International Journal of Surgery 28 (2016) S22–S32

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Complications in thyroid surgery. *Harmonic Scalpel*, *Harmonic Focus* versus Conventional Hemostasis: A meta-analysis

Luca Revelli [a], Gianfranco Damiani [b], Caterina Bianca Neve Aurora Bianchi [c, *], Serafino Vanella [a], Walter Ricciardi [b], Marco Raffaelli [a], Celestino Pio Lombardi [a]

[a] *Department of Surgical Sciences, University Hospital Agostino Gemelli, Catholic University of Sacred Heart, Rome, Italy*
[b] *Department of Public Health, University Hospital Agostino Gemelli, Catholic University of Sacred Heart, Rome, Italy*
[c] *Cooperative OSA Onlus, Associated Health Care Workers, Rome, Italy*

ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form
29 April 2015
Accepted 20 May 2015
Available online 6 January 2016

Keywords:
Complications in thyroidectomy
Harmonic Scalpel
Harmonic Focus
Hemostasis
Thyroid
Thyroid surgery
Ultrasonic dissector
Ultrasonic scalpel

ABSTRACT

Background: To evaluate the incidence of postoperative complications, hemostatic effects and safety of Total Thyroidectomy (TT) performed using the *Harmonic Scalpel* (HS), the *Harmonic Focus* (HF) or Conventional Hemostasis (CH).

Methods: The meta-analysis was performed according to PRISMA guidelines. A literature search was conducted from 2003 to 2014 and stringent criteria were required for inclusion. Thirteen studies concerning an overall population of 1458 compared HS versus CH, whilst 8 studies with 1667 patients compared HF versus CH.

Results: There was a significant reduction of operative time (Mean Difference [MD] = −25.49 min.; 95% CI −32.43 to −18.55), intraoperative blood loss (MD = −30.49 mL; 95% CI −53.01 to −7.97), postoperative drainage volume (MD = −12.90 mL; 95% CI −22.83 to −2.98) and postoperative pain (MD = −0.87; 95% CI −1.27 to −0.46) in patients underwent TT with HS.

Regarding HF group, a significant reduction of operative time (MD = −25.99 min., 95% CI −34.56 to −17.41), length of hospital stay (MD = −0.57; 95% CI −0.97 to −0.17), transient hypocalcemia (OR = 0.56; 95% CI 0.39 to 0.81) and postoperative pain (MD = −1.33 days; 95% CI −2.49 to −0.17) resulted.

Conclusions: HS TT can be a safe, useful and fast alternative to conventional TT. The newer HF can reduce the rate of hypocalcemia. Future RCTs of larger patient cohorts with more detailed data of postoperative complications, cost-effectiveness and cosmetic results, randomization procedures, intention-to-treat analyses and blinding of outcome assessors are needed to draw more meaningful conclusions.

1. Introduction

Surgery is the standard therapy for many thyroid diseases [1]. In the United States the surgical volume reaches 80,000 thyroidectomies per year [2]. In Italy it exceeds 40,000 [3].

Safe thyroid surgery requires meticulous hemostasis and careful control of bleeding. Whereas the thyroid has rich blood supply, prompt hemostasis is crucial to avoid intraoperative bleeding, obtain good visualization of the surgical field and prevent damage to structures such as parathyroid glands or laryngeal nerves. The main sources of bleeding are injured thyroid vessels and thyroid parenchymal bleeding [4]. Hemorrhage (intra- or postoperative) may cause some complications as seromas and/or hematomas, occasionally responsible for potentially lethal asphyxia. Hemostasis is a critical factor determining also the frequency of other problems, as well as the prolongation of the operative time, thereby increasing the length of hospital stay and costs [1,5,6].

In the mid-19th century, thyroid surgery was regarded as a "*proceeding by no means to be thought of*" in Britain (Robert Liston, 1794–1847), "*foolhardy*" in Germany (Johann Friedrich Dieffenbach, 1792–1847), and "*horrid butchery*" that "*no honest and sensible surgeon would ever engage in it*" in United States (Samuel D. Gross,

* Corresponding author.
E-mail addresses: luca.revelli@unicatt.it (L. Revelli), gdamiani@rm.unicatt.it (G. Damiani), caterinablanc@gmail.com (C.B.N.A. Bianchi), nekroma@yahoo.it (S. Vanella), wricciardi@rm.unicatt.it (W. Ricciardi), marco.raffaelli@unicatt.it (M. Raffaelli), celestinopio.lombardi@unicatt.it (C.P. Lombardi).

http://dx.doi.org/10.1016/j.ijsu.2015.12.050
1743-9191/

1805–1884) [7]. The very bad outcomes of thyroidectomy (mortality up to 40% for intra-postoperative bleeding) brought the *Académie Royale de Médecine* to ban any operation on the thyroid in 1850 [8].

In the late 19th century, thyroidectomy was associated with the massive blood loss and a mortality rate of 50% [7]. However, after Emil Theodor Kocher (Bern, 1841–1917) revolutionized thyroid surgery with the introduction of suture ligation of the major arteries, the mortality rate decreased from the 40% reported by Christian Albert Theodor Billroth (Prussia, 1829–1894) to 0.2% in 1895 [9]. The ligation and division of the thyroid vessels is the most time-consuming part of the operation. Many attempts to reduce the mean operative time by introducing new methods of vessel ligation and division without increasing the risk of postoperative complications have been made [10].

Many methods designed to maintain surgical hemostasis are presently used: ligation and suturing (threads, clips, staplers), coagulation (monopolar and bipolar electrocoagulation), ultrasonic coagulation (*Ultracision*, *Harmonic Scalpel*®; Ethicon Endo-Surgery, Cincinnati, OH), electroligation sealing (*LigaSure*® *Vessel Sealing System*; Valleylab, Boulder, CO, USA). Electrosurgical devices use heat energy to denature proteins and the heating of the surgical field – due to lateral dispersion – may damage vital structures. In the recent years, research has been looking for new instruments with less thermal spread, in the effort to reduce intraoperative complications and operative time. Among these instruments we focalized our attention on the *Harmonic Scalpel*® (HS) because this is the oldest and studied hemostatic device. Among the *Ultracision* system devices, the CS14C is the most frequently used instrument.

A large number of studies using HS have recently been included in recent meta-analysis which showed shorter operative time, lower intraoperative blood loss and lower volume drainage [11–13,16].

An innovative technical improvement of the device for thyroid surgery has very recently been implemented and was made available in 2008: *Harmonic Focus*® (HF) shears. Recent trials compared HF with conventional techniques.

The objective of this study is to provide through a meta-analysis of the literature the updated results regarding the comparison between HS–HF and classic vessel ligation with electrocoagulation in thyroid surgical patients, and to focalize the attention on the single complications as Recurrent Laryngeal Nerve (RLN) palsy, hypocalcemia, postoperative pain (due to neck hyperextension and brachial plexus stretching) and unsatisfactory cosmetic results (wound infection, keloid, hypertrophic scar) [1,14].

2. Material and methods

2.1. Search methods

This systematic review and meta-analysis was performed in accordance with PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) statement and checklist [15].

An extensive search of the scientific literature was carried out by querying electronic databases (*Medline*, *Scopus* and *Cochrane Central Register of Controlled Trials*) and was supplemented with a snowball search including references from the most recent papers relating to this subject and from previous reviews or meta-analysis [1,11–13,16].

The following search strategies were used in the search: "*Harmonic Scalpel*" OR "*Harmonic Focus*" AND "thyroid surgery" AND "thyroidectomy"; "ultrasonic scalpel" OR "ultrasonic dissector" AND "thyroid surgery" AND "thyroidectomy".

