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Association of Autofluorescence-Based Detection of the Parathyroid Glands During Total Thyroidectomy With Postoperative Hypocalcemia Risk
Results of the PARAFLUO Multicenter Randomized Clinical Trial

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Invited Commentary

Supplemental content

IMPORTANCE Because inadvertent damage of parathyroid glands can lead to postoperative hypocalcemia, their identification and preservation, which can be challenging, are pivotal during total thyroidectomy.

OBJECTIVE To determine if intraoperative imaging systems using near-infrared autofluorescence (NIRAF) light to identify parathyroid glands could improve parathyroid preservation and reduce postoperative hypocalcemia.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial was conducted from September 2016 to October 2018, with a 6-month follow-up at 3 referral hospitals in France. Adult patients who met eligibility criteria and underwent total thyroidectomy were randomized. The exclusion criteria were preexisting parathyroid diseases.

INTERVENTIONS Use of intraoperative NIRAF imaging system during total thyroidectomy.

MAIN OUTCOMES AND MEASURES The primary outcome was the rate of postoperative hypocalcemia (a corrected calcium <8.0 mg/dL [to convert to mmol/L, multiply by 0.25] at postoperative day 1 or 2). The main secondary outcomes were the rates of parathyroid gland autotransplantation and inadvertent parathyroid gland resection.

RESULTS A total of 245 of 529 eligible patients underwent randomization. Overall, 241 patients were analyzed for the primary outcome (mean [SD] age, 53.6 [13.6] years; 191 women [79.3%]): 121 who underwent NIRAF-assisted thyroidectomy and 120 who underwent conventional thyroidectomy (control group). The temporary postoperative hypocalcemia rate was 9.1% (11 of 121 patients) in the NIRAF group and 21.7% (26 of 120 patients) in the control group (between-group difference, 12.6% [95% CI, 5.0%-20.1%]; *P* = .007). There was no significant difference in permanent hypocalcemia rates (0% in the NIRAF group and 1.6% [2 of 120 patients] in the control group). Multivariate analyses accounting for center and surgeon heterogeneity and adjusting for confounders, found that use of NIRAF reduced the risk of hypocalcemia with an odds ratio of 0.35 (95% CI, 0.15-0.83; *P* = .02). Analysis of secondary outcomes showed that fewer patients experienced parathyroid autotransplantation in the NIRAF group than in the control group: respectively, 4 patients (3.3% [95% CI, 0.1%-6.6%) vs 16 patients (13.3% [95% CI, 7.3%-19.4%]; *P* = .009). The number of inadvertently resected parathyroid glands was significantly lower in the NIRAF group than in the control group: 3 patients (2.5% [95% CI, 0.0%-5.2%]) vs 14 patients (11.7% [95% CI, 5.9%-17.4%], respectively; *P* = .006).

CONCLUSIONS AND RELEVANCE The use of NIRAF for the identification of the parathyroid glands may help improve the early postoperative hypocalcemia rate significantly and increase parathyroid preservation after total thyroidectomy.

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Identification and preservation of the parathyroid glands (PGs) are crucial during thyroid surgery. Indeed, PG damage, devascularization, autotransplantation, and/or inadvertent resection can lead to postoperative hypocalcemia. Postoperative hypocalcemia is the most frequent complication after total thyroidectomy, occurring in 20% to 30% of patients and remaining permanent in 1% to 4% of them.[1] This complication can be severely symptomatic and even life-threatening and can the increase length of a hospital stay, require substitutive treatment and prolonged surveillance after discharge, and thus impair quality of life.[2] Recently, a large Scandinavian cohort study observed an increased risk of mortality in patients with permanent hypocalcemia.[3]

Conventional means to reduce the risk of surgical hypoparathyroidism were mainly based on surgeon-dependent identification and meticulous preservation of the PGs and their vascular pedicles. However, despite all efforts, autotransplantation and inadvertent resection are common: Sitges-Serra et al[4] reported that 25% to 50% of patients had 1 or more PGs autotransplanted and 22% had 1 or more PGs inadvertently resected.

