

Effectiveness of harmonic scalpel in patients submitted to total thyroidectomy: systematic review with meta-analysis

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SUMMARY

OBJECTIVE: The objective of this study was to evaluate the efficacy and safety of the harmonic scalpel compared to the conventional technique in patients submitted to total thyroidectomy.

METHOD: This is a systematic review with inclusion of randomized controlled trials (RCTs) that compared both techniques. An electronic search was carried out in the Medline and Lilacs databases until June 2017. The outcomes analysed were operation time, intraoperative bleeding, surgical morbidity, and costs.

RESULTS: Data from 31 primary studies were included. The use of the harmonic scalpel correlates to a shorter operation time ($p < 0.001$) and a lower volume of intraoperative bleeding ($p < 0.001$). There were no differences in the risk of transient ($p = 0.53$) and permanent ($p = 0.70$) hypocalcaemia, transient ($p = 0.61$) and permanent ($p = 0.50$) dysfunctions of the inferior laryngeal nerve and hematoma ($p = 0.14$).

CONCLUSION: Total thyroidectomy using a harmonic scalpel is effective and safe compared to the conventional technique.

KEYWORDS: Thyroidectomy. Haemostasis, surgical/methods. Ultrasonic surgical procedures. Review.

INTRODUCTION

Thyroidectomy is the most performed operation by head and neck surgeons and is considered a safe procedure, with virtually no mortality. Due to the rich vascularization of the thyroid gland, its resection is based on haemostasis both to prevent bleeding that can become fatal and to keep the surgical field clean and facilitate the visualization of noble structures such as the laryngeal nerves and the parathyroid glands^{1,2}.

In order to provide bleeding control, haemostatic devices have been developed to try to make the operation even safer. One of the most studied is the

harmonic (or ultrasonic) scalpel, which consists of the use of high frequency wave that is converted into mechanical energy and simultaneously promotes the sealing and sectioning of blood vessels, as well as fibrous and muscular tissue structures, providing adequate haemostasis at temperatures lower than those of mono- and bipolar scalpels^{3,4}.

The objective of this study was to perform a systematic review to evaluate the efficacy and safety of the harmonic scalpel compared to the conventional technique in patients submitted to total thyroidectomy.

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METHOD

Selection criteria

We selected all randomized and controlled clinical trials comparing the use of harmonic scalpel with the conventional ligature technique in patients submitted to total thyroidectomy. The studies were selected from the reading of the respective titles and abstracts. When it was not possible to identify whether the study would be included or not, the full text was requested for the detailed analysis.

Studies that included patients with thyroid gland disease, regardless of the nature of the diagnosis (benign or malignant), who underwent total thyroidectomy were included. Studies that included patients submitted to total thyroidectomy, associated with other concomitant procedures, and with a history of previous surgery and/or cervical irradiation were excluded.

The intervention group included patients who used the harmonic scalpel during the surgical procedure, while the control group underwent conventional ligation surgery. At first, there was no restriction on the description of the harmonic scalpel technology used.

The outcomes analysed were operating time, intraoperative bleeding volume, incidences of inferior laryngeal nerve injury (temporary and permanent), hypocalcaemia (temporary and permanent), and hematoma requiring surgical intervention and procedure costs.

SEARCH STRATEGY

The electronic databases Medline (via PubMed) and Lilacs were consulted for identification of the primary studies. These were closed in June 2017.

For the recovery of the primary articles, the search strategy (thyroidectomy OR thyroid surgery) AND (electrocoagulation OR ultrasonic surgical procedures OR ligation OR constriction OR surgical haemostasis OR suture techniques OR harmonic OR ultrasonic OR surgical instruments OR) was used.

In addition, the references of the selected studies and of published reviews were consulted through manual search to select articles that were not included in the electronic searches.

STATISTICAL ANALYSIS

The measures of effectiveness or damage expressed in absolute numbers were analysed through the relative risk difference adopting a 95% confidence

interval. For all statistically significant results, the numbers needed to treat (NNT) and numbers needed to harm (NNH) were calculated. The continuous data were analysed when the average and its standard deviation of the final measurements were presented. The weighted average difference between groups was used.

Inconsistencies between clinical trials were estimated by the chi-square test (χ^2) of heterogeneity and quantified using the I^2 test. Values above 50% were considered as high heterogeneity.