2.2. Selection criteria

Stringent criteria were required for inclusion:

1) studies must to be only Randomized Controlled Trials (RCTs);
2) studies had to compare HS (HS or HF) to other hemostatic procedures (tying and knots …);
3) studies had to evaluate only Total Thyroidectomy.

Studies including additional procedure (lymph node dissection) or evaluating *Ligasure* as surgical technique were excluded. The meta-analysis was restricted to studies of adults (aged ≥18) published in English, French and Italian language from 2003 to 2014.

The study evaluated the following outcomes:

- operative time
- length of hospital stay
- intraoperative blood loss
- postoperative drainage volume
- wound complications (infection and seroma)
- transient and permanent postoperative hypocalcemia
- transient and permanent postoperative Recurrent Laryngeal Nerve (RLN) palsy
- postoperative pain

2.3. Data extraction

Two authors (CB, SV) independently assessed titles and abstracts of all identified studies and obtained full text of all eligible studies according to inclusion criteria mentioned. Data from selected studies were extracted with help of a standardized form referring to authors, country, year of publication, study design, number of patients enrolled in each study, type of surgical technique and principal outcomes evaluated. Effect estimates for dichotomus and continuous variables with related variability (standard deviation) or precision (standard error) measures were recorded.

2.4. Qualitative assessment

The *Cochrane Collaboration's risk of bias tool* [17] was used to evaluate the methodological quality of RCTs. Two reviewers independently assessed risk of bias using the following domains:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and researchers (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)

Risk of bias was assessed for each criteria as low risk, unclear, high risk. Disagreements between reviewers were resolved by discussion or by a third reviewer. A risk of bias table that summarized key criteria used to assessed study limitations for each domain was showed in the results section.

2.5. Statistical analysis

The principle meta-analysis compared HS technique to CH; the second analysis compared HF to CH. The statistical software *Review Manager 5.1* provided by the Cochrane Collaboration was used for performing both analysis.

Mean Differences (MD) were used as treatment effect measures

for operative times, length of hospital stay, intraoperative blood loss, postoperative drainage volume and postoperative pain. Regarding wound complications, postoperative hypocalcemia and RLN palsy data were analyzed using Odds Ratio (ORs) with 95% of Confidence Interval (CI).

Statistical heterogeneity was tested using $\chi^2$and I^2 tests. If heterogeneity was high (I > 50%), the random effects model was performed; otherwise, the fixed-effects model was considered appropriate.

Funnel plots were produced to investigate the possibility of publication bias.

3. Results

3.1. Identification and characteristics of studies

Of 51 citations identified from electronic databases and by hand searching, 21 RCTs matched the predefined inclusion criteria [6,18–37]. Fig. 1 summarized the process of identifying eligible clinical trials. Characteristics of studies were showed in Table 1. Thirteen studies published between 2003 and 2014 compared thyroidectomy using HS and CH whilst 8 studies from 2011 to 2014 compared HF versus CH. Patients enrolled by the studies were 1458 for RCTs regarding HS and 1677 for RCTs about HF. The largest study was based on 778 patients and 2 studies were based on 19 and 34 patients.

Concerning evaluation of outcomes, only operative time and transient hypocalcemia were considered by the most of studies (n = 21).

Inspection of funnel plots revealed slight asymmetry, which could be an indicator of publication bias. Results about quality assessment were showed in Table 2.

3.2. Harmonic Scalpel (HS) versus Conventional Hemostasis (CH) Figs. 2–10

The mean reduction for HS in **operating time** was 25.49 min (95% CI −32.43 to −18.55), resulting from all studies estimates. **Length of hospital stay** after HS was reduced by a mean difference of 0.17 days (95% CI −0.54 to 0.20) but the difference was statistically not significant. The **intraoperative blood loss** was reported in 6 studies with mean reduction of 30.49 mL (95% CI −53.01 to −7.97) for HS.

Meta-analysis of 6 studies showed that the **postoperative drainage volume** in the HS group was significantly lower compared with CH group with an MD of 12.90 mL (95% CI −22.83 to −2.98).

With regard to postoperative complications, 13 studies reported **transient hypocalcemia** in 142 patients undergoing TT with HS and 137 undergoing TT with CH: ORs were slightly lower in HS group than CH one (ORs 0.76; 95% CI 0.46 to 1.27) but the difference was statistically not significant. After HS TT with 22 patients experienced **transient postoperative RLN palsy** and no significant difference was found compared with CH (ORs 1.27; 95% CI 0.68 to 2.39). Only 3 studies reported permanent postoperative complications.

Wound complications (infection and seroma) was reported in 5 studies with 336 patients for HS and 341 participants for control intervention: HS was associated with higher complications compared with CH but without statistical significance (ORs 1.32; 95% CI 0.59 to 2.96).

Four studies reported data regarding **postoperative pain** assessed according to patients responses to a Visual Analog Scale (VAS). A significant reduced risk of postoperative pain in the first 24 h was found among patients undergoing TT with HS compared with the CH groups (MD −0.87; 95% CI = −1.27 to −0.46).

3.3. Harmonic Focus (HF) versus Conventional Hemostasis (CH) Figs. 11–16

Quantitative meta-analysis regarding all 8 studies revealed a significantly less **operative time** in the HF group when compared with the CH group with a mean difference of 25.99 minutes (95% CI −34.56 to −17.41). Similarly, **length of hospital stay** after HF was reduced by a mean difference of 0.57 days (95% CI −0.97 to −0.17). Meta-analysis of 4 studies showed that the amount of **postoperative drainage volume** in the HF group was lower compared with CH group with an MD of −7.04 (95%CI −18.00 to 3.93] but the

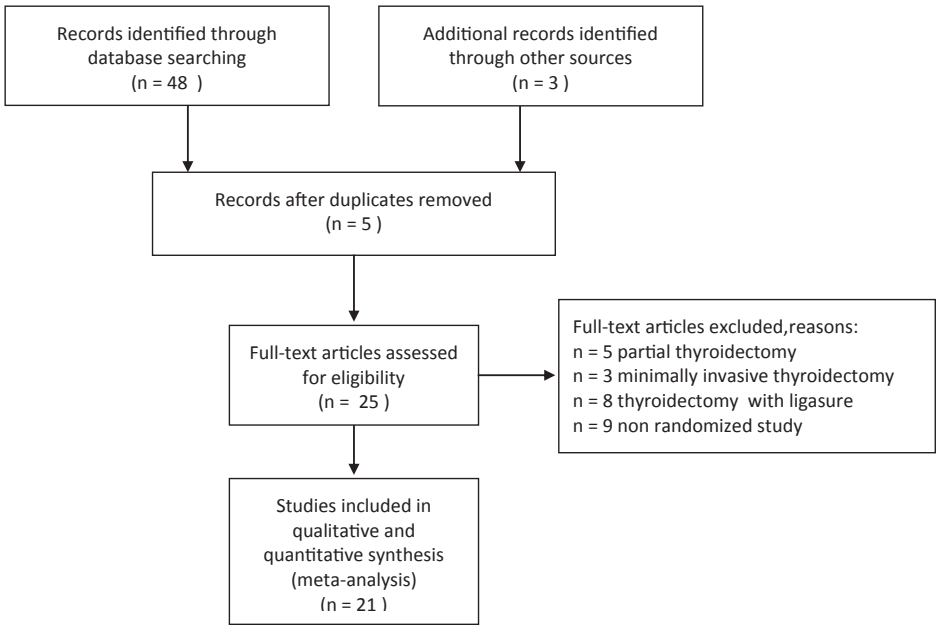

Fig. 1. Flow diagram.

