial muscles.

The parameters considered in this study were: total operating time (since initiation of the incision until conclusion of skin closure), amount of drainage, time of positioning of drainage balloons (the drains were removed if drainage volume was less than 10 ml in 24 hours), post-operative hospitalization and occurrence of complications (Table I). Serum parathyroid hormone, serum Ca and P levels were obtained in all patients during the first post-operative day. We considered post-operative biochemical hypoparathyroidism when serum parathyroid hormone level resulted below 15 ng/L (normal, 15-65 ng/L) and we handed out oral calcium carbonate and calcitriol supplementation to patients with transient biochemical hypoparathyroidism,

Table I. Operative and postoperative parameters between 2 groups.

Variable	Focus group (No. = 174)	Conventional group (No. = 187)	*p*-value
Mean thyroid weight (g)	46.8 ± 18.5	50.6 ± 14.2	> 0.05
Total operating time (min)	78.8 ± 16.1	133.6 ± 33.4	**< 0.05**
Amount of drainage (ml)	36.9 ± 2.3	57.2 ± 4.4	**< 0.05**
Time of drainage (h)	36 ± 12	84 ± 12	**< 0.05**
Serum PTH (ng/L):			
Preoperative	46.90 ± 18.58	43.87 ± 17.21	> 0.05
Postoperative	20.6 ± 14.3	19.06 ± 16.88	> 0.05
Serum Ca (mmol/L):			
Preoperative	2.32 ± 0.13	2.28 ± 0.21	> 0.05
Postoperative	2.12 ± 0.17	2.05 ± 0.23	> 0.05
Serum P (mmol/L):			
Preoperative	1.36 ± 0.31	1.39 ± 0.33	> 0.05
Postoperative	1.45 ± 0.24	1.48 ± 0.27	> 0.05
Hypoparathyroidism	9	10	> 0.05.
Postoperative hospitalization (d)	4.8 ± 1.28	6.9 ± 1.74	**< 0.05**
Parathyroid gland autotransplantation(n)	14	16	> 0.05.
RLN paralysis:			
Temporary (n)	1	2	> 0.05
Permanent (n)	0		0
Superior laryngeal nerve injury	0		0
Lymphatic ducts injured chyle leakage (n)	1	1	> 0.05

Abbreviations: PTH, parathyroid hormone; RLN, recurrent laryngeal nerve.

even if they didn't show any clinical symptoms of hypocalcemia. We defined recurrent laryngeal nerve palsy as temporary when it resolved between 6 months after surgery and as permanent when it persisted more than 6 months.

About the phoniatric part of the study, the preoperative and post-operative voice assessment protocol included three procedures, performed in a single session:

1. **Evaluation of Voice Handicap Index (VHI)**: we submitted patients 30 questions about the discomfort related to the use of their voice. The VHI includes 30 items, each scored on a 5-point scale ranging from "never" to "always", divided into three subscales including functional, emotional and physical features related to voice dysfunction. The normal limit and threshold for significant changes were based on the values reported by Jacobson et al[9]. A difference of up to 8 points on the subscales and 18 points on the total score was considered to indicate significant discomfort.
2. **Laryngo-stroboscopy**: we studied patients performing a laryngeal examination using a 3.5 mm diameter fiberscope (Storz 11101RP) connected to a stroboscopic light source (ATMOS Endo Stroboscope L) to evaluate the morphology and motility of the larynx, to assess vocal fold vibratory pattern (mucosal wave) and to appreciate symmetry and regularity of the vocal fold vibration as well as signs of functional dysphonia. The examination was video-recorded for every patient to eliminate any kind of bias. Esophageal-laryngeal reflux (ELR) symptoms were reported according to the Reflux Finding Score[10].
3. **Spectrographyc analysis**: the vocal quality of patients was evaluated by means of a software tool for quantitative acoustic assessment of voice quality (MDVP KAYPENTAX Mod. 5101). We selected the following acoustic parameters: Jitt (Jitter percent, the relative variability of the pitch in the short-term); sPPQ (smoothed Pitch Perturbation Quotient); Shim (Shimmer percent, the relative variability of the peak-to-peak amplitude in the short-term) and the sAPQ (smoothed Amplitude Perturbation Quotient).