Recently, several articles[5-7] described how the parathyroid tissue, when submitted to a near-infrared stimulation, emitted a spontaneous autofluorescent signal 2 to 11 times superior to the signal of surrounding tissues. These case series, based on spectroscopic measures, were followed by several studies[8-11] showing that, using various systems, near infrared-induced autofluorescence (NIRAF) could provide real-time objective images of normal and pathologic PGs and that these images were reliable, corresponding to the PGs in 76% to 100% of the cases. Other studies[12,13] showed that the PGs could be revealed before becoming visible to the naked eye. In a before-and-after study,[14] we showed that the use of NIRAF in routine thyroid surgery could help reduce the risk of parathyroid postoperative dysfunction. Very recently, Dip et al[15] published a single-center randomized clinical study in which a nearly significant reduction of the primary outcome (postoperative hypocalcemia, <8.0 mg/dL; to convert to mmol/L, multiply by 0.25) was found, although the rate of patients with the calcium level less than 7.6 mg/dL was significantly lower with the use of the NIRAF system. The aims of this prospective multicenter randomized clinical study were to assess if the use of NIRAF could reduce postoperative hypocalcemia (primary outcome) and improve parathyroid identification, autotransplantation, and inadvertent resection rates (secondary outcomes).

Key Points

Question Do intraoperative imaging systems using near-infrared autofluorescence light to identify parathyroid glands influence parathyroid preservation and postoperative hypocalcemia?

Findings In this randomized clinical trial of 241 adults, the use of near-infrared autofluorescence during total thyroidectomy helped lower the temporary postoperative hypocalcemia rate from 22% to 9% and the parathyroid autotransplantation and parathyroid inadvertent resection rates from 16% to 4% and 14% to 3%, respectively.

Meaning Near-infrared autofluorescence–based identification of parathyroid glands during thyroid surgery may limit parathyroid risk.

Methods

Study Design

Between September 2016 and October 2018, we conducted a randomized clinical study in 3 French hospitals, involving 8 surgeons. Participants were patients who underwent total thyroidectomy with or without lymph node dissection. Exclusion criteria were any less-than-total thyroidectomy (ie, lobectomy or isthmusectomy) and preoperative parathyroid disease. Using a computer-generated model, patients were randomly assigned to either the standard-thyroidectomy group or the NIRAF group and had total thyroidectomy without or with the use of NIRAF, respectively. Further details are available in the Trial Protocol in Supplement 1.

Consent was requested for all study interventions and assessments. Informed consent of patients was obtained by the participating surgeons at least 24 hours before the intervention. Ethical approval was obtained from the regional ethical committee, Comité de Protection des Personnes, Sud Méditerranée I. The study was registered in ClinicalTrials.gov (NCT02892253).

Randomization and Masking

Patients were assigned to 1 of the 2 groups by a random 1:1 allocation sequence. The allocation sequence was generated using a block-randomization method (10 patients for each block), using SAS version 9.4 software (SAS Institute). The random allocation sequence was generated by the statistician (G.P.) and given to each center. Participants were enrolled by the surgeons, who also assigned participants to the interventions. The assignment was made just before the surgeon started the intervention. The intervention was performed during general anesthesia. Patients were blinded to the intervention until the first postoperative visit, which was 10 days after surgery. Clinicians inside the operating room were aware of the intervention, while other clinicians in the surgical unit, such as nurses, were blinded to the intervention. The assessment of the primary outcome (the postoperative hypocalcemia rate) was blinded, because calcemia was measured independently of the allocated groups.