A sensitivity analysis was carried out regarding the methodological risk, which was established according to the Jadad criteria⁵.

RESULTS

Results of electronic searches

Electronic and manual searches resulted in a total of 2,137 studies. After reading the respective titles and abstracts, 2,099 studies that clearly did not fit the proposed theme were excluded. Thirty-eight studies potentially eligible for inclusion were selected for reading the full texts. After this step, seven studies were excluded, since four did not separately describe the results regarding total and partial thyroidectomy⁶⁻⁹, one was not a randomized clinical trial¹⁰, one was published in duplicate¹¹ (the most recent article was considered) and one included only 7% of the sample submitted to total thyroidectomy¹². Thus, the results of this review are based on data from 31 studies.

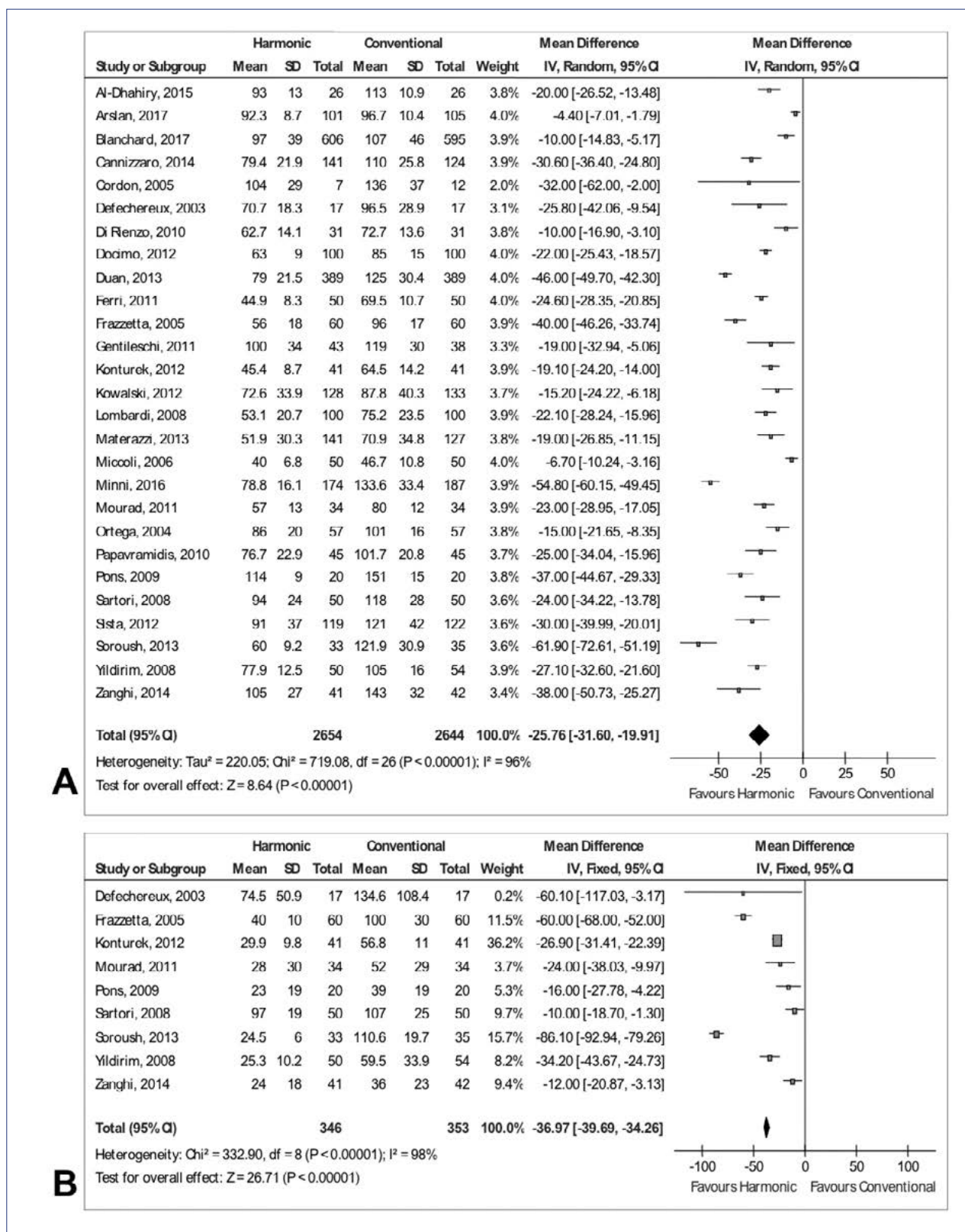
Assessment of methodological risk of primary studies