The evaluation of vocal alterations using the protocol of three procedures (VHI, laryngo-stroboscopy and spectrographyc analysis with Multi Dimensional Voice Program MDVP) showed interesting differences between C group and F group (Tables II, III, IV, V).

Table II. Pre-operative parameters in 152 men patients (one way Anova analysis).

Variable	Focus group (No. = 73)	Conventional group (No. = 79)	*p*-value
Shim	2.54	2.73	> 0.05
sAPQ patients	2.88	2.94	> 0.05
Jitt	0.54	0.51	> 0.05
sPPQ	0.52	0.58	> 0.05
VHI p (perception of vocal patients emission characteristics)	0.00	0.00	> 0.05
VHI f (daily activities impact)	0.00	0.00	> 0.05
VHI e (psychological impact)	0.00	0.00	> 0.05

Table III. Pre-operative parameters in 209 women patients (one way Anova analysis).

Variable	Focus group (No. = 101)	Conventional group (No. = 108)	*p*-value
Shim	2.21	2.17	> 0.05
sAPQ patients	2.44	2.35	> 0.05
Jitt	0.59	0.61	> 0.05
sPPQ	0.48	0.52	> 0.05
VHI p (perception of vocal patients emission characteristics)	0.00	0.00	> 0.05
VHI f (daily activities impact)	0.00	0.00	> 0.05
VHI e (psychological impact)	0.00	0.00	> 0.05

Table IV. Post-operative parameters in 152 men patients (one way Anova analysis).

Variable	Focus group (No. = 73)	Conventional group (No. = 79)	*p*-value
Shim	3.95	5.78	**< 0.05**
sAPQ patients	3.28	4.91	**< 0.05**
Jitt	0.63	1.09	**< 0.05**
sPPQ	0.62	1.28	**< 0.05**
VHI p (perception of vocal patients emission characteristics)	3.58	3.70	> 0.05
VHI f (daily activities impact)	0.48	0.56	> 0.05
VHI e (psychological impact)	0.19	0.21	> 0.05

Table V. Post-operative parameters in 209 women patients (one way Anova analysis).

Variable	Focus group (No. = 101)	Conventional group (No. = 108)	*p*-value
Shim	3.65	5.03	**< 0.05**
sAPQ patients	4.26	5.95	**< 0.05**
Jitt	0.72	1.21	**< 0.05**
sPPQ	0.69	1.18	**< 0.05**
VHI p (perception of vocal patients emission characteristics)	4.18	4.31	> 0.05
VHI f (daily activities impact)	0.98	1.09	> 0.05
VHI e (psychological impact)	0.89	0.96	> 0.05

(Shim: absolute shimmer, sAPQ: smoothed amplitude perturbation quotient, jitter: irregularity index of vibration glottic, sPPQ: Smoothed Pitch Period Perturbation Quotient, F0: fundamental frequency, vAm: peak to peak amplitude variation, VHI: Voice Handicap Index).

Statistical Analysis

Statistical analysis of the differences between groups was performed using the 2-sample *t*-test and c2 test. Statistical analysis was made by SPSS 13 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

One-way ANOVA *(Analysis of Variance)* with LSD procedure for the post hoc test were used to test the differences in the selected MDVP variables in four subgroups; *p*-values less than or equal to 0.05 were considered to indicate significance. Data were analyzed with a PC version of the Statistical Package for Social Sciences 16.0 (SPSS Inc., Chicago, IL, USA).