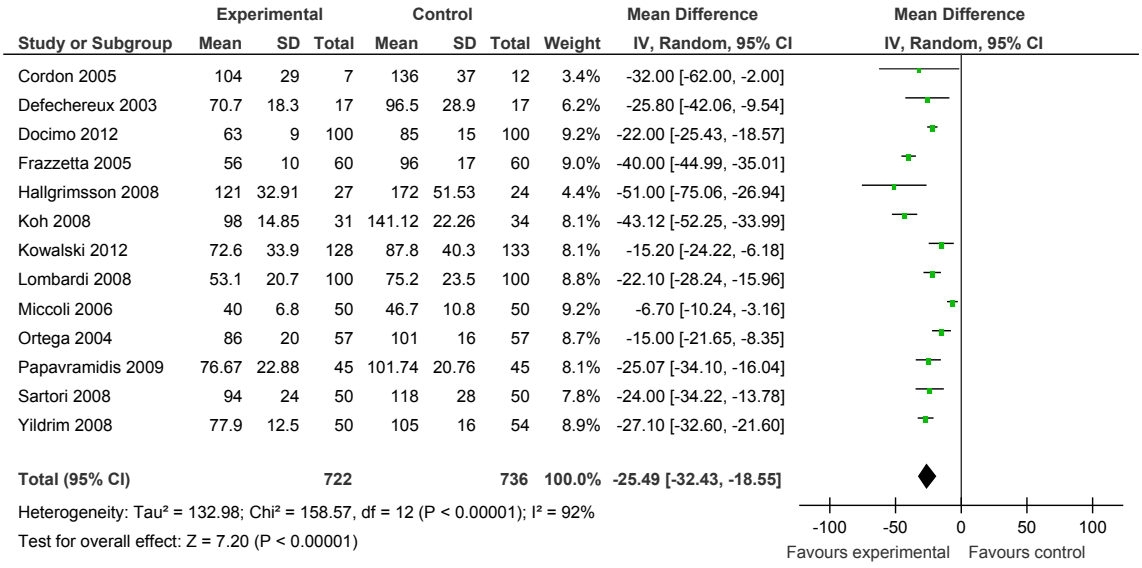

Fig. 2. Meta-analysis of operative time with *Harmonic Scalpel* versus Conventional Hemostasis.

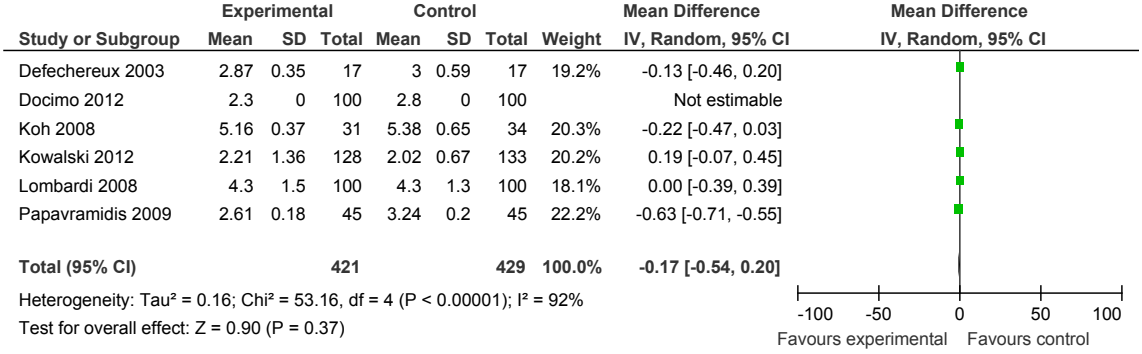

Fig. 3. Meta-analysis of lenght of hospital stay with *Harmonic Scalpel* versus Conventional Hemostasis.

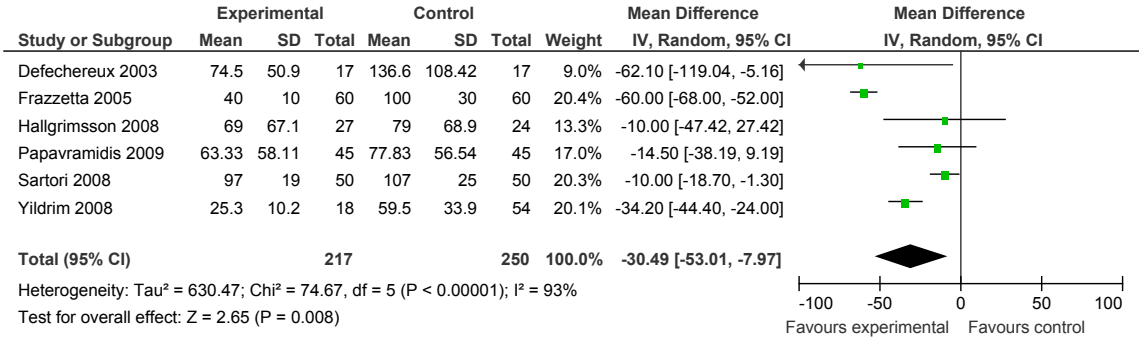

Fig. 4. Meta-analysis of intraoperative blood loss with *Harmonic Scalpel* versus Conventional Hemostasis.

difference was statistically not significant.

A significant reduced risk of **transient hypocalcemia** resulted by using HF compared with CH with an ORs of 0.56 (95% CI 0.39 to 0.81), whilst no significant difference was found compared HF with CH with regard to **postoperative RLN palsy** (OR = 0.42; 95% CI 0,13 to 1,38).

Postoperative pain was reported in 2 studies showing a significant reduction in HF group compared with CH one with an MD of −1.33 (95% CI −2.49 to −0.17).

4. Discussion

This meta-analysis is the first specifically designed and powered to detect a difference in operative and peri-operative complications and to compare the use of HF with CH.

The HF is an evolution of HS that allows the surgeon to easily dissect as well as coagulate and cut vessels in narrow spaces. These hand-activated shears were completely redesigned but kept the same effective ultrasonic coagulation mechanism and reproduced

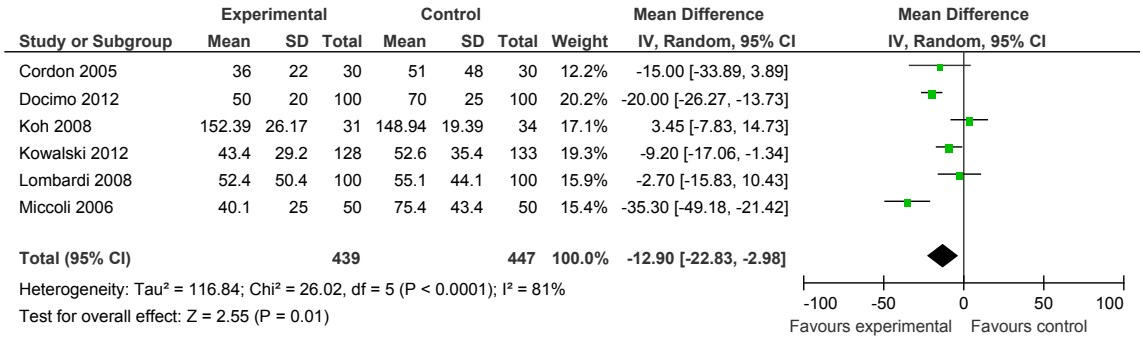

Fig. 5. Meta-analysis of postoperative drainage with *Harmonic Scalpel* versus Conventional Hemostasis.

