

Concordance of Near-Infrared Autofluorescence in Parathyroid Glands with Definitive Histopathology Result

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ABSTRACT

Summary

Introduction: Hypoparathyroidism is the most frequent complication of thyroidectomy, which is influenced by multiple factors, mainly unintentional resection, due to its location, size and difficulty in identification, leading to post-surgical hypocalcemia in 20 to 30% of which 1 to 3% of cases, hypocalcemia may be permanent; due to this techniques have been described for its identification, Benmiloud et al. conducted a case-control study where they compared the efficacy of near-infrared light in detecting parathyroid glands. Parathyroid identification rates were higher in the near-infrared light group compared to the control group (76.3% vs 65.7%).

Material and Methods: Cross-sectional, prospective, comparative and analytical study in a third-level hospital in Mexico City, in 20 patients diagnosed with primary and secondary hyperparathyroidism undergoing partial or total parathyroid surgery, with the aim of determining the concordance of near-infrared autofluorescence in these glands and the result at which final histopathological, statistical analysis was performed in SPSS 24, with the Kappa and ji-square coefficient,

Results: A total of 20 patients undergoing parathyroid surgery, the most common histopathological finding with 44.2% was parathyroid hyperplasia, with a sensitivity for autofluorescence with the result of histopathology of 82.4% and specificity of 88.9% with PPV of 93.3% and NPV 72.7% and a Kappa coefficient with a value of 0.67 with a $p < 0.005$.

Conclusions: The concordance of near-infrared autofluorescence in parathyroid glands with the result of histopathology is considerable, with a good overall performance for timely detection of parathyroid tissue

KEYWORDS: Parathyroids, Near-infrared autofluorescence, Primary hyperparathyroidism, Secondary hyperparathyroidism, Parathyroidectomy, Hypoparathyroidism, Hypocalcemia.

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INTRODUCCION

Hypoparathyroidism is the most common complication of thyroidectomy, because although experienced surgeons can identify the parathyroid gland without technical difficulty, less experienced surgeons may have trouble clearly distinguishing the parathyroid glands from surrounding tissues. Therefore, temporary or permanent hypocalcemia can

be caused by inadvertent resection or devascularization of the parathyroid glands¹

Accidental removal of the parathyroid gland during thyroidectomy results in post-surgical hypocalcemia in 20-30%¹, of which 1-3% of cases hypocalcemia may be permanently¹.

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Parathyroid damage and unintentional parathyroid resection could be largely avoided by better intraoperative identification of parathyroid².

The most accurate method to identify the parathyroid gland is transsurgical biopsy, however, during this procedure devascularization and consequent destruction of function may occur, consequently, the surgeon must rely on visual inspection to identify these glands³.

Due to this, intraoperative techniques have been developed for its correct identification and preservation, autofluorescence is one of these techniques which consists of the natural emission of light by intrinsic fluorophores. The

term is used to distinguish light that originates from artificially added fluorescent markers (exogenous contrast dye) such as indocyanine green. The application of this phenomenon to visualize the parathyroid gland using the near-infrared wavelength during thyroid or parathyroid surgery is the latest technique in this field⁴

Vanderbilt's group studied the autofluorescence of the parathyroid, thyroid and other surrounding tissues generating an emission in a safe spectrum range set at a maximum emission at 785nm, for both tissues. This occurs in near-infrared autofluorescence in a range of 820 -830 nm. ⁵

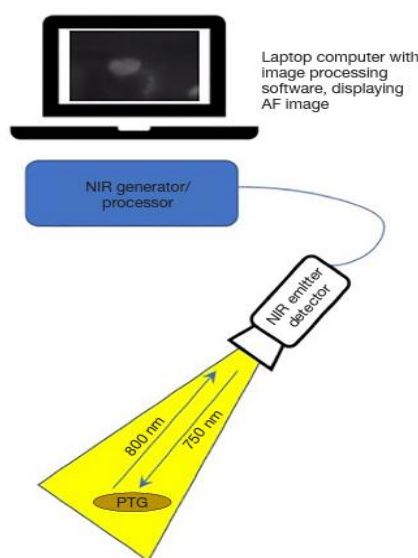


Figure 1. Example of Using Near-Infrared Autofluorescence System, showing an emitter (750-800nm) a detector (optimized 800-830nm) with its processor and display screen.