Results

All the parameters studied in the two groups were extensively presented in Table I. Total operating time (in minutes) was significantly shorter in F group ($p < 0.05$); this allowed a one-third time saving in confront of C group. About postoperative transient biochemical hypoparathyroidism, it occurred more frequently in Classic group than in Focus group, but this was not statistically significant, while about permanent biochemical hypoparathyroidism we did not register any case. 3 temporary palsies of the recurrent laryngeal nerve occurred (2 in the C group, 1 in the F group), with full recovery in three months, but we did not observe cases of permanent laryngeal nerve palsy, derived probably from the accurate and precise surgical technique and mostly from knowledge and recognition of anatomical structures. We didn't observe injuries to superior laryngeal nerve.

Intraoperative bleeding was not excessive in all the patients; so, there were neither blood transfusions nor postoperative definitive sequelae. The amount of total drainage was significantly higher in patients of C group vs patients of F group. Besides, the days of drainage maintenance before removal were significantly increased in C group compared with F group. The mean postoperative hospital stay was significantly reduced in the Focus group. The rate of parathyroid gland autotransplantation was not statistically significant between Focus group and Classic group (Table I).

Two patients of C group with cervical hematomas required re-exploration within 24 hours. No other postoperative complications were observed.

Discussion

The thyroid gland has an extensive and complex vascular network. Therefore, it is essential to perform a good haemostasis to avoid postoperative hemorrhage which potentially causes patient's asphyxia and death[11].

Besides, total thyroidectomy requires massive clamp-and-tie maneuvers for the small thyroid vessels and if the use of conventional technique is time-consuming, on the other hand using instruments as mono or bipolar diathermy can be unsafe because of the risk of damaging the surrounding structures caused by adjacent thermal spread. FOCUS Harmonic scalpel is a good solution because it is a device specifically designed for having an accurate dissection and an efficient haemostasis in all the procedures realized in a narrow operating field as in thyroid surgery.

Even if previous harmonic scalpel instruments were probably too much large and bulky, the Harmonic Focus is smaller and more maneuverable and probably for this reason many surgeons use it as an alternative to conventional hand-tied ligation for haemostasis in thyroid surgery[12-16].

The Harmonic Focus uses high frequency mechanical energy to cut and coagulate tissues at the same time. Ultrasonic coagulation achieved by the FOCUS is similar to that of electrocautery because at last remains a denatured protein coagulum that close blood vessels. Nevertheless, the mechanism by which the proteins become denatured is completely different. Electrocautery and lasers form the coagulum by heating tissue to denature the protein. The FOCUS instead denatures proteins by using ultrasonic vibration and transferring mechanical energy sufficient to break tertiary hydrogen bonds and this allows to create a smaller area of adjacent thermal damage compared to the bipolar cautery[17-19]. It is important to underline that using FOCUS, blood vessels with a diameter until 5 mm did not need for an additional protection by ligation, and this implicates a significant decrease of total operative time (about one third saving in confront of classic haemostasis in our study) and even a significant reduction of use of material (sutures, clips).

Besides, we noticed that using FOCUS ultrasonic scalpel there was a significantly decreased amount of drainage after surgery, and this is confirmed by numerous randomized trials that reported an important intra-operative blood loss reduction in addition to a post-operative drainage decrease[20-31]. This led also to a reduction of postoperative hospital stay.

The reduced tissue injury and the better haemostasis are confirmed by the statistically significant reduction of drainage volume for patients that we observed in the Focus group, even if there are some authors that did not reach similar conclusions regarding the quantity of intra-operative and post-operative drainage[32-36].

Furthermore, Miccoli et al[37,38] underline the reduced traction and manipulation of thyroid allowed by the use of Harmonic Focus (particularly when the surgeon has to separate the upper pedicle and cut the superior pole).

In the end, we observed that there wasn't a significant difference of complication rate (hypoparathyroidism, superior and inferior laryngeal nerve damages) between F group and C group.