Procedures

In the standard-thyroidectomy group, a conventional extracapsular dissection of the thyroid gland was performed in which the PGs were meticulously preserved when they were visible, although they were not extensively searched for. In the NIRAF group, after a first visual inspection, operating room lights were turned off, and then the surgeon examined the surgical field seeking each thyroid lobe using the Fluobeam 800 system (Fluoptics). After having visually verified the nature of the fluorescent spots provided by the imaging system, surgery was resumed conventionally. All total thyroidectomies were performed by experienced surgeons (define as those who completed >25 thyroidectomies/year).[16]

Outcomes

Postoperative hypocalcemia, the primary outcome, was defined as a corrected calcium level of less than 8.0 mg/dL during hospitalization. We used the Payne formula to calculate corrected calcium level: Corrected calcium (in mg/dL) = measured calcium (in mg/dL) − 0.8 × (albumin [in g/dL] − 40).[17] All patients with postoperative hypocalcemia were treated with oral calcium. Oral calcitriol (rocaltrol) with or without injected calcium gluconate was prescribed when needed, depending on calcium level and clinical signs. We used the most widely admitted cut-off of 6 months to differentiate between transient and permanent postoperative hypocalcemia, [18] so that follow-up for patients with hypocalcemia was for up to 6 months to assess the rate of permanent hypoparathyroidism. No patient in this study received preoperative preventive treatment by rocaltrol or oral calcium prior to surgery.

Secondary outcomes were the number of PGs identified, the rate of PG autotransplantation, and the rate of inadvertent PG resection. Autotransplantation was decided on when the PGs appeared to be disconnected from their vascular supply. Inadvertent PG resection was reported by the pathologists.

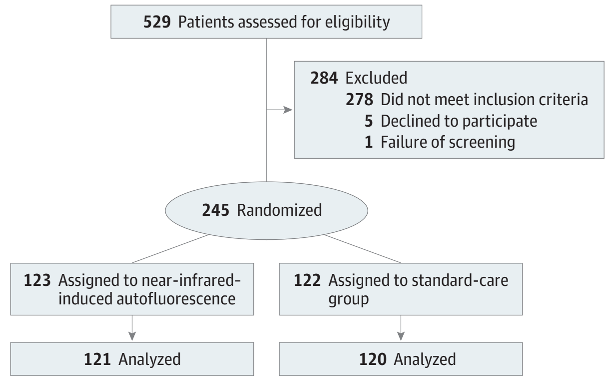
The data collected included age, sex ratio, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), preoperative diagnosis, preoperative corrected calcium level, preoperative parathyroid hormone (PTH) level, number of PGs identified by the surgeon, number of PGs identified by the NIRAF system, number of PGs identified by the system before the naked eye could see them, number of autotransplanted PGs, duration of the operation, corrected calcium level during hospitalization, PTH level at postoperative day 1 (considered in the normal range when it was ≥15 pg/mL; to convert to ng/L, multiply by 1.0), prescription of a substitutive treatment by oral calcium only or oral calcium plus vitamin D (with or without intravenous calcium gluconate), duration of postoperative hypocalcemia, occurrence of other surgical complications, number of inadvertently resected PGs, thyroid weight, size of the largest nodule, and final diagnosis.

Statistical Analysis

First, the sample size of 150 patients (75 in each group) was calculated to achieve 90% power to detect a difference of hypocalcemia rates of at least 20% in favor of NIRAF. The hypocalcemia rate was assumed to be 25% in the standard-thyroidectomy group.[1] The sample-size calculation was based on the intention-to-treat cohort (a 1-sided hypothesis with a significance level of .025). A first interim analysis was planned to estimate the hypocalcemia rate difference after 75 patients and conducted to upgrade the sample size to 300 patients. A second interim analysis was performed after 150 patients. For all interim analyses, the Peto approach was used to correct the α risk; the same low threshold was used at each interim analysis (ie, $P < .001$ for the stopping rule), so that the final analysis was performed using a .023 level of significance.[19] The total sample size was then fixed at 242 after this second interim analysis (121 patients in each group).