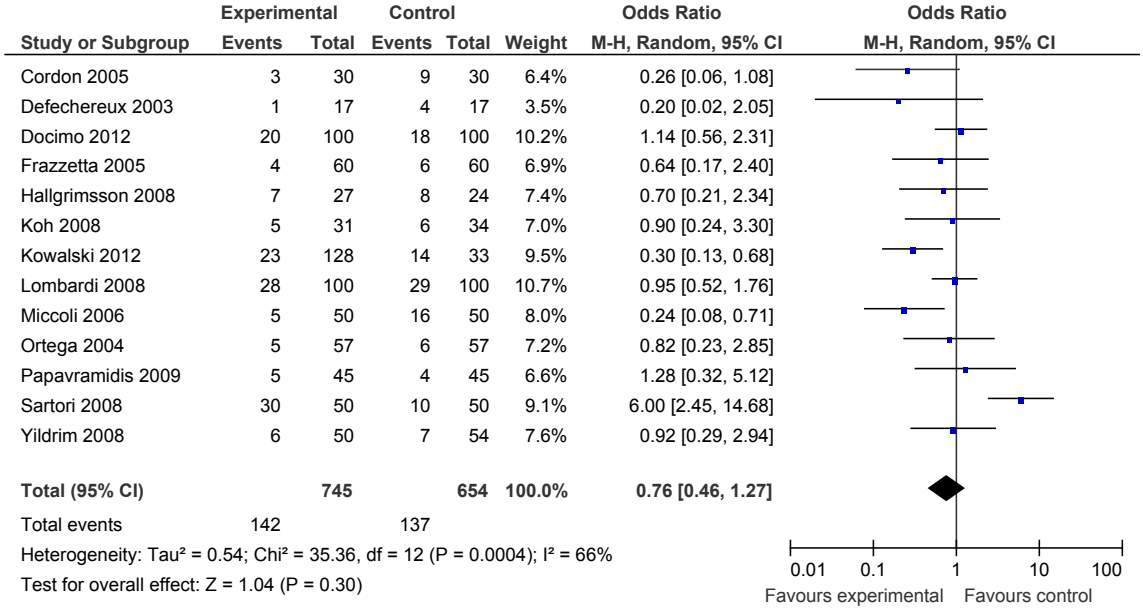

Fig. 6. Meta-analysis of transient postoperative hypocalcemia with *Harmonic Scalpel* versus Conventional Hemostasis.

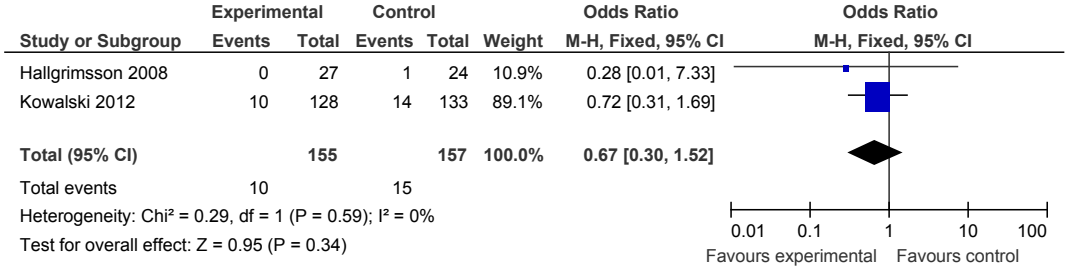

Fig. 7. Meta-analysis of permanent postoperative hypocalcemia with *Harmonic Scalpel* versus Conventional Hemostasis.

the familiar "Kelly clamp" in shape, with very thin and delicate tips.

Previous meta-analysis have shown conflicting results regarding post-surgical outcomes such as hypocalcemia and RLN palsy, due to limited number of cases reported in single studies. Moreover in some trials there was any differentiation between Total and Subtotal Thyroidectomies.

This meta-analysis takes into account only the results on TT.

A shorter operative duration was noted for HS and HF TT in accord to previous meta-analysis [1,11–13,16]. Significantly less bleeding occurred during HS TT. The reduced operative time associated with HS is likely related to better intraoperative hemostatic control.

In the HS group there was a significant reduction in postoperative drainage volume that can be also related to the reduction in blood loss. These advantages were evidenced by previous systematic reviews and meta-analysis.

In the Ecker [12] meta-analysis the data about drainage volume were not significant. In the meta analysis of Melck [13] were available operative time, transient hypocalcemia and RLN palsy. Transient hypocalcemia observed after TT is believed to be related

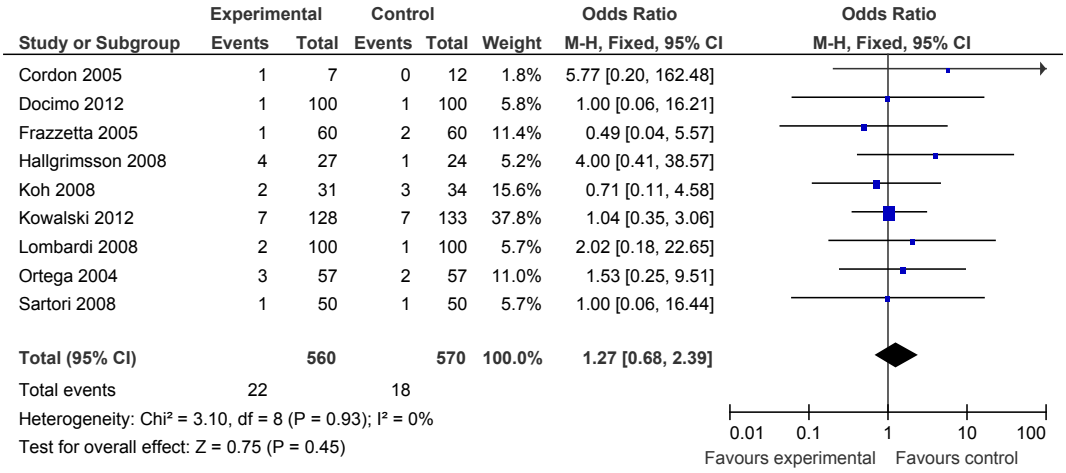

Fig. 8. Meta-analysis of transient postoperative RLN dysfunction with *Harmonic Scalpel* versus Conventional Hemostasis.

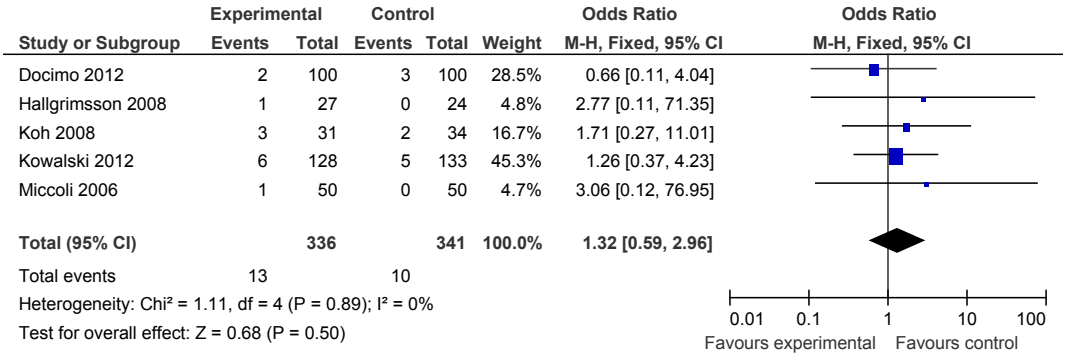

Fig. 9. Meta-analysis of wound complications (infection and seroma) with *Harmonic Scalpel* versus Conventional Hemostasis.

to traumatization of the parathyroid glands, which are anatomically intimately related to the thyroid gland and share its blood supply. We speculate that use of the HS may facilitate dissection of the parathyroid glands in a plane farther away from the parathyroid gland capsule, thus reducing the chance of damaging their blood supply, directly or indirectly, with either mechanical forces or electrical currents. Thus, this finding of reduced transient postoperative hypocalcemia with HS utilization ($p = 0.002$ in HF group) does seem biologically plausible and highlights an important rationale for conducting the meta-analysis.