All primary studies were described as a randomized clinical trial. Of the 31 studies, only ten adequately described the randomization and allocation of patients^{14,16,22,24,28,30,33,34,42,43}. In 17 studies the method of randomization was not described^{15,17-20,25,26,27,29,31,32,35-39,41} and in another four it was considered inappropriate^{13,21,23,40}.

Since it is a surgical study, double blinding is very difficult to apply. Only one study was described as double-blind²⁵, while other nine^{18,20,23,29,34,35,37,42,43} applied blinding only in the patients. In the remaining 21 studies, there was no blinding.

Whenever present, loss of follow-up or protocol break were described, and accounted for less than 20% in all studies.

FIGURE 1. META-ANALYSIS ON (A) OPERATION TIME AND (B) INTRAOPERATIVE BLEEDING COMPARING THE HARMONIC SCALPEL WITH THE CONVENTIONAL TECHNIQUE.



Operation time

Twenty-seven primary studies evaluated the operation time of total thyroidectomy comparing the harmonic scalpel to the conventional technique. Two studies did not provide the standard deviations of the averages and were not included in the overall analysis of the result.

For the calculation of the meta-analysis the random effect method was used due to the high heterogeneity of the results ($I^2 = 96\%$). Patients submitted to total thyroidectomy with the aid of the harmonic scalpel showed a reduction of approximately 26 minutes in the operation time when compared to the conventional group (95% CI 19.91 to 31.60, $p < 0.001$, Figure 1A).

Volume of intraoperative bleeding

Ten primary studies evaluated the intraoperative bleeding volume of total thyroidectomy comparing the harmonic scalpel to the conventional technique. One study was excluded because it did not present the standard deviations of the averages²². All studies showed a statistically significant reduction in bleeding volume in the group submitted to thyroidectomy with the aid of a harmonic scalpel. The overall analysis results in a decrease of approximately 35 ml of bleeding (95% CI 16.31 to 54.35, $p < 0.001$, Figure 1B).

Incidence of postoperative complications

Hematoma requiring surgical revision was studied in 18 primary studies presenting an incidence of 0.83%, 13 cases (0.60%) in the harmonic scalpel group and 23 cases (1.06%) in the conventional group. There was no significant difference between the groups (95% CI -0.01 to 0.00, $p = 0.14$ and $I^2 = 0\%$).

The incidence of transient inferior laryngeal nerve dysfunction (24 studies) occurred in 200 patients, 104 cases (4.1%) in the harmonic scalpel group and 96 cases (3.9%) in the conventional group. There was no significant difference between the groups (95% CI -0.01 to 0.01, $p = 0.61$ and $I^2 = 0\%$, Figure 2A). In relation to permanent dysfunction (19 studies), there was also no significant difference between the groups (0.6% x 0.4%, 95% CI -0.00 to 0.01, $p = 0.50$ and $I^2 = 0\%$, Figure 2B).

