Randomized Controlled Trial Comparing White Light with Near-Infrared Autofluorescence for Parathyroid Gland Identification During Total Thyroidectomy

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BACKGROUND: Parathyroid glands are difficult to identify during total thyroidectomies, and accidental resection can lead to problematic postoperative hypocalcemia. Our main goals were to evaluate the effectiveness of using near-infrared light (