The incidence of postoperative hypocalcemia was similar in 2 groups in the meta-analysis of Cirocchi [11]. There was a reduction in transient hypocalcemia in the meta-analysis of Melck [13] and in permanent hypocalcemia in the meta-analysis of Garas in HS group [16].

It is difficult to draw any conclusions regarding permanent hypoparathyroidism and HS utilization. Permanent hypoparathyroidism is a rare complication of TT, and there were only 3 trials included studying this topic, 2 of which in favors of the HS group. The data of permanent hypocalcemia are available only in the reviews of Cirocchi [11] and Garas [16].

The complication of RLN palsy after TT is also an extremely uncommon occurrence. HS has been shown to cause less collateral thermal injury than conventional electrocautery, we would expect to see less Recurrent Laryngeal Nerve Dysfunction (RLND) in the HS group. This meta-analysis showed no significant differences in the RLND. In the previous meta-analysis data about permanent RLN palsy are available only in the analysis of Garas [16] with a higer risk

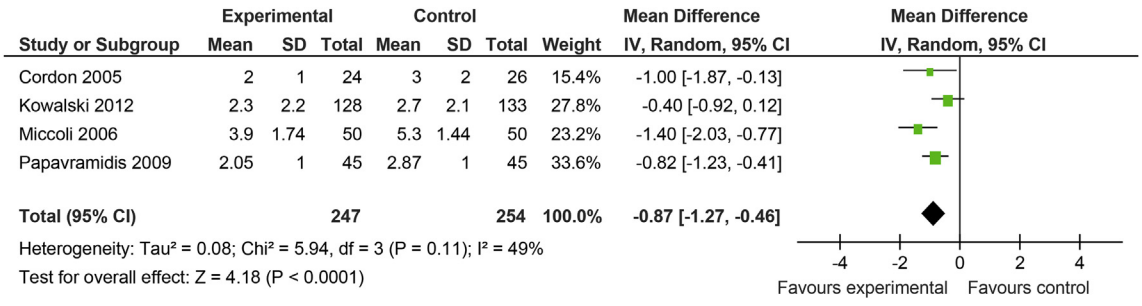

Fig. 10. Meta-analysis of postoperative pain (24 h) with *Harmonic Scalpel* versus Conventional Hemostasis.

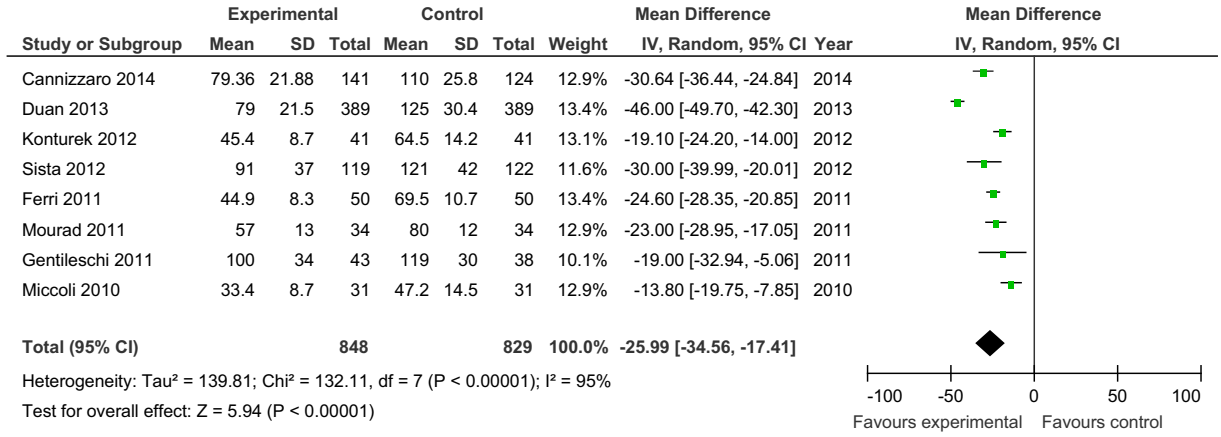

Fig. 11. Meta-analysis of operative time with *Harmonic Focus* versus Conventional Hemostasis.

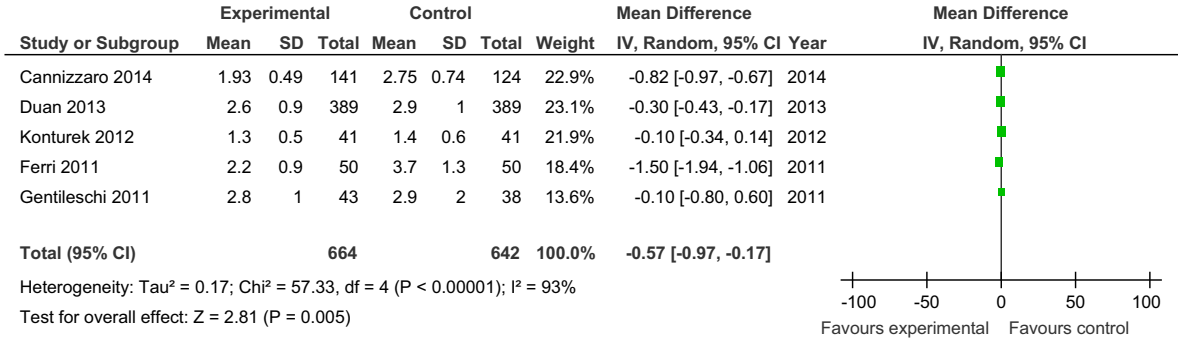

Fig. 12. Meta-analysis of lenght of hospital stay with *Harmonic Focus* versus Conventional Hemostasis.

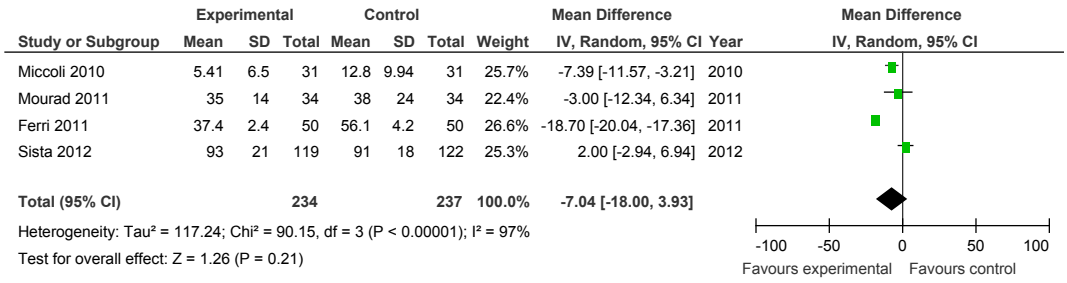

Fig. 13. Meta-analysis of postoperative drainage with *Harmonic Focus* versus Conventional Hemostasis.

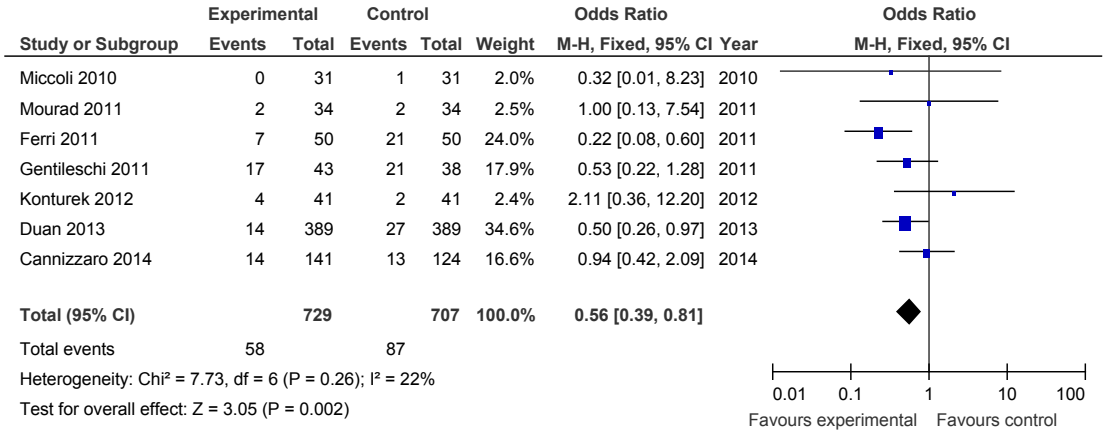

Fig. 14. Meta-analysis of transient postoperative hypocalcemia with *Harmonic Focus* versus Conventional Hemostasis.