In 2018 Benmiloud et al. conducted a case-control study where they compared the effectiveness of near-infrared light in detecting parathyroid glands. Parathyroid identification rates were higher in the near-infrared light group compared to the control group (76.3% vs 65.7%). Inadvertent parathyroid resection occurred in a single patient in the near-infrared light group (1.1%) versus 7.2% of patients in control group⁵

It is for this reason that, in the present research, the use of this technique as a safe diagnostic tool during parathyroid surgery is proposed, with the primary objective of the preservation of these glands comparing their performance with the final histopathological findings, in order to provide the expert or inexperienced surgeon who performs neck surgery, one more diagnostic instrument for your daily surgical practice.

MATERIALS AND METHODS

A cross-sectional, prospective, comparative and analytical study was carried out at the "Dr. Antonio Fraga Mouret" Specialty Hospital of the La Raza National Medical Center. The objective was to determine the concordance of near-infrared autofluorescence in parathyroid glands with definitive histopathology result in patients undergoing

selective or total parathyroidectomy. Therefore, 20 patients were included (14 presented female gender and 6 presented male gender), with a diagnosis of primary hyperparathyroidism and secondary hyperparathyroidism, within the exclusion criteria of the present study were patients with a history of neck surgery for another indication (tracheostomy, neck trauma, excisional biopsy), history of parathyroidectomy or patients who did not have a report of definitive pathology.

In total, 52 surgical pieces were extracted, and subsequently the application of near-infrared autofluorescence was submitted in the transoperative period, with a laser diode with a wavelength of 780 nm, with an estimated time of five minutes after the extraction of the surgical piece, at a distance not greater than 15 cm in relation to the laser diode with respect to the surgical piece, with a Sony camera with a 760 nm infrared lens, to later compare the results with those of histopathology defined by the presence of parathyroid tissue, in the case of being positive, or extra parathyroid in case of being negative.

We performed the statistical analysis with the SPSS software version 24, descriptive statistics were used using the Correlation Coefficient of Kappa and chi square between the

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ratio of positive or negative near-infrared autofluorescence and the positive or negative histopathology result.

RESULTS

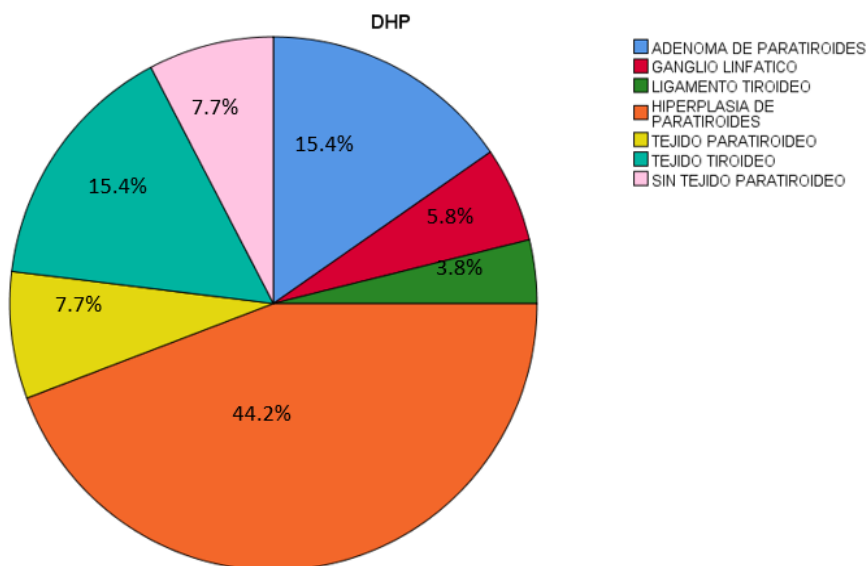
Of the results obtained starting with the operationalization of variables, within the demographic characteristics, by age groups of patients undergoing total or selective parathyroidectomy, the following was found in Table

Table 1. Clinical and demographic characteristics of patients undergoing selective or total parathyroidectomy.