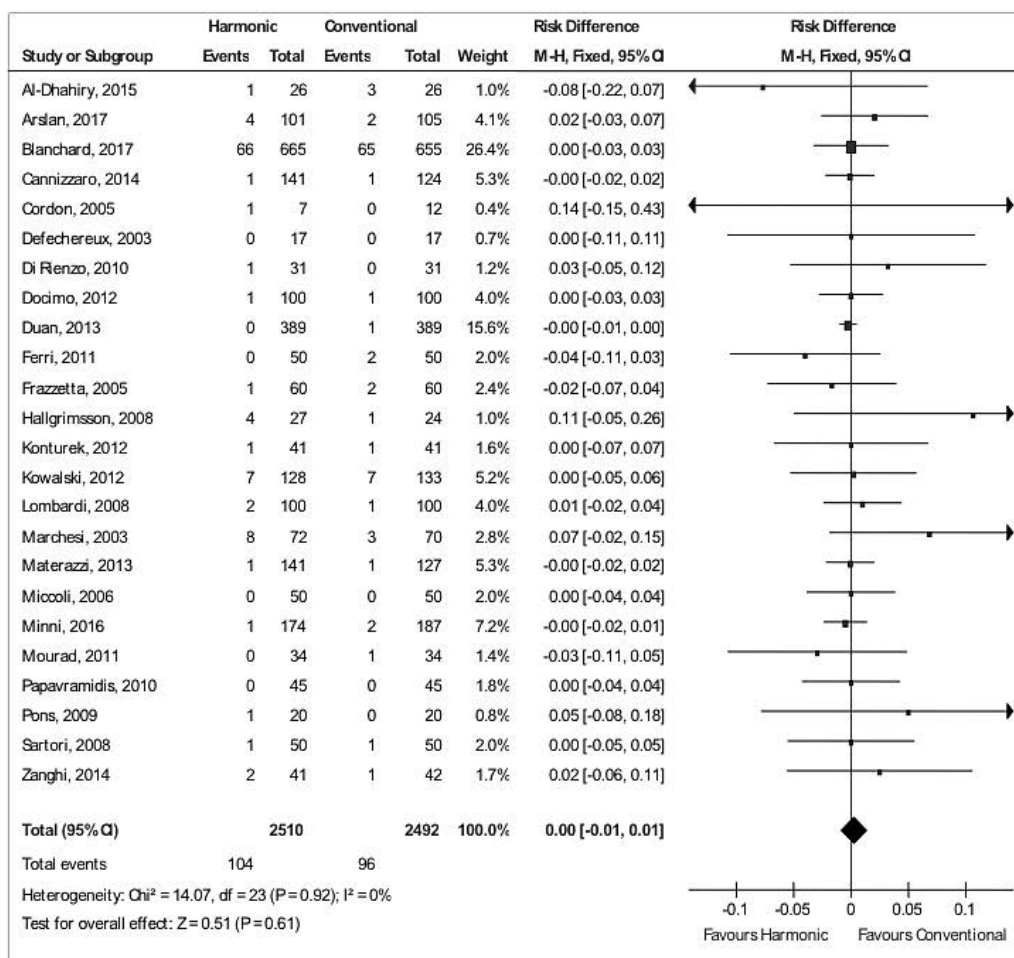
Transient hypocalcaemia (25 studies) occurred in 15.3%. In the group with harmonic scalpel, the incidence was 14.9%, while in the conventional group it was 15.6%. There was no significant difference between the groups (95% CI -0.04 to 0.02, $p = 0.40$ and $I^2 = 56\%$, Figure 2C). Excluding the primary studies responsible for the high heterogeneity ($I^2 = 56\%$)^{18,21,29}, the same effect of the previous analysis was maintained (95% CI -0.03 to 0.01, $p = 0.53$ and $I^2 = 0\%$).