Continuous variables were reported using medians and interquartile ranges (IQRs); categorical variables were reported using counts, percentages, and their 95% CIs. Initial crude comparisons of the NIRAF and standard-thyroidectomy groups for primary and secondary outcomes were done using 1-sided χ^2 or Fisher tests for count variables and the Wilcoxon test for continuous variables. The significance level was .023, taking into account the Peto correction. To analyze risk factors associated with postoperative hypocalcemia, we then used negative-binomial generalized linear mixed models, aiming to account for the heterogeneity of centers and surgeons included in this multicenter trial. The intervention group (NIRAF or standard care), final diagnosis (a malignant or benign mass), age, BMI, and preoperative corrected calcium were defined as fixed effects of the model. Surgeons and centers were modeled as random-effect variables, with surgeons nested within centers. For univariate analyses of each factor, including the intervention group, we systematically included surgeons nested within centers as random effect variables in models where each factor was modeled as a unique fixed-effect variable. This led to estimates of the crude odds ratios and their 95% CIs. For the multivariate analysis, we included the fixed-effect variables for which *P* values were less than .25, the intervention group, final diagnosis (a malignant or benign mass), age, BMI, and preoperative corrected calcium, as fixed-effect variables, and surgeons nested within centers as random-effect variables, which lead to estimates of the adjusted odds ratios and their 95% CIs. Statistical computations were performed using SAS version 9.4 software (SAS Institute).

Figure. Trial Flowchart



Results

Overall, 245 patients were randomly assigned: 123 in the NIRAF group and 122 in the standard-care group (**Figure**). A total of 241 patients were analyzed for the primary outcome: 121 in the NIRAF group and 120 in the standard-care group. There were no losses in the follow-up period, but 4 exclusions occurred after randomization: 2 patients (1 in the NIRAF group and 1 in the standard-care group) because of patient decisions after consent forms were signed; and 1 patient (in the NIRAF group) because a lobectomy was performed instead of the total thyroidectomy initially planned. One final patient in the standard-care group was subsequently excluded after the

Table 1. Baseline Characteristics of Participants

Characteristic	Patients, No. (%) Near Infrared-Induced Autofluorescence (n = 121)	Standard Care (n = 120)	Total (N = 241)
Preoperative Variables			
Sex			
Male	25 (20.7)	24 (20.0)	49 (20.3)
Female	96 (79.3)	95 (79.2)	191 (79.3)
Not determined	0	1 (0.8)	1 (0.4)
Age, median (IQR), y	52.5 (46.0-63.0)	51.0 (45.0-64.0)	52.0 (45.0-64.0)
BMI, median (IQR)	27.0 (22.5-30.0)	26.5 (23.0-30.5)	27.0 (23.0-30.0)
Preoperative corrected calcium, median (IQR), mg/dL	9.30 (9.10-9.50)	9.30 (9.03-9.50)	9.30 (9.10-9.50)
Preoperative parathyroid hormone, median (IQR), pg/mL	48.5 (41.0-66.0)	45.0 (35.0-65.5)	47.0 (38.0-66.0)
Diagnosis			
Cancer	20 (16.5)	18 (15.0)	38 (15.8)
Multinodular goiter	63 (52.1)	73 (60.8)	136 (56.4)
Toxic multinodular goiter	4 (3.3)	8 (6.7)	12 (5.0)
Graves disease	33 (27.3)	20 (16.7)	53 (22.0)
Thyroiditis	0	1 (0.8)	1 (0.4)
Not determined	1(0.8)	0	1(0.4)
Operative Variables			
Duration of operation, median (IQR), min	99 (88-114)	91 (77-103)	94 (81-107)
Patients who were operated on per center, No.			
1	97	99	196
2	16	16	32
3	8	5	13
Postoperative Variables			
Specimen weight, median (IQR), g	41.1 (24.0-68.0)	35.6 (23.4-58.0)	37.1 (24.0-64.5)
Size of the largest nodule, median (IQR), mm	21.5 (13.5-35.0)	25.0 (15.0-32.0)	25.0 (15.0-35.0)
Final diagnosis			
Benign condition	90 (74.4)	95 (79.2)	185 (76.8)
Malignant condition	31 (25.6)	25 (20.8)	56 (23.2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

SI conversion factor: To convert calcium to mmol/L, multiply by 0.25; to convert parathyroid hormone to ng/L, multiply by 1.

groups were already constituted, because a mild biological primary hyperparathyroidism, which had not been detected at an initial screening, was identified retrospectively. The study groups were well balanced on baseline characteristics (**Table 1**).