The symptomatic cases of hypocalcemia of F group were lower than C group, even if in our study we didn't find a significant difference at first post-operative day in PTH and calcium level, which were considered as reliable parameters for parathyroid function evaluation[39].

Perhaps, the decreased tissue damage resulting from less heat produced by the FOCUS might lead to a reduced injury to the vascularization of parathyroids glands, but we need other series to confirm it.

We observed 3 patients with temporary palsy of recurrent laryngeal nerve which resolved within 60 days, while we did not register permanent palsy of the recurrent laryngeal nerve.

On the other hand, the main problem of FOCUS is related to its cost[40-42]; in fact, the Harmonic Focus is a single-use and high-priced device and must be considered an additional cost for hospital. Anyway, we think that evaluating the decreased operating time and hospitalization, the utilization of this instrument might be considered advantageous.

In a previous report[43], we observed that after total thyroidectomy, some patients showed some vocal parameters alterations despite intra-operative and post-operative integrity of both superior and inferior laryngeal nerves. We presumed that these alterations resulted from abnormal fibrosis of prelaryngeal muscles after dissection and suturing.

For this reason, we controlled vocal parameters of patients that underwent a total thyroidectomy to observe if there was a correlation between surgical technique and vocal parameters related to eventual fibrosis and abnormal scarring of laryngotracheal unit. After thyroidectomy, the laryngotracheal unit is supported only by the prelaryngeal muscles. An abnormal scarring after dissection and suturing or even simple manipulation during surgery may lead to a functional deficit[44] and this vocal individual deficit may constitute a moderate or severe handicap in professional and social life of patients.

We observed that in patients of C group the quantitative acoustic assessment of voice quality showed important alterations in several parameters, more evident in those concerning the variability of loudness than pitch, instead that patients of F group. Hence, to have a more accurate voice acoustic evaluation, we studied the generally used relative variability of the pitch (Jitt) and of the peak-to-peak amplitude (Shim) in the short term, but even the smoothed corresponding parameters (sPPQ and sAPQ).

In our series, we noticed important differences in foniatric parameters (Shim, Jitt, sPPQ, sAPQ) studied with the MDVP evaluation between the C group and F group. Specifically, patients who underwent a thyroidectomy with conventional technique (C group) showed significantly worst values of pitch and amplitude vocal parameters than patients who underwent a thyroidectomy in which it was used FOCUS (Tables II, III, IV, V).

The patients' subjective perception of voice discomfort evaluated with VHI was instead quite similar between two groups.

Our data, particularly the alterations found in the acoustic parameters related to peak-to-peak amplitude variability (Shim, sPPQ, sAPQ), suggest that in many patients we examined after thyroidectomy with conventional technique (C group), the muscles of larynx were unable to maintain a stable voice emission. Although we cannot directly attribute these findings to the thyroidectomy technique, we can assume that, despite the preservation of the EBSLN, the surgical maneuvers we used for sectioning and resuturing the sternothyroid muscles in patients in whom dissection and haemostasis were performed using conventional materials, could have induced fibrosis, thus, altering our patients' laryngeal muscle balance. We suppose that surgically-related fibrosis might explain why[45], whereas in other series mild or severe vocal changes reported reversed within a month, in our patients, vocal alterations persisted for one year or more[46]. Finally, we can affirm that, using FOCUS, is possible to avoid the muscular resection of pre-thyroid muscles, thus performing a less traumatic injury to the tissues and a smaller fibrosis.