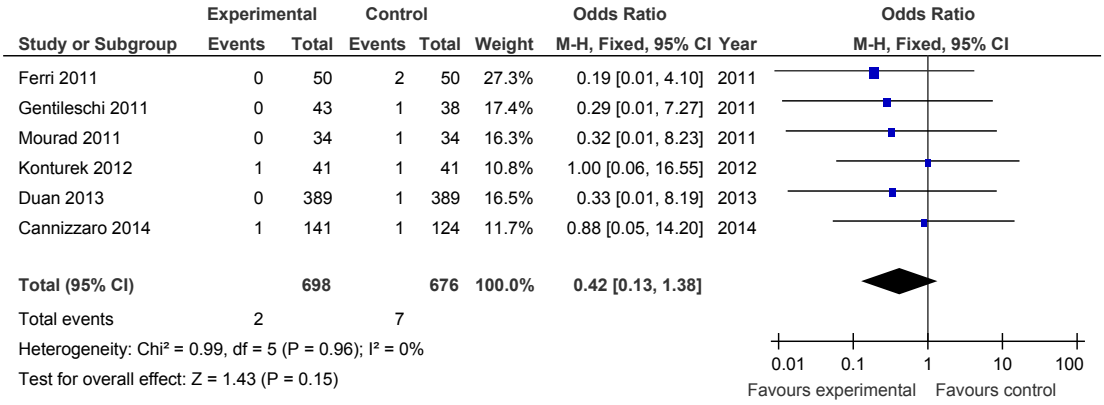

Fig. 15. Meta-analysis of transient postoperative RLN dysfunction with *Harmonic Focus* versus *Conventional Hemostasis*.

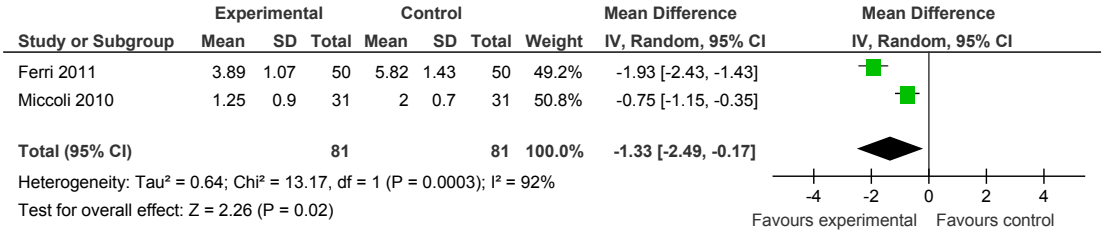

Fig. 16. Meta-analysis of postoperative pain with *Harmonic Focus* versus Conventional Hemostasis.

in HS group.

It is of fundamental importance to properly use this device in the vicinity of extremely delicate structures such as the RLN [39]. Though Carlander et al. [40] in a recent study showed that HS cause less trauma to adjacent nerve fibers than bipolar electrosurgery, also HS may cause nerve injury at close distances. The potential electrical energy dispersion may cause damage to the surrounding tissue. The temperature of peripheral tissue is dependent upon the distance to the HS blade and the length of time the HS is used. The closer to the activated HS tip and the longer the duration of HS use, the higher the tissue temperature. The tissue will be injured if the temperature increases to a harmful level, so a safety margin to use the HS around the RLN is required.

Jiang et al. [41] in their experimental study showed that when activating the HS within 3 s, lateral injury involved a tissue thickness of <2 mm. To activate the HS at a power level of 3 at a distance ≥2 mm away from the RLN for ≤3 s is therefore safe. Nevertheless, if the time is prolonged to 5 s, the thickness of injured lateral tissue will be > 2 mm. If used around the RLN at a power level of 3, the activated HS tip should be ≥ 2 mm from the nerve and the duration

Table 1
Studies characteristics.

Study	Ref.	Country	Intervention (A)	Control (B)	N. patients	
					A	B
Cannizzaro 2014	[6]	Italy	HF	CH	141	124
Duan 2013	[18]	China	HF	CH	389	389
Sista 2012	[19]	Italy	HF	CH	119	122
Docimo 2012	[20]	Italy	HS	CH	100	100
Konturek 2012	[21]	Poland	HF	CH	41	41
Gentileschi 2011	[22]	Italy	HF	CH	43	38
Mourad 2011	[23]	Belgium	HF	CH	34	34
Ferri 2011	[24]	Italy	HF	CH	50	50
Kowaslki 2011	[25]	Brazil	HS	CH	128	133
Miccoli 2010	[26]	Italy	HF	CH	31	31
Papavramidis 2009	[27]	Greece	HS	CH	45	45
Lombardi 2008	[28]	Italy	HS	CH	100	100
Sartori 2008	[29]	Italy	HS	CH	50	50
Yildirim 2008	[30]	Turkey	HS	CH	50	54
Koh 2008	[31]	Korea	HS	CH	31	34
Hallgrimsson 2008	[32]	Sweden	HS	CH	27	24
Miccoli 2006	[33]	Italy	HS	CH	50	50
Frazzetta 2005	[34]	Italy	HS	CH	60	60
Cordon 2005	[35]	Mexico	HS	CH	7	12
Ortega 2004	[36]	Spain	HS	CH	57	57
Defechereux 2003	[37]	Belgium	HS	CH	17	17

HS = *Harmonic Scalpel*, HF = *Harmonic Focus*, CH = Conventional Hemostasis.

Table 2
Risk of bias measurement of RCTs studies included in meta-analysis.

	Randomization	Allocation Concealment	Blinding of participants and personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cannizzaro 2014	+	+	?	?	+	+	+
Duan 2013	+	?	+	?	+	+	+
Sista 2012	+	?	?	?	?	+	+
Gentileschi 2011	+	?	?	?	?	+	+
Docimo 2012	+	?	+	?	+	+	?
Konturek 2012	+	?	?	?	+	+	?
Mourad 2011	+	?	+	?	+	+	?
Ferri 2011	+	?	?	?	?	+	?
Kowaslki 2011	+	+	?	?	+	+	?
Miccoli 2010	+	?	+	?	?	+	?
Papavramidis 2009	+	?	?	?	+	+	?
Lombardi 2008	+	?	+	?	+	+	+
Sartori 2008	+	?	+	?	+	+	?
Yildirim 2008	+	?	?	?	+	+	?
Koh 2008	+	+	+	?	+	+	?
Hallgrimsson 2008	+	?	?	?	+	+	?
Miccoli 2006	+	?	?	?	+	+	+
Frazzetta 2005	+	?	?	?	?	+	?
Cordon 2005	+	?	?	+	?	+	?
Ortega 2004	+	?	?	?	?	+	?
Defechereux 2003	+	?	?	?	?	+	?

Key: (+) = Low risk of bias; (?) = Unclear risk of bias; (−) = High risk of bias.

of incision should be $\leq$ 3 seconds.