In the initial analysis, postoperative hypocalcemia rate was significantly lower in the NIRAF group (11 of 121 patients; 9.1% [95% CI, 4.0%-14.2%]) than in the standard-care group (26 of 120 patients; 21.7% [95% CI, 14.3%-29.0%]; *P* = .007) (**Table 2**). Only 2 patients (from the standard-care group) experienced a confirmed permanent hypocalcemia.

After accounting for center and surgeon heterogeneity and adjusting for confounders using a multivariate generalized linear mixed model, the use of NIRAF was associated with a significantly lower risk of postoperative hypocalcemia than nonuse (adjusted odds ratio, 0.35 [95% CI, 0.15-0.83]; *P* = .017) (**Table 3**). Final diagnosis, age, BMI, and preoperative corrected calcium levels were not significantly associated with postoperative hypocalcemia (Table 3).

Analysis of secondary outcomes showed that the calcium nadir difference was numerically but not significantly lower in the standard-care group (median [IQR] calcemia, 8.74 [8.25-9.03] mg/dL) than in the NIRAF group (median [IQR], 8.86 [8.62-9.18] mg/dL; *P* = .025) (Table 2). The PTH concentration at postoperative day 1 was not significantly lower in the standard-care group (median [IQR], 28.6 [12.0-46.5] pg/mL) than in the NIRAF group (median [IQR], 33.2 [21.9-48.1] pg/mL) (Table 2). There was a significant difference in the number of identified PGs between the 2 groups: the rate of patients with 4 identified PGs was higher in the NIRAF group (57 of 121 patients; 47.1% [95% CI, 38.5%-56.4%]) compared with the standard-care group (23 of 120 patients; 19.2% [95% CI, 12.1%-26.2%]; *P* < .001); conversely, the rate of patients with 1 or 2 identified PGs was lower in the NIRAF group (1 PG: 2 patients; 1.7% [95% CI, 0.0%-4.0%]; 2 PGs: 20 patients; 16.5% [95% CI, 10.0%-23.3%]) compared with the standard-care group (1 PG: 19 patients; 1.7% [95% CI, 0.0%-4.0%]; 2 PGs: 40; 33.3% [95% CI, 24.9%-41.8%]; Table 2). In the NIRAF group, 241 of the 391 identified PGs (61.6%) were identified by the near-infrared camera before the surgeon saw them with a naked eye (ie, without the use of the