TABLE 1. DESCRIPTION OF PROCEDURES COSTS COMPARING TOTAL THYROIDECTOMY WITH AND WITHOUT THE USE OF HARMONIC SCALPEL

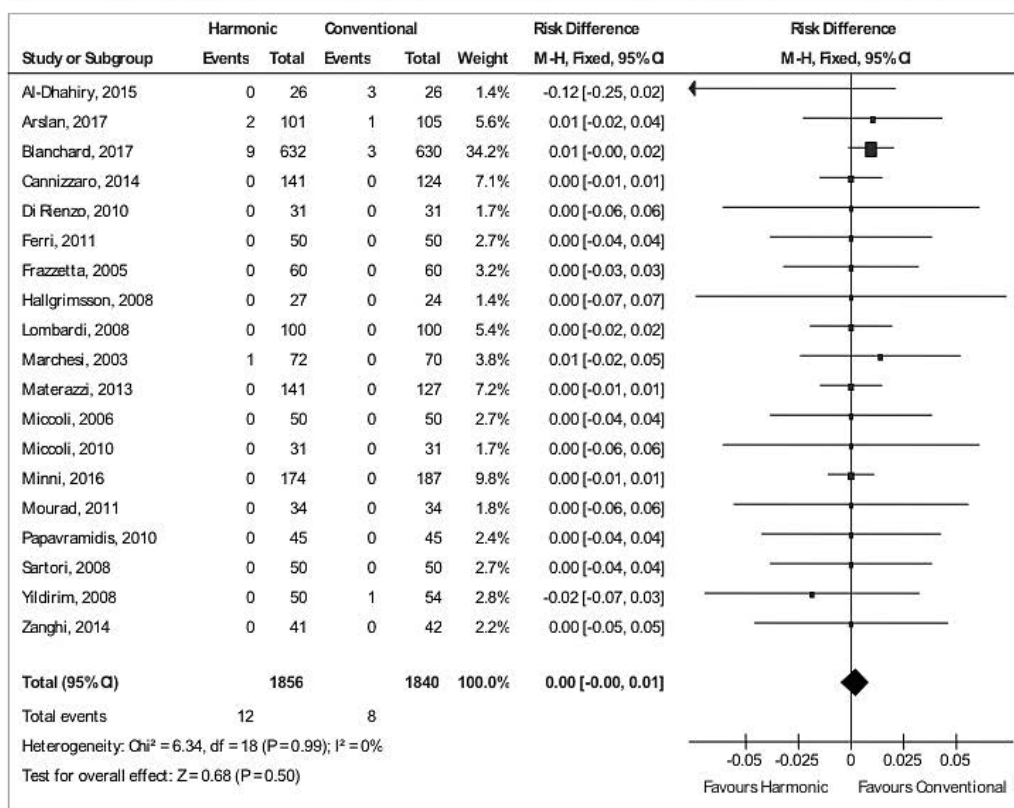
Study	Expenses considered	Harmonic	Conventional	Difference between averages	p
Ortega, 2004*	Medications; Operating room time; Materials; Hospitalization period	985.77 ± 107.08	1,148.40 ± 153.25	-162.6	<0.001
Frazzetta, 2005*	Materials; Operating room time; Medications; Human Resources	978.6 ± 120	1,328.7 ± 105.7	-350.1	<0.001
Lombardi, 2008*	Human Resources; preoperative tests; Medications; Operating room time; Materials; Admission/Discharge	2,238.1 ± 406.5	2,368.1 ± 489.9	-130.0	0.04
Hallgrímsson, 2008*	Materials; Operating room time	2,040 (1,614 – 3,214)	2,413 (922 – 3,798)	-373.0	-
Pons, 2009#	Materials; Human Resources; Medications	2,486 ± 153	2,571 ± 296	-85.0	0.25
Ruggeri, 2012*	Medications; Operating room time; Materials; Hospitalization period; Human Resources; Admission/Discharge	2,292.52	2,411.49	-118.9	-
Kowalski, 2012#	Operating room time; Materials; Medications; Hospitalization time	2,554.7 ± 525.1	2,470.1 ± 923.9	+84.6	0.36
Konturek, 2012*	Operating room time; Materials; Hospitalization time	666.2 ± 32.1	718 ± 27.2	-51.8	<0.001
Blanchard, 2017*	Operating room time; Hospitalization period; Human Resources; Materials	3,954 ± 792	3,728 ± 831	+226	<0.001