Conventional vessel knotting ligation still remains important when the handpiece of HS is very close to the RLNs. Permanent nerve injury is a rare complication of TT, and the only one trial included in this analysis was in favor of the HS group ($p = 0.53$).

In the meta-analysis of Ecker [12] HS decreased the complications rate but single complications are not differentiated.

Manipulating the tip of the harmonic scalpel requires by far less operative space as compared with the operative space required for exact bimanual placement of ligatures. In one hand, this allows better cosmetic results, in other hands the temperature (50–100°), though less than electrocautery, of the activated tip of the HS can determine thermal injury to adjacent tissue.

In this analysis HS was associated with higher wound complications without significant differences ($p = 0.32$).

Few studies compared postoperative pain. We analyzed postoperative pain and found that HS use reduced pain in accord to the reviews of Cirocchi [11] and Garas [16]. Some of the studies that reported less pain intensity with HS also found less analgesic use. This pain relief may be related to reduction in operative time with a shorter time of neck hyperextension, brachial plexus stretching and tissue traumatism.

Patients who underwent HS TT had earlier pain-free return to normal activity and to work. Theorically this finding may influence the length of hospital stay and costs, but in this meta-analysis there were no significant differences. These data may be related to a short hospital stay in the two groups and a small number of trials with length of hospital stay available data. The reduction in postoperative pain, in drainage volume in HS group and in hypocalcemia in HF group represent the really important factors that could decrease postoperative hospital stay as is showed in the meta-analysis of Ecker [12] and Garas [16].

This meta-analysis has some limitations. It was observed a significant heterogeneity across studies for several of pooled analyses. Since clinical and methodological diversity always occur in meta-analysis, a statistical heterogeneity is inevitable [38] and when studies have small sample size or a few in number the chi-squared test has low power. On the other hand, there are several strengths. First. the evidence is based on the meta-analysis of RCTs, which is the highest level of evidence (Level I). Second, a rigorous studies selection with restricted inclusion criteria and a meticulous studies quality assessment were carried out. Furthermore, visual inspection of various forest plots suggests that there is a quite consistency with reference to magnitude and direction of effects.

5. Conclusion

The results of this meta-analysis showed that HS TT can be a safe, useful, and fast alternative to CH TT. The main advantage of this device is that it simplifies the procedure and eliminates the need for clips and suture ligations while also achieving efficient hemostasis. It significantly reduced operative time, postoperative pain, blood loss and hypocalcemia in HF group, compared with the CH. In sutureless open thyroid surgery and endoscopic thyroid surgery, the operating space is limited because of the anatomical features of the neck. Maintaining a bloodless operating space is therefore essential.

Obviously, since time spent in the operating room is expensive, this would counterbalance the cost of the HS handpiece and eventually result in a overall cost saving. Nonetheless, the shorter operative time implies the possibility to treat more patients in the same operative sessions. Unfortunately, the RCTs included in this meta-analysis reported limited cost data.

The HS is the device of choice for TT, though inappropriate use of this device may harm vital peripheral structures. In patients undergoing thyroidectomy, HS is a reliable and safe tool. Comparing with CH techniques, its use reduces operative times, postoperative pain, drainage volume and transient hypocalcemia.

Future prospective, randomized trials of larger patient cohorts with more detailed data of postoperative complications, cost-effectiveness, postoperative pain, cosmetic results, randomization procedures, intention-to-treat analyses, and blinding of outcome assessors are needed to draw more meaningful conclusions.

Conflicts of interests

All authors have no conflicts of interests to disclose.

Role of funding source

No authors received any funding.

Ethical approval

Nil required.

Author contributions

Revelli L. – study design, data collections, data analysis, writing, final corrections.

Damiani G. – study design, data collections, data analysis, writing, final corrections.

Bianchi C.B.N.A. – study design, data collections, data analysis, writing.

Vanella S.– study design, data collections, data analysis, writing.

Ricciardi W.– study design, final corrections.

Raffaelli M.– study design, final corrections.

Lombardi C.P.– study design, final corrections.

All authors approve final version of paper for submission.

Acknowledgments

Nil.

References

[1] P. Contin, K. Gooßen, K. Grummich, K. Jensen, H. Schmitz-Winnenthal, M.W. Büchler, M.K. Diener, ENERgized vessel Seal. Syst. versus CONventional hemostasis Tech. thyroid Surg. – ENERCON Syst. Rev. Netw. meta-analysis, vol. 398, 2013, pp. 1039–1056, http://dx.doi.org/10.1007/s00423-013-1137-7.

[2] N. Bhattacharyya, M.P. Fried, Assessment of the morbidity and complications of total thyroidectomy, Arch. Otolaryngol. Head Neck 128 (2002) 389–392, http://dx.doi.org/10.1001/archotol.128.4.389.

[3] www.agenas.it.

[4] A. Khafagy, I. Abdelnaby, Total thyroidectomy: ligasure versus clamp & knot technique for intraoperative hemostasis, Egypt. J. Ear Nose Throat Allied Sci. 14 (2013) 59–65.

[5] L. Rosato, N. Avenia, P. Bernante, M. De Palma, G. Gulino, P.G. Nasi, M.R. Pelizzo, L. Pezzullo, Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years, World J. Surg. 28 (2004) 271–276, http://dx.doi.org/10.1007/s00268-003-6903-1.

[6] M.A. Cannizzaro, S.L. Bianco, L. Borzì, A. Cavallaro, A. Buffone, The use of Focus Harmonic scalpel compared to conventional haemostasis (knot and tie ligation) for thyroid surgery: a prospective randomized study, Springerplus 28 (2014), http://dx.doi.org/10.1186/2193-1801-3-639, 3:639.

[7] S. Alam Hannan, The magnificent seven: a history of modern thyroid surgery, IJS 4 (2006) 187–191, http://dx.doi.org/10.1016/j.ijsu.2006.03.002.

[8] W.S. Halsted, The operative story of goitre. The author's operation, Johns Hopkins Hosp. Rep. 19 (1920) 71–257.

[9] R. Udelsman, H. Chen, The current management of thyroid cancer, Adv. Surg. 33 (1999) 1–27.

[10] H.Y. Kwak, B.J. Chae, Y.G. Park, S.H. Kim, E.Y. Chang, E.J. Kim, B.J. Song, S.S. Jung, J.S. Bae, Comparison of surgical outcomes between papillary thyroid cancer patients treated with the harmonic ACE scalpel and LigaSure precise instrument during conventional thyroidectomy: a single-blind prospective randomized controlled trial, J. Surg. Res. 187 (2014) 484–489, http://dx.doi.org/10.1016/j.jss.2013.11.1093.

[11] R. Cirocchi, F. D'Ajello, S. Trastulli, A. Santoro, G. Di Rocco, D. Vendettuoli, F. Rondelli, D. Giannotti, A. Sanguinetti, L. Minelli, A. Redler, A. Basoli, N. Avenia, Meta-analysis of thyroidectomy with ultrasonic dissector versus conventional clamp and tie, World J. Surg. Oncol. 23 (2010) 8–112.

[12] T. Ecker, A.L. Carvalho, J.H. Choe, G. Walosek, K.J. Preuss, Hemostasis in thyroid surgery: harmonic scalpel versus other techniques: a meta-analysis, Otolaryngol. Head Neck Surg. J. 143 (2010) 17–25, http://dx.doi.org/10.1016/j.otohns.2010.03.018.

[13] A.L. Melck, S.M. Wiseman, Harmonic scalpel compared to conventional hemostasis in thyroid surgery: a meta-analysis of randomized clinical trials, Int. J. Surg. Oncol. 2010 (2010) 306079, http://dx.doi.org/10.1155/2010/396079. ID 396079.