Table 2. Primary and Secondary Outcomes

Characteristic	No. (%) [95% CI] Near Infrared-Induced Autofluorescence (n = 121)	Standard Care (n = 120)	*P* Value
Primary outcome			
Postoperative hypocalcemia at postoperative day 1 or 2	11 (9.1) [4.0-14.2]	26 (21.7) [14.3-29.0]	.007[a]
Secondary outcomes			
Nadir of postoperative corrected calcium, median (IQR), mg/dL	8.86 (8.62-9.18)	8.74 (8.25-9.03)	.025[b]
Parathyroid hormone at postoperative day 1, median (IQR), pg/mL	33.2 (21.9-48.1)	28.6 (12.0-46.5)	.07[b]
Supplementation			
Calcium only	11 (9.1) [4.0-14.2]	24 (20.0) [12.8-27.2]	.016[a]
Calcium and vitamin D	6 (5.0) [1.1-8.9]	8 (6.7) [2.9-12.8]	.78[c]
Identified parathyroid glands, No.			
0	1 (0.8) [0.0-2.5]	2 (1.7) [0.0-4.0]	<.001[a]
1	2 (1.7) [0.0-4]	19 (15.8) [9.3-22.4]	
2	20 (16.5) [10.0-23.3]	40 (33.3) [24.9-41.8]	
3	40 (33.1) [24.9-41.8]	36 (30.0) [21.8-38.2]	
4	57 (47.1) [38.5-56.4]	23 (19.2) [12.1-26.2]	
Not determined	1 (0.8) [0-2.5]	NA	
Inadvertently resected parathyroid glands, No.	3 (2.5) [0-5.2]	14 (11.7) [5.9-17.4]	.006[c]
Autotransplanted parathyroid glands, No.			
0	116 (95.9) [93.5-99.9]	104 (86.7) [80.6-92.8]	.009[a]
≥1	4 (3.3) [0.1-6.6]	16 (13.3) [7.3-19.4]	
Not determined	1 (0.8) [0.0-2.5]		
Permanent hypocalcemia	0	2 (1.7) [0.0-4.0]	.15[c]
Nonparathyroid complication	3 (2.5) [0.0-5.3]	3 (2.5) [0.0-5.3]	>.99[c]
Duration of hospitalization, median (IQR), d	3 (3.0-4.0)	3.0 (3.0-4.0)	.98[b]

Abbreviation: IQR, interquartile range; NA, not applicable.

SI conversion factor: To convert calcium to mmol/L, multiply by 0.25; to convert parathyroid hormone to ng/L, multiply by 1.

[a] χ^2 test applied.

[b] Wilcoxon test applied.

[c] Fisher test applied.

Table 3. Univariate and Multivariate Analysis for Factors Associated With Postoperative Hypocalcemia[a]

Factor	Univariate Analysis Odds Ratio (95% CI)	Univariate Analysis *P* Value	Multivariate Analysis Odds Ratio (95% CI)	Multivariate Analysis *P* Value
Use of near infrared–induced autofluorescence camera[b]	0.35 (0.17-0.71)	.004	0.35 (0.15-0.83)	.017
Final diagnosis[c]	1.93 (1.16-3.22)	.01	1.97 (.97-4.04)	.06
Age per y	0.98 (0.96-1.00)	.10	0.98 (0.95-1.02)	.29
BMI	0.95 (0.87-1.04)	.25	0.94 (0.82-1.07)	.33
Preoperative corrected calcium, per mg/dL	0.97 (0.91-1.05)	.47	1.00 (0.95-1.05)	.88

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factor: To convert calcium to mmol/L, multiply by 0.25.

[a] Univariate and multivariate analyses using generalized linear mixed models with a negative binomial distribution. Surgeons and centers were modeled as random-effect variables, with surgeons nested within centers.

[b] Reference: standard thyroidectomy.

[c] Comparing malignant vs benign findings.

device). Parathyroid autotransplantation was significantly less frequent in the NIRAF group (3.3% [95% CI, 0.1%-6.6%]) than in the standard-care group (13.3% [95% CI, 7.3%-19.4%]; *P* = .009) (Table 2). None of the 4 autotransplanted PGs from the NIRAF group were identified after they were already removed from the patient; they were all identified before removal but were impossible to keep in situ during dissection. Similarly, the number of inadvertently resected PGs was significantly lower in the NIRAF group (n = 3; 2.5% [95% CI, 0%-5.3%]) than in the standard-care group (n = 14; 11.7% [95% CI, 5.9%-17.4%]; *P* = .006) (Table 2).

The duration of operations was significantly longer in the NIRAF group than in the standard-care group (median [IQR] time, 99 [88-114] minutes vs 91 [77-103] minutes; *P* = .002). There was no difference in length of hospital stay nor in other nonparathyroid complications between the 2 groups (Table 2). There was no harm or unintended effect relative to the use of the Fluobeam in any group.