* Values in euros; # Values in US dollars

A



B



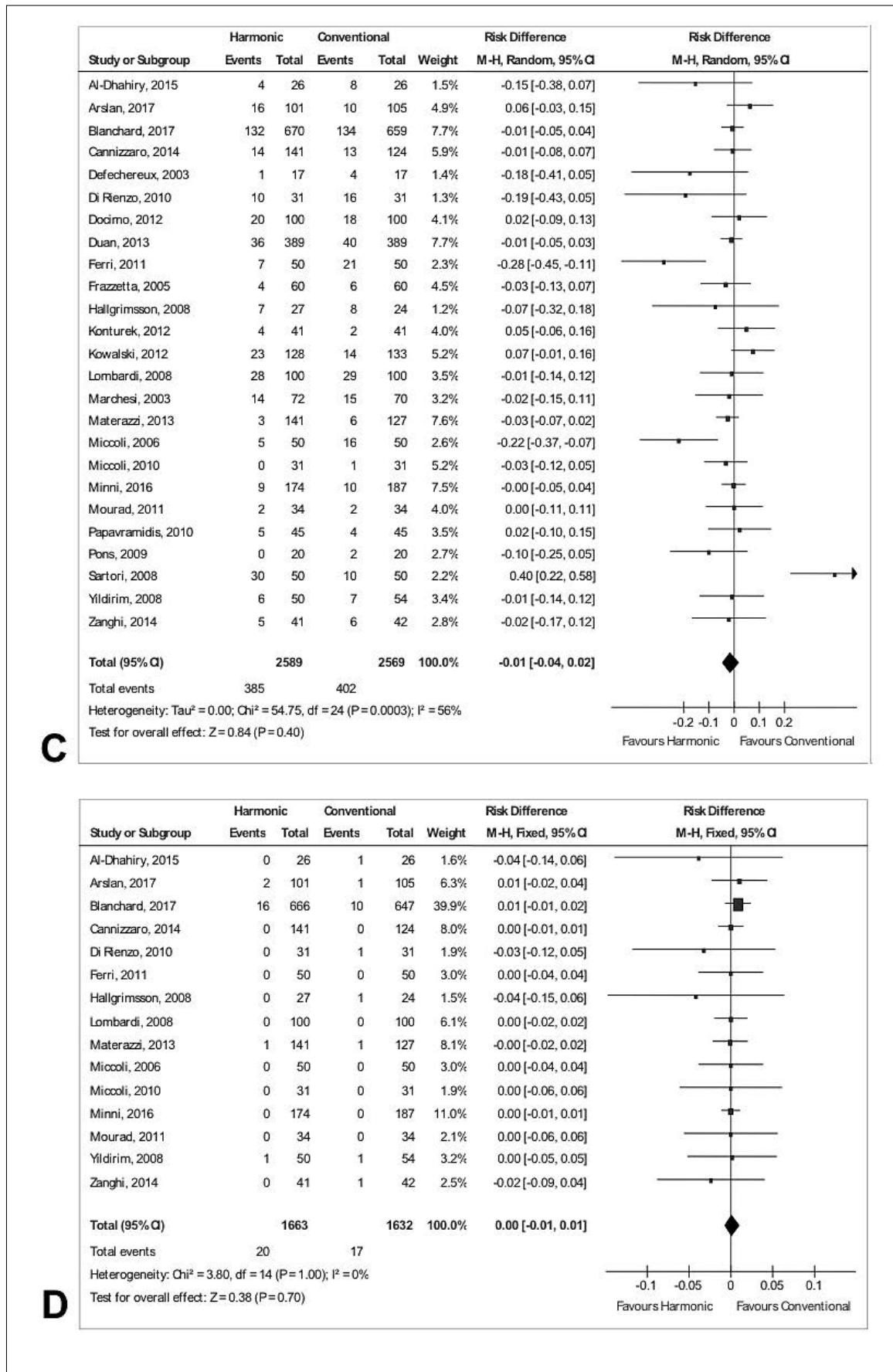


FIGURE 2. META-ANALYSIS ON POSTOPERATIVE COMPLICATIONS COMPARING THE HARMONIC SCALPEL WITH THE CONVENTIONAL TECHNIQUE. A) TEMPORARY DYSFUNCTION OF THE RLN; B) PERMANENT DYSFUNCTION OF THE RLN; C) TRANSIENT HYPOCALCAEMIA; D) PERMANENT HYPOCALCAEMIA.

Regarding permanent hypocalcaemia, there were no significant differences between groups (1.2% x 1.0%, 95% CI -0.01 to 0.01, $p = 0.70$ and $I^2 = 0\%$, Figure 2D).

COST ASSESSMENT

Nine primary studies assessed the costs of the treatments comparing the use of the harmonic scalpel to the conventional technique. Data is shown in Table 1. Two studies did not provide the values of standard deviations and were not analyzed^{22,33}. Four studies showed a significant decrease in hospital costs,^{15,17,20,34} in one study there was a significant increase in costs⁴³ and in two others^{23,30} there was no difference between the groups.

Sensitivity analysis

A sensitivity analysis was performed for all outcomes related to the methodological risk of primary articles, excluding those at high risk. There was a significant difference in operation time (17.3 minutes, $p < 0.001$) and intraoperative bleeding volume (-26.8 ml; $p < 0.001$) in the group of patients submitted to surgery using a harmonic scalpel. There was no significant difference in the incidence of hematoma ($p = 0.16$), permanent and temporary paralysis ($p = 0.66$ and $p = 0.10$, respectively) and transient and permanent hypocalcaemia ($p = 0.33$ and $p = 0.31$).