		Frequency	Percentage
Age groups	18-30	1	5%
	31-40	6	30%
	41-50	4	20%
	51-60	6	30%
	61-70	3	15%
	Total	20	100%

A total of 52 samples were obtained from the total number of patients treated surgically, of which it is outlined in the

following graph according to each histopathological diagnosis:



He underwent near-infrared autofluorescence (Figure 1) after extraction of the selective or total parathyroidectomy product of which 30 samples with 57.7% presented positive autofluorescence and 22 samples with 42.3% negative autofluorescence. It was considered a positive histopathology

result due to the presence of parathyroid tissue reported by a pathologist with 34 samples with 65.4%: finally, it was considered a negative histopathology result in case of finding extra parathyroid tissue in definitive result of pathology of which there were 18 samples representing 34.6%.

a)

b)



Figure.1

Concordance of Near-Infrared Autofluorescence in Parathyroid Glands with Definitive Histopathology Result

An image of surgical pieces subjected to a near-infrared light is observed with a 780 nm laser diode, a photograph obtained through a Sony camera with a 760nm lens. (a) Selective parathyroidectomy product with positive autofluorescence; (b) selective parathyroidectomy product with negative autofluorescence.

A double-entry table was performed with the results of near-infrared autofluorescence against histopathology result. A sensitivity of 82.4% and a specificity of 88.9% were obtained; with respect to the positive predictive value, 93.3% was obtained and a negative predictive value of 72.7%.

Table 2.

Tabla cruzada AUTOFLUORESCENCIA*RESULTADO DE HISTOPATOLOGIA (RHP)

			RHP		Total
			POSITIVO	NEGATIVO	
AUTOFLUORESCENCIA	POSITIVO	Recuento	28	2	30
		% dentro de AUTOFLUORESCENCIA	93.3%	6.7%	100.0%
		% dentro de RHP	82.4%	11.1%	57.7%
	NEGATIVO	Recuento	6	16	22
		% dentro de AUTOFLUORESCENCIA	27.3%	72.7%	100.0%
		% dentro de RHP	17.6%	88.9%	42.3%
Total	Recuento	34	18	52	
	% dentro de AUTOFLUORESCENCIA	65.4%	34.6%	100.0%	
	% dentro de RHP	100.0%	100.0%	100.0%	

This table shows Pearson's chi square values of 24.47 with degrees of freedom of 1, with a $p < 0.05$, so we consider that the ratio of relationship between near-infrared

autofluorescence and the histopathology result is statistically significant.

Table 3. Chi-Square Results

	Value	Degrees of freedom	Asymptotic (bilateral) significance	Exact significance (bilateral)	Exact (unilateral) significance
Pearson's Chi-square	24.473 ^a	1	.000		
Continuity correction ^b	21.641	1	.000		
Likelihood ratio	26.606	1	.000		
Fisher's exact test				.000	.000
Linear-by-linear association	24.002	1	.000		
N of valid cases	52				

a. 0 boxes (0.0%) have expected a count less than 5. The minimum expected count is 7.62

b. It has only been calculated for a 2x2 table.

Table 4. Near-infrared autofluorescence and Histopathology result

	Positive histopathology result	Negative histopathology result	Total	p*
Positive near-infrared autofluorescence	28	2	30	
	53.84 %	3.82 %		<0.05
Near-infrared negative autofluorescence	6	16	22	
	11.53 %	30.76 %		<0.05
Total	34	18	52	
	100%	100%	100%	

The result of near-infrared autofluorescence with histopathology result is presented, where 28 samples corresponding to 53.84% present near-infrared autofluorescence with positive histopathology result with statistical significance ($p < 0.05$) are described, we observe that 16 samples corresponding to 30.76% present near-infrared autofluorescence with negative histopathology result; 6 samples with 11.53% presented negative near-infrared autofluorescence with positive histopathology result, in the same way 2 samples with 3.82% presented negative histopathology result with positive near-infrared autofluorescence result.

DISCUSSION

Near-infrared autofluorescence is a property present in the parathyroid glands, which in recent years have been used for their identification, it is believed that this property is derived from a calcium receptor regulatory protein that is present in higher concentrations in the main cells of the parathyroid⁴.

The identification of the parathyroid glands depends on the direct visualization of the surgeon. Several methods have been described for timely identification during the surgical procedure, including indocyanine green, methylene blue, transoperative gammagrama with several technical difficulties, including the technical difficulty of obtaining adequate inputs for transoperative assessment of parathyroid glands, adverse effects in case of methylene blue including encephalopathy, the surgical time for its identification, turn off the operating room lights at each measurement. The most accurate method for the identification of parathyroid glands is transsurgical biopsy, however, the possible devascularization and subsequent destruction of function presents a great disadvantage. Near-infrared autofluorescence is a replicable method, feasible to reproduce during the parathyroidectomy surgical procedure, it is worth mentioning that its application is very useful in the monitoring of parathyroid glands during a total thyroidectomy with a decrease in post-surgical hypocalcemia.