Conclusions

The FOCUS Harmonic Scalpel reduces the operative time, post-operative blood loss and length of hospital stay in thyroidectomy. Another notable observation is also that, even if patients' subjective perception of voice discomfort was similar between two groups, important vocal alterations after thyroidectomy (Shim, Jitt, sPPQ, sAPQ studied with Multi Dimensional Voice Program) seemed more severe using the conventional technique instead of FOCUS. In contrast, some post-operative parameters (serum calcium at 12 and 48 hours, hypocalcemia, RLN palsy, hypoparathyroidism) showed not statistical difference. We conclude that the use of FOCUS Harmonic Scalpel during surgery for total thyroidectomy is advantageous, even if a scrupulous and careful care of surgical technique and haemostasis should however always be observed, in order to avoid every kind of surgical complication.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Becker AM, Gourin CG. New technologies in thyroid surgery. Surg Oncol Clin N Am 2008; 17: 233-248.
2) Zhang P, Zhang HW, Han DX, Di JZ, Zheng Q. Meta-analysis of comparison between minimally invasive video-assisted thyroidectomy and conventional thyroidectomy. Eur Rev Med Pharmacol Sci 2015; 19: 1381-1387.
3) Zullino A, Maiuolo A, Fumarola A, Gargiulo P, Mercuri V, Pacini FM, Ruggieri M. Minimally invasive thyroidectomy and the differentiated lesions: the way to follow. Eur Rev Med Pharmacol Sci 2012; 16: 519-524.
4) Bellantone R, Lombardi CP, Bossola M, Boscherini M, De Crea C, Alesina P, Traini E, Princi P, Raffaelli M. Total thyroidectomy for management of benign thyroid disease: review of 526 cases. World J Surg 2002; 26: 1468-1471.
5) Bandi G, Wen CC, Wilkinson EA, Hedican SP, Moon TD, Nakada SY. Comparison of blade temperature dynamics after activation of Harmonic Ace scalpel and the Ultracision Harmonic Scalpel LCS-K5. J Endourol 2008; 22: 333-336.
6) Manouras A, Markogiannakis H, Koutras AS, Antonakis PT, Drimousis P, Lagoudianakis EE, Kekis P, Genetzakis M, Koutsoumanis K, Bramis I. Thyroid surgery: comparison between the electrothermal bipolar vessel sealing system, harmonic scalpel, and classic suture ligation. Am J Surg 2008; 195: 48-52.
7) Aydin M, Deveci U, Orman A, Taskin E, Kilic M. A prospective randomized trial comparing the harmonic scalpel with conventional knot tying in thyroidectomy. Adv Ther 2007; 24: 632-638.
8) Amaral JF. The experimental development of an ultrasonically activated scalpel for laparoscopic use. Surg Laparosc Endosc 1994; 4: 92-99.
9) Jacobson BH, Jonson A, Grywalsky C, Silbergleit A, Jacobson G, Benninger MS. The voice handicap index (VHI): development and validation. Am J Speech Lang Pathol 1997; 6: 66-70.
10) Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001; 111: 1313-1317.
11) Rosato L, Avenia N, Bernante P, De Palma M, Gulino G, Nasi PG, Pelizzo MR, Pezzullo L. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg 2004; 28: 271-276.
12) Prgomet D, Janjanin S, Bili M, Prstaci R, Kovac L, Rudes M, Kati V. A prospective observational study of 363 cases operated with three different harmonic scalpels. Eur Arch Otorhinolaryngol 2009; 266: 1965-1970.
13) Markogiannakis H, Kekis PB, Memos N, Alevizos L, Tsamis D, Michalopoulos NV, Lagoudianakis EE, Toutouzas KG, Manouras A. Thyroid surgery with the new harmonic scalpel: A prospective randomized study. Surgery 2011; 149: 411-415.
14) Manouras A, Markogiannakis HE, Kekis PB, Lagoudianakis EE, Fleming B. Novel hemostatic devices in thyroid surgery: electrothermal bipolar vessel sealing system and harmonic scalpel. Expert Rev Med Devices 2008; 5: 447-466.
15) Koh YW, Park JH, Kim JW, Lee SW, Choi EC. Clipless and sutureless endoscopic thyroidectomy using only the harmonic scalpel. Surg Endosc 2010; 24: 1117-1125.
16) Cirocchi R, D'Ajello F, Trastulli S, Santoro A, Di Rocco G, Vendettuoli D, Rondelli F, Giannotti D, Sanguinetti A, Minelli L, Redler A, Basoli A, Avenia N. Meta-analysis of thyroidectomy with ultrasonic dissector versus conventional clamp and tie. World J Surg Oncol 2010; 8: 112-128.
17) Walker RA, Syed ZA. Harmonic scalpel tonsillectomy versus electrocautery tonsillectomy: a comparative pilot study. Otolaryngol Head Neck Surg 2001; 125: 449-455.
18) McCarus SD. Physiologic mechanism of the ultrasonically activated scalpel. J Am Assoc Gynecol Laparosc 1996; 3: 601-608.
19) Landman J, Kerbl K, Rehman J, Andreoni C, Humphrey PA, Collyer W, Olweny E, Sundaram C, Clayman RV. Evaluation of a vessel sealing system, bipolar electrosurgery, harmonic scalpel, titanium clips, endoscopic gastrointestinal anastomosis vascular staples and sutures for arterial and venous ligation in a porcine model. J Urol 2003; 169: 697-700.