DISCUSSION

Since the first thyroidectomy documented by Abu al-Qasim in 952, until the mid-19th century, with the experience of Theodor Billroth, surgery on the thyroid gland was considered virtually prohibitive^{1,2}. It was only at the beginning of the 20th century, with the improvement of anaesthetic and aseptic techniques and a better knowledge of haemostatic techniques, that Emil Theodore Kocher obtained satisfactory results, making thyroidectomy a safe surgery, with mortality around 0.5%. Since then, the surgical technique has changed very little^{1,2}.

The success of thyroid surgery is primarily based on adequate haemostasis both to prevent bleeding, which can become fatal, and to keep the surgical site clean and facilitate dissection of tissues, especially vital structures such as the lower laryngeal nerve and parathyroid glands. Given this premise, the results of this review show that there is a statistically significant decrease in intraoperative bleeding volume (35

ml). However, this data was not correlated with the reduction of perioperative complications.

In attempting to make thyroidectomy an even safer and more efficient procedure, haemostatic devices were developed with the purpose of adequate haemostasis without the need for numerous ligatures, which theoretically could save time. One of the most studied is the harmonic scalpel, which consists of mechanical energy in the form of ultrasonic vibrations (up to 55,000 Hz) that seal the blood vessels by breaking the hydrogen and protein bonds of the tissues and vessels and creating endovascular clot^{3,4}. One of the theoretical benefits of using the harmonic scalpel is that it acts under lower temperatures (50° C-100° C), resulting in decreased heat transfer by adjacent tissues and, consequently, less thermal trauma^{3,4}. Moreover, it does not transmit any type of current to the patient^{3,4}.

One of the most frequent and feared complications during thyroidectomy is injury to the inferior laryngeal nerve, which occurs due to surgical trauma, either mechanical (manipulation, traction or section) or thermal trauma. Experimental studies in pigs with histological analysis have demonstrated that the use of the ultrasonic scalpel in the dissection of adjacent tissues (1 mm) to the inferior laryngeal nerve does not cause thermal nerve damage^{44,45}. In another experimental pig model, it was concluded that there is thermal lesion of the inferior laryngeal nerve by lateral heat dissipation in dissections that are distant <1 mm from the nerve⁴⁶. The dissipation of heat to adjacent tissues is directly related to the power and time used by the harmonic scalpel. Studies show that the use of the harmonic scalpel for more than 5 seconds with 4/5 intensities or for more than 20 seconds with lower intensities can generate thermal trauma to the tissues^{47,48}. In this review, no significant difference was observed in the incidence of both temporary and permanent inferior laryngeal nerve dysfunction, comparing surgeries with and without harmonic scalpel.

Voice quality is a poorly assessed outcome in clinical trials that examine the efficacy of various haemostatic devices. Two prospective randomized studies have demonstrated that there are no significant differences in voice quality (objective and subjective) of patients undergoing thyroidectomy with the aid of the harmonic scalpel compared to the conventional technique^{41,49}.

All new technology that is developed must present, in addition to proven efficacy through comparative

studies with proper methodology, also an economic analysis that assesses its implementation costs. For this, there are specific economic assessment tools and methodologies. Studies based on the concepts of cost-effectiveness, cost-benefit and cost-utility should be encouraged in order to obtain better information for decision-making on the incorporation or not of a new technology. In this review, the cost analysis was not considered a primary outcome and was not explored in detail, but there was a tendency to decrease costs in operations with the aid of the harmonic scalpel. This economy was mainly due to the shorter operating time observed in this group, which was directly related to lower operating room and human resources costs. A systematic review with meta-analysis on hospital costs, published in 2016, has shown that there is an absolute reduction of approximately US\$ 229 in harmonic scalpel surgeries⁵⁰.

This systematic review updates the data available in the literature with published clinical trials up to the mid-2017. The clinical data found in this study are in line with the latest published reviews on the subject⁵¹⁻⁵⁴ and show that there is apparently no doubt about the actual efficacy and safety of the harmonic scalpel, questioning only the cost-effectiveness of the implementation of this technology in thyroid surgery.

CONCLUSION

In patients submitted to total thyroidectomy, the use of the harmonic scalpel is effective, reducing operation time and intraoperative bleeding volume when compared to the conventional technique. There is no difference in the incidence of postoperative complications with the aid of the technology.

PALAVRAS-CHAVE: *Tireoidectomia. Hemostasia cirúrgica/métodos. Procedimentos cirúrgicos ultrassônicos. Revisão.*

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