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Editorial

Fluorescence in endocrine surgery[☆]

Fluorescencia en cirugía endocrina



Endocrine surgery is constantly evolving. In recent years, we have focused on patient safety in order to further minimize the morbidity associated with thyroid surgery. Nonetheless, we are aware that the standards of quality are very difficult to improve.

Thyroidectomy is by far the most frequently performed procedure in endocrine surgery. Meanwhile, hypoparathyroidism, either due to altered vascularization of the parathyroid glands (PG) or direct injury, continues to be the most frequent complication.

Despite being the most frequent complication, hypoparathyroidism is underestimated and managed as a “minor” complication, probably for several reasons. First if all, its actual frequency is underestimated and difficult to quantify, especially if patient follow-up is not continued for at least one year after surgery. In addition, there are no consensus-based definitions for permanent hypoparathyroidism. Lastly, since the symptoms do not appear to be serious and the treatment is as simple as “taking a few pills”, we are not aware of the costs incurred by the healthcare system or the burden of permanent hypoparathyroidism on the quality of life of the patient, as it results in chronic dependence of the patient on the system.¹

Endocrine surgeons trained in specific high-volume surgery units and the routine use of new technologies have minimized the complications related with hemorrhage and injury to the inferior laryngeal nerve. However, regarding the management of the parathyroid glands and until the advent of fluorescence, no other innovation had allowed us to minimize the trauma to the parathyroid glands during thyroidectomy beyond developing a meticulous surgical technique.

Systematic identification of the parathyroid glands is controversial since excessive zeal used in their identification is associated with transient hypoparathyroidism. In contrast, their identification is associated with fewer episodes of permanent hypocalcemia.²⁻⁵

In any event, 4 key steps should be followed during thyroidectomy to avoid or reduce permanent hypoparathy-

roidism: first, identify the PG in their usual position; second, if possible, identify the arterial vessels that supply them; third, use this information to preserve the glands with a meticulous surgical technique; and fourth, once the thyroidectomy has been completed, the parathyroid function is predicted during the immediate postoperative period (either during a short-stay or outpatient basis), thereby avoiding episodes of clinical hypocalcemia.

The identification of PG is not easy and is linked to the experience of the surgeon. It is not surprising for less experienced surgeons or those who work in low-volume centers to see more than one gland in the same position; conversely, expert surgeons may not be able to identify all 4. In this situation, the use of devices capable of detecting PG autofluorescence (AF) has proven to be highly useful and effective.

AF is the intrinsic property of some tissues (including PG) to spontaneously emit light in the infrared range, which is detectable with the use of cameras designed for this purpose. In the randomized multicenter PARAFLUO trial, Benmiloud et al. demonstrated that AF would allow us to reduce episodes of transient hypocalcemia, the rate of parathyroid autotransplantation, and the incidence of inadvertent parathyroidectomies.⁶

The other type of fluorescence imaging used in endocrine surgery is indocyanine green (ICG) angiography, which has proven to be very useful when the PG have been identified. However, the chronological order is the inverse of the previously described steps.

Initially, ICG was used to predict post-thyroidectomy parathyroid function based on a scoring system that simplifies the assessment of the functional status of PG. Three categories have been defined based on the intensity of the perfusion and uptake of ICG (white = 2, gray = 1, black = 0) versus visual evaluation of the macroscopic gland appearance, which is even more subjective and has little sensitivity to predict

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parathyroid function.⁷ ICG angiography makes it possible to predict parathyroid function immediately and with the same reliability as intraoperative PTH, which supports intraoperative decision-making and is also superior to other published scoring systems.⁸⁻¹⁰

The drawback is that it is a technique that remains subjective to some degree and requires overcoming a learning curve. A recent study by our group has shown that the rate of agreement in the perception of well-perfused glands was only 80% among the evaluations made by surgeons participating in the study (unpublished data). Currently, we are incorporating ICG uptake quantification as a more objective measure to predict PG function in the immediate postoperative period, although this technology is still in the development phase.

We have recently taken a more significant step — the use of fluorescence imaging to visualize the vascular map that supplies the PG, which then guides the thyroidectomy procedure. The 2022 cohort study published by our group demonstrates how arteriography-guided thyroidectomy has allowed us to leave significantly more PG *in situ* and with better perfusion. We have had no episodes of permanent hypocalcemia in a patient cohort with associated VGCC in more than 60% of the cases.¹¹

This has led to a paradigm shift in thyroidectomy surgery. With the classic technique, once the PG is identified, the surgeon draws an imaginary thyroidectomy line, attempting to leave the PG *in situ*. Only the color or bleeding of the glandular parenchyma would give any indication about the functional status of the PG. However, knowledge of the vascular map leads us first to develop the ability to preserve the small blood vessels, reach the gland, and finally complete the thyroidectomy.

We have taken surgery to very fine levels of detail, handling very small caliber vessels, and we have been able to observe and verify intraoperatively what we all imagined, and which is logical: glandular function is maintained if we preserve PG perfusion.

Thus, it is not only the quantity of the remaining glands *in situ* but also the quality of their perfusion, which is fundamental and will be a key factor for predicting the functional status of the postoperative PG. According to our data, a single well-perfused PG will maintain normal calcium levels with 94% diagnostic accuracy. With this evidence, it will not be necessary to systematically identify the remaining PG, especially if this involves more aggressive dissection that could compromise the viability of the PG.⁸

In recent years, the use of fluorescence has provided intraoperative information about the functionality of PG to make immediate decisions. However, unanswered questions remain, such as: the possibility that poorly perfused PG (score = 0) have of recovering, or whether they should be systematically transplanted; the possibility that arteriography-guided thyroidectomy could enable us to achieve ZERO hypoparathyroidism; etc.

It will not be easy to answer these questions or others that may arise, but those that can be answered will require carefully designed studies with very strict recruitment criteria. To begin with, having at least 4 PG identified [in situ + autotransplanted + inadvertent parathyroidectomy = 4] is

essential, since any PG not found may be responsible for maintained calcium levels.

It remains to be seen whether arteriography-guided thyroidectomy will be able to significantly reduce permanent hypoparathyroidism or even, ideally, lower it to zero.

Our group is currently leading a randomized multicenter trial that aims to validate this hypothesis. This study is ambitious, and we are aware of its complicated nature and limitations. On one hand, surgeons from high-volume units who already have low hypocalcemia outcomes will need many cases in each study arm to demonstrate significant changes. On the other hand, the study focuses on one complication with the intention of reducing its frequency, which challenges the surgeon to do even better. Last of all, the fact that several medical centers and surgeons participate in the study increases its variability and affects the results.¹²

It is not clear whether fluorescence with ICG will be the technique of choice in the future to reduce permanent hypoparathyroidism to zero, but there is no doubt that with this biomarker we have taken a step towards “functional surgery of the parathyroid glands”.

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