20) Defechereux T, Rinken F, Maweja S, Hamoir E, Meurisse M. Evaluation of the ultrasonic dissector in thyroid surgery. A prospective randomized study. Acta Chir Belg 2003; 103: 274-277.

21) Kilic M, Keskek M, Ertan T, Yoldas O, Bilgin A, Koc M. A prospective randomized trial comparing the harmonic scalpel with conventional knot tying thyroidectomy. Adv Ther 2007; 24: 632-638.

22) Konturek A, Barczynski M, Cichon S. Ultrasonic scalpel versus classic procedures with limited access in thyroid gland surgery. Pol J Surg 2007; 79: 848-859.

23) Defechereux T, Meurisse M. Hemostasis and ultrasonic shears for thyroid surgery. Ann Chir 2006; 131: 154-156.

24) Barczy ski M, Konturek A, Cicho S. Minimally invasive videoassisted thyreoidectomy (MIVAT) with and without use of harmonic scalpel: a randomized study. Langenbecks Arch Surg 2008; 393: 647-654.

25) Hallgrimsson P, Lovén L, Westerdahl J, Bergenfelz A. Use of the harmonic scalpel versus conventional haemostatic techniques in patients with Grave disease undergoing total thyroidectomy: a prospective randomised controlled trial. Langenbecks Arch Surg 2008; 393: 675-680.

26) Bove A, Papanikolaou I, Bongarzoni G, Mattei P, Markogiannakis H, Chatzipetrou M, D'Addetta V, Di Renzo R, Fiordaliso M, Corbellini L. Thyroid surgery with harmonic focus, ligasure precise and conventional technique: a retrospective case-matched study. Hippokratia 2012; 16: 154-159.

27) Cannizzaro MA, Lo Bianco S, Borzì L, Cavallaro A, Buffone A. The use of FOCUS Harmonic scalpel compared to conventional haemostasis (knot and tie ligation) for thyroid surgery: a prospective randomized study. Springerplus 2014; 3: 639.

28) Ferri E, Armato E, Spinato G, Spinato R. Focus harmonic scalpel compared to conventional haemostasis in open total thyroidectomy: a prospective randomized trial. Int J Otolaryngol 2011; 2011: 357195.

29) He Q, Zhuang D, Zheng L, Zhou P, Chai J, Lv Z. Harmonic focus in total thyroidectomy plus level III-IV and VI dissection: a prospective randomized study. World J Surg Oncol 2011; 9: 141.

30) Konturek A, Barczy ski M, Stopa M, Nowak W. Total thyroidectomy for non-toxic multinodular goiter with versus without the use of harmonic FOCUS dissecting shears--a prospective randomized study. Wideochir Inne Tech Maloinwazyjne 2012; 7: 268-274.