Discussion

This randomized clinical study, which to our knowledge is the first on this topic to be conducted in multiple centers, found an increased rate of identification and preservation of the parathyroid glands and a lower rate of early postoperative hypocalcemia with the use of NIRAF. In this study, we observed a greater number of identified PGs in a greater number of patients with the use of NIRAF, which is consistent with results from Falco et al,[9] who reported a significantly higher mean number of identified PGs per patient using NIRAF than in standard thyroidectomy. Furthermore, PGs were identified by the NIRAF system before the surgeon could see them in nearly two-thirds of the patients. This is concordant with a study by Kahramghil et al,[13] which showed that 37% to 67% of PGs were perceived by NIRAF systems more quickly than with a naked eye, and a study by Kim et al,[12] which found that up to 93% of PGs could be detected by NIRAF before the naked eye detected them. The significant reduction in the autotransplantation rate and inadvertent resection rate, which are both risk factors for postoperative hypocalcemia,[18] are in line with the results obtained in the previous single-center, before-and-after study, in which we observed a similar range of reduction in autotransplantation rates (from 25% to 2%) and inadvertent resection rate (from 7% to 1%) using NIRAF.[14] Importantly, the reduction in postoperative hypocalcemia rates (9% in the NIRAF group vs 22% after conventional surgery) that we observed in the current trial mirrors both results we already reported[14] as well as the recent results from Dip et al,[15] who reported a 50% relative reduction in the hypocalcemia rate and a significant difference in the number of patients with profound hypocalcemia (<7.6 mg/dL). However, their trial was conducted at a single center, their primary outcome (postoperative hypocalcemia rate, defined as a calcium level <8.0 mg/dL) was not significantly reduced by NIRAF, and heterogeneity between the 4 surgeons involved in the study was not taken into account in their statistical analyses.

Our interpretation of the positive effect measured with NIRAF is that the images provided at an early stage help surgeons to prepare for a better preservation of the PGs. Indeed, during conventional thyroidectomy, because PGs have a large area of dispersion, surgeons have to be constantly attentive to avoid damaging these tiny, barely distinguishable glands, and when surgical difficulty is high (for patient-dependent or surgeon-dependent reasons), lapses of attention may occur, because capacities of mental mobilization are limited.[20] Moreover, these lapses of attention do occur; otherwise, it would be difficult to explain why thyroid surgeons, who are all aware of parathyroid risk and know how to recognize PGs, can have such high and heterogenous rates of parathyroid autotransplantation, inadvertent resection, and postoperative hypocalcemia rates.[21] The NIRAF procedure obliges the surgeon to interrupt the operation for a few minutes dedicated to the PGs. This procedure can produce images to focus on and may allow surgeons to efficiently mobilize their attention and mentally plan the best possible parathyroid dissection. This whole process may also explain the increased length of operating duration in the NIRAF group observed in this study.

Limitations

This multicenter trial exhibited discrepancies between patient inclusions in the different centers, with 1 center including 81% of all patients. These differences are explained by inclusion difficulties in certain centers, as well as common variability of surgical volumes between the centers.[16] To avoid this bias and take into account this heterogeneity, we selected only experienced surgeons, and we used generalized linear mixed models including surgeons nested in centers as a random effect that confirmed the consistency of our results in favor of the use of NIRAF.

Conclusions

In conclusion, this study shows the clinical utility of autofluorescence as an adjunct to surgical assessment for the reduction of postoperative hypocalcemia risk after total thyroidectomy. This process appears to work through improvement of identification and preservation of the parathyroid glands.

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Author Contributions: Dr Benmiloud had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Benmiloud was the principal investigator.
Concept and design: Benmiloud, Chéreau, Gaudart, Chiche, Rebaudet.
Acquisition, analysis, or interpretation of data: All authors.
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Administrative, technical, or material support: Benmiloud, Chéreau, Chiche.
Supervision: Benmiloud, Gras, Gillot, Turrin, Chiche, Rebaudet.

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