There are studies where the need to assess the usefulness of near-infrared autofluorescence in patients diagnosed with secondary hyperparathyroidism due to the hypothesis of depletion of calcium ducts in the parathyroid glands is discussed, however, in our study no statistically significant difference was identified between patients with a diagnosis of primary and secondary hyperparathyroidism.

A similar, retrospective study conducted by the department of endocrine surgery of the Cleveland Clinic, Ohio in the United States, between July 2016 and 2019 reported the use of near-infrared fluorescence in identifying those specimens that were subjected to identification by video or photo in ex vivo tissue before their sending to pathology, these measurements were compared with histopathological findings to determine the values of sensitivity and specificity to detect parathyroid tissue finding 166 parathyroid, 154 thyroid, 58 lymphatic tissue and 5 thymic tissue, the ex vivo measurements performed, autofluorescence had a sensitivity of 86.1% and a specificity of 84.8% with a statistically significant p in both funds, the surgical field and with Telfa⁷

The present study is important, as it demonstrates the correlation between the histopathology result and the autofluorescence property in the parathyroid glands. The applicability of this procedure can be very useful in surgeons with little experience in neck surgery. Once we have assessed the usefulness of near-infrared autofluorescence for the identification of parathyroid glands, the next step is the monitoring of parathyroid glands for the prevention of post-surgical hypocalcemia.

Unfortunately, although hypocalcaemia and hypoparathyroidism following thyroid surgery are well documented in the medical literature, there are significant limitations in the results of published studies. Possibly the most relevant is the wide variability reported in the incidence of hypocalcemia and hypoparathyroidism; rates of hypocalcemia ranging from 0.3% to 66.2% are reported, and rates of hypoparathyroidism from 0 to 40%.³. Part of this variation originates from the fact that the reports include various types of thyroid procedure. Some series contemplate

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only patients undergoing total thyroidectomy, while others include less extensive procedures, such as lobectomies, which have a lower risk of hypocalcemia and hypoparathyroidism. Such reports can underestimate the rate of hypocalcemia and lead to misinterpretations.

In a meta-analysis in which the performance of near-infrared autofluorescence was studied, with a total of 1480 patients included, for 7 analyzes included in this meta-analysis, although the heterogeneity of the analyzed studies was reported on the first postoperative day was lower than in the control group with a $p < 0.001$, however, compared to the incidence of severe hypocalcemia in which patients required vitamin D and calcium on the 1 postoperative day was not statistically significant, nor was there a difference in incidence between one group and another at 6 months postoperatively, so the authors conclude that near-infrared autofluorescence is associated with a reduction in the risk of inadvertent parathyroid gland resection and hypocalcemia in on day 1, however at 6 months there was no difference, so more studies are needed to demonstrate its protective effect. ⁶

The current literature indicates that incidences of hypocalcaemia and hypoparathyroidism may be affected by a number of factors. More extensive procedures, for example, result in a higher incidence of calcium decline. Other potentially predictors of hypocalcemia and hypoparathyroidism are previous surgery, association with cervical lymphadenectomy, in the case of regionally metastatic malignancies, as well as the surgeon's experience in surgical procedures involving the thyroid.

CONCLUSION

In this study a considerable correlation was found between near-infrared autofluorescence and the result of histopathology in parathyroid glands, we consider an overall good performance for timely detection of parathyroid tissue. It is a replicable and feasible method for identification of parathyroid tissue in patients with indication of parathyroidectomy, no statistically significant difference was identified between patients with diagnosis of primary and secondary hyperparathyroidism and the property of near-infrared autofluorescence. This method can be used in parathyroid gland monitoring in patients with indication of total thyroidectomy or hemithyroidectomy, to preserve the function of the parathyroid glands with the aim of reducing

transoperative complications in relation to hypoparathyroidism and post-surgical hypocalcemia, this study also despite having a small sample, compared to current international literature, has similar results, being a prospective study, it can be given continuity, leaving opportunity to expand this research.

CONFLICT OF INTEREST: The authors stated that they had no conflict of personal, financial, intellectual, economic and corporate interest with the Metropolitan Hospital and members of the journal MetroCiencia.

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