31) Duan YF, Xue W, Zhu F, Sun DL. FOCUS harmonic scalpel compared to conventional hemostasis in open total thyroidectomy - a prospective randomized study. J Otolaryngol Head Neck Surg 2013; 42: 62.

32) McNally MM, Agle SC, Williams RF, Pofahl WE. A comparison of two methods of hemostasis in thyroidectomy. Am Surg 2009; 75: 1073-1076.

33) Koh YW, Park JH, Lee SW, Choi EC. The harmonic scalpel technique without supplementary ligation in total thyroidectomy with central neck dissection: a prospective randomized study. Ann Surg 2008; 247: 945-949.

34) Barczy ski M, Konturek A, Cicho S. Minimally invasive video-assisted thyreoidectomy (MIVAT) with and without use of harmonic scalpel--a randomized study. Langenbecks Arch Surg 2008; 393: 647-654.

35) Sartori PV, De Fina S, Colombo G, Pugliese F, Romano F, Cesana G, Uggeri F. Ligasure versus Ultracision in thyroid surgery: a prospective randomized study. Langenbecks Arch Surg 2008; 393: 655-658.

36) Mourad M, Rulli F, Robert A, Scholtes JL, De Meyer M, De Pauw L. Randomized clinical trial on Harmonic Focus shears versus clamp-andtie technique for total thyroidectomy. Am J Surg 2011; 202: 168-174.

37) Miccoli P, Materazzi G, Miccoli M, Frustaci G, Fosso A, Berti P. Evaluation of a new ultrasonic device in thyroid surgery: comparative randomized study. Am J Surg 2010; 199: 736-740.

38) Miccoli P, Materazzi G, Berti P. Minimally invasive thyroidectomy in the treatment of well differentiated thyroid cancers: indications and limits. Curr Opin Otolaryngol Head Neck Surg 2010; 18: 114-118.

39) Grodski S, Serpell J. Evidence for the role of perioperative PTH measurement after total thyroidectomy as a predictor of hypocalcemia. World J Surg 2008; 32: 1367-1373.

40) Sebag F, Fortanier C, Ippolito G, Lagier A, Auquier P, Henry JF. Harmonic scalpel in multinodular goiter surgery: impact on surgery and cost analysis. J Laparoendosc Adv Surg Tech A 2009; 19: 171-174.

41) D'Ajello F, Cirocchi R, Docimo G, Catania A, Ardito G, Rosato L, Avenia N. Thyroidectomy with ultrasonic dissector: a multicentric experience. G Chir 2010; 31: 289-292.

42) Scilletta B, Cavallaro MP, Ferlito F, Li Destri G, Minutolo V, Frezza EE, Di Cataldo A. Thyroid surgery without cut and tie: the use of Ligasure for total thyroidectomy. Int Surg 2010; 95: 293-298.

43) Minni A, Ruoppolo G, Barbaro M, Di Lorenzo E, Sementilli G, Bononi M. Long-term (12 to 18 months) functional voice assessment to detect voice alterations after thyroidectomy; Eur Rev Med Pharmacol Sci 2014; 18: 1704-1708.

44) Pereira JA, Girvent M, Sancho JJ, Parada C, Sitgesserra A. Prevalence of long-term upper aerodigestive symptoms after uncomplicated bilateral thyroidectomy. Surgery 2003; 133: 318-322.

45) Stojadinovic A, Shaha AR, Orlikoff RF, Nissan A, Kornak MF, Singh B, Boyle JO, Shah JP, Brennan MF, Kraus DH. Prospective functional voice assessment patients undergoing thyroid surgery. Ann Surg 2002; 236: 823-832.

46) Maeda T, Saito M, Otsuki N, Morimoto K, Takahashi M, Iwaki S, Inoue H, Tomoda C, Miyauchi A, Nibu K. Voice quality of voice after surgical treatment for thyroid cancer. Thyroid 2013; 23: 847-853.