[14] C.P. Lombardi, R. Bracaglia, L. Revelli, C. Insalaco, F. Pennestrì, R. Bellantone, M. Raffaelli, Aesthetic result of thyroidectomy: evaluation of different kinds of skin suture, Ann. Ital. Chir. 82 (2011) 449–455 discussion 455-6.

[15] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, The PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (6) (2009) e1000097, http://dx.doi.org/10.1371/journal.pmed1000097.

[16] G. Garas, K. Okabayashi, H. Ashrafian, K. Shetty, F. Palazzo, N. Tolley, A. Darzi, T. Athanasiou, E. Zacharakis, Which hemostatic device in thyroid surgery? A Network meta-analysis of surgical Technologies, Thyroid (2013) 1138–1150, http://dx.doi.org/10.1089/thy.2012.0588. September 23.

[17] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, The Cochrane Collaboration's tool for assessing risk of bias in randomized trials, BMJ 343 (2011), http://dx.doi.org/10.1136/bmj.d5928 d5928.

[18] Y.F. Duan, W. Xue, F. Zhu, D.L. Sun, FOCUS harmonic scalpel compared to conventional hemostasis in open total thyroidectomy – a prospective randomized study, J. Otolaryngol. Head Neck Surg. 20 (2013) 42–62, http://dx.doi.org/10.1186/1916-0216-42-62.

[19] F. Sista, M. Schietroma, C. Ruscitti, G. De Santis, F. De Vita, F. Carlei, G. Amicucci, New ultrasonic dissector versus conventional hemostasis in thyroid surgery: a randomized prospective study, J. Laparoendosc. Adv. Surg. Tech. A 22 (2012) 220–224, http://dx.doi.org/10.1089/lap.2011.0266.

[20] Docimo G., R. Ruggiero, A. Gubitosi, G. Casalino, A. Bosco, S. Gili, G. Conzo, L. Docimo, Ultrasound scalpel in thyroidectomy. Prospective randomized study, Ann. Ital. Chir. 83 (2012) 491–496.

[21] Konturek A., M. Barczyński, M. Stopa, W. Nowak, Total thyroidectomy for nontoxic multinodular goiter with versus without the use of harmonic FOCUS dissecting shears – a prospective randomized study, Wideochir Inne Tech. Malo Inwazyjne 7 (2012) 268–274, http://dx.doi.org/10.5114/wiitm.2011.30675.

[22] Gentileschi P., S. D'Ugo, E. Iaculli, A.L. Gaspari, Harmonic Focus versus "knot tying" during total thyroidectomy: a randomized trial, Updat. Surg. 63 (2011) 277–281, http://dx.doi.org/10.1007/s13304-011-0099-y.

[23] Mourad M., F. Rulli, A. Robert, J.L. Scholtes, M. De Meyer, L. De Pauw, Randomized clinical trial on Harmonic Focus shears versus clamp-and-tie technique for total thyroidectomy, Am. J. Surg. 202 (2011) 168–174, http://dx.doi.org/10.1016/j.amjsurg.2010.07.047.

[24] E. Ferri, E. Armato, G. Spinato, R. Spinato, Focus harmonic scalpel compared to conventional haemostasis in open total thyroidectomy: a prospective randomized trial, Int. J. Otolaryngol. (2011) 357195, http://dx.doi.org/10.1155/2011/357195.

[25] Kowalski L.P., et al., Total thyroidectomy with ultrasonic scalpel: a multicenter, randomized controlled trial, Head Neck 34 (2012) 805–812, http://dx.doi.org/10.1002/hed.21815.

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

[27] T.S. Papavramidis, K. Sapalidis, N. Michalopoulos, K. Triantafillopoulou, G. Gkoutzamanis, I. Kesisoglou, S.T. Papavramidis, Ultracision harmonic scalpel versus clamp-and-tie total thyroidectomy: a clinical trial, Head Neck 32 (2010) 723–727.

[28] C.P. Lombardi, M. Raffaelli, A. Cicchetti, M. Marchetti, C. De Crea, R. Di Bidino, L. Oragano, R. Bellantone, The use of "harmonic scalpel" versus "knot tying" for conventional "open" thyroidectomy: results of a prospective randomized study, Langenbecks Arch. Surg. 393 (2008) 627–631, http://dx.doi.org/10.1007/s00423-008-0380-9.

[29] P.V. Sartori, S. De Fina, G. Colombo, et al., Ligasure versus Ultracision(R) in thyroid surgery: a prospective randomized study, Langenbecks Arch. Surg. 393 (2008) 655–658, http://dx.doi.org/10.1007/s00423-008-0386-3.

[30] O. Yildirim, T. Umit, M. Ebru, et al., Ultrasonic harmonic scalpel in total thyroidectomies, Adv. Ther. 25 (2008) 260–265, http://dx.doi.org/10.1007/s12325-008-0024-z.

[31] Y.W. Koh, J.H. Park, S.W. Lee, E.C. Choi, The harmonic scalpel technique without supplementary ligation in total thyroidectomy with central neck dissection: a prospective randomized study, Ann. Surg. 247 (2008) 945–949, http://dx.doi.org/10.1097/SLA.0b013e31816bcd61.

[32] P. Hallgrimsson, L. Lovén, J. Westerdahl, A. Bergenfelz, Use of the harmonic scalpel versus conventional haemostatic techniques in patients with Grave disease undergoing total thyroidectomy: a prospective ran- domised controlled trial, Langenbecks Arch. Surg. 393 (2008) 675–680, http://dx.doi.org/10.1007/s00423-008-0361-z.

[33] P. Miccoli, P. Berti, G. Dionigi, J. D'Agostino, C. Orlandini, G. Donatini, Randomized controlled trial of harmonic scalpel use during thyroidectomy, Arch. Otolaryngol. Head Neck Surg. 132 (2006) 1069–1073.

[34] Frazzetta M., G. Furgiuele, D. Raimondo, A. Sammartano, E. Mannino, G. De Simone, G. Vetri, S. Bonventre, G. Di Gesú, Ultrasonic dissector for total thyroidectomy: results of prospective randomized study, G. Chir. 26 (2005) 295–301.

[35] C. Cordón, R. Fajardo, J. Ramírez, M.F. Herrera, A randomized, prospective, parallel group study comparing the harmonic scalpel to electrocautery in thyroidectomy, Surgery 137 (2005) 337–341.

[36] J. Ortega, C. Sala, B. Flor, S. Lledo, Efficacy and cost-effectiveness of the ultracision harmonic scalpel in thyroid surgery: an analysis of 200 cases in a randomized trial, J. Laparoendosc. Adv. Surg. Tech. A 14 (2004) 9–12.

[37] T. Defechereux, F. Rinken, S. Maweja, E. Hamoir, M. Meurisse, Evaluation of the ultrasonic dissector in thyroid surgery. A prospective randomized study, Acta Chir. Belg. 103 (2003) 274–277.

[38] J.P.T. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (2003) 557–560.

[39] G. Ardito, L. Revelli, L. D'Alatri, V. Lerro, M.L. Guidi, F. Ardito, Revisited anatomy of the recurrent laryngeal nerves, Am. J. Surg. 187 (2004) 249–253.
[40] J. Carlander, C. Koch, L. Brudin, C. Nordborg, O. Gimm, K. Johansson, Heat production, nerve function, and morphology following nerve close dissection with surgical instruments, World J. Surg. 36 (2012) 1361–1367, http://dx.doi.org/10.1007/s00268-012-1471-x.
[41] Y. Jiang, B. Gao, X. Zhang, J. Zhao, J. Chen, S. Zhang, D. Luo, Prevention and treatment of recurrent laryngeal nerve injury in thyroid surgery, Int. J. Clin. Exp. Med. 7 (2014) 101–107.