Comment on Garas *et al.*, “Which Hemostatic Device in Thyroid Surgery? A Network Meta-Analysis of Surgical Technologies”

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Dear Editor:

We disagree with the conclusions of the recent article by Garas *et al.* (1) on permanent recurrent laryngeal nerve injury (p-RLN) following thyroidectomy with different energy-based technologies using network meta-analysis. Since network meta-analysis extends the number and type of studies being combined, there is potential for combining studies that are not adequately similar, possibly leading to erroneous conclusions (2). One of the fundamental requirements of network meta-analysis to improve accuracy is that they include only very similar studies, under similar conditions, with similar patient populations, and clearly defined endpoints. Evaluation of the articles included by Garas *et al.* shows they have included a study using Starion (3), an electrocautery device, in the Harmonic arm and a nonrandomized trial in the Harmonic arm (4). Furthermore, not all devices are similar in a given treatment arm nor are the procedures performed, patients studied, or diseases treated similar. For example, within the Ultrasound group, devices used include CS-14C, Wave, and Focus, and within the LigaSure arm, Precise, Small Jaw, and unstated devices. Many of the studies in the Harmonic and LigaSure treatment arms combine the use of monopolar and/or bipolar electrosurgery. The disease state and procedures performed vary significantly from total thyroidectomy with central neck dissection to partial thyroidectomy to videoscopic thyroidectomy and from cancer to Graves' disease to multinodular goiter. Thus, to conclude that the populations are suitably similar and satisfactory for comparison through network meta-analysis is erroneous and raises serious questions regarding the conclusions reached.

The conclusions of network meta-analysis performed by Garas *et al.* are that ultrasonic devices and advanced bipolar devices provide less blood loss, less drain output, shorter operative time, and shorter hospital stay compared to the conventional methods of clamp-cut-and-tie (CCT) thyroidectomy, but that the rate of p-RLN paralysis is significantly higher for ultrasonic devices and LigaSure devices compared to CCT. How they came to that conclusion is not evident from the studies they reviewed. When the total actual number of individual cases of p-RLN paralysis reported in

the randomized control trials used by Garas *et al.* (excluding the two studies noted above) are totaled, there were 2/992 cases (0.2%) of p-RLN paralysis for CCT versus 1/1006 (0.1%) for Harmonic in RCTs where both are compared (and 1/266 cases [0.4%] of p-RLN paralysis for CCT vs. 1/266 [0.4%] for LigaSure in studies where CCT and LigaSure were compared directly). Consistent with the absence of a difference in p-RLN paralysis is the I^2 value of 0.00% for p-RLN paralysis reported by the authors in Table 2. This statistic is a measure of heterogeneity, and values below 25% represent low heterogeneity. A value of 0.00% suggests no heterogeneity or variability across the studies and is consistent with the finding that the vast majority of studies reported no p-RLN paralysis.

What is particularly troubling is that the authors state that the results of this network meta-analysis suggest that the superior safety profile of the CCT technique can contribute to future international thyroidectomy guidelines because they believe there is relative risk of permanent RLN. Based on direct comparison methods using the randomized clinical trials identified in the Garas *et al.* study, one would logically conclude that there is no increase in the risk of recurrent laryngeal nerve injury when Harmonic or LigaSure devices are used and that the use of these energies will provide less blood loss, less drain output, shorter operative time, and shorter hospital stay compared to the conventional methods of CCT thyroidectomy, all these being of significant benefit to patients, hospitals, and societies.

References

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Response to Amaral *et al.*

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WE WELCOME THE OPPORTUNITY to respond to the recent expression of concern regarding our surgical technology network meta-analysis (1) declared by employees of a surgical instruments company (2). As a university-based unit with no conflicts of interest, our evaluation leads us to conclude that our original article followed appropriate unbiased principles and does not require a correction. Seven basic assertions were made in the expression of concern, and we would like to address these point by point.

First, the authors primarily expressed disapproval of our results for permanent recurrent laryngeal nerve (RLN) injury (favoring traditional clamp-and-tie hemostasis when compared with surgical devices), and did not identify reservations regarding other endpoints, suggesting that there may be an undue focus on an individual result rather than an objective concern with our methodology.

Second, many device analyses suffer from an underdetection and underreporting of RLN injury because of inadequate assessment and underpowering for this endpoint. We only included studies that assessed RLN function according to the gold-standard methodology of pre- and post-operative laryngoscopy, and included the two studies that were adequately powered for a comparative assessment.

Third, the authors also inaccurately state that Starion is “an electrocautery device” and that one of the studies we used was “not randomized.” Starion utilizes thermal fusion technology to seal and divide vessels simultaneously in “the absence of electrical transit through tissues” (3), and the study to which they refer is classified as a randomized controlled trial (4).

Fourth, in this case we felt that conventional meta-analysis offered a restricted view as there are several hemostatic devices and outcomes to consider (5). Limiting our study to a standard meta-analysis in such a case where multiple comparisons are required may have led to selection bias. As an example, there are 14 pair-wise comparisons for the Harmonic

scalpel versus clamp-and-tie in the literature but only 3 for the Harmonic scalpel versus Ligasure with regard to permanent RLN paralysis. The disproportionate representation of direct comparisons (known as “co-occurrence”) has previously been reported and can bias results through device comparisons against inferior “straw men” (agents perceived as easy to beat) while avoiding comparisons against other effective treatments (5).

Fifth, even when conventional meta-analysis is applied, the Harmonic scalpel is associated with an increased risk of permanent RLN injury over clamp-and-tie hemostasis. From the direct comparisons in our article, there is an odds ratio of 1.74 and a statistical trend ($p=0.08$) favoring clamp-and-tie hemostasis over the Harmonic scalpel.

Sixth, from a technical perspective, dissection near any nerve is safer in the absence of heat. Lateral thermal spread is a well-recognized problem associated with ultrasonic coagulation and bipolar systems that can place the RLN at risk. The clamp-and-tie technique is not associated with this problem as it involves no heat production.

Seventh, while we note the comment that “not all devices are similar in a given treatment arm,” this is a recognized limitation of studies where there is rapid evolution of surgical technology. We accounted for this factor in our methodology by adjusting the results by year. Similarly, to answer the authors’ comments about heterogeneity, we limited the heterogeneity between studies by conducting a metaregression analysis that adjusted for publication year (technological evolution of devices) and Jadad score (quality of randomized controlled trials).

Network meta-analysis is a valuable evidence synthesis technique developed precisely to overcome the limitations associated with conventional meta-analysis. By integrating all the data from both direct and indirect comparisons, network meta-analysis provides an unbiased, wider view of the evidence landscape (5). As a result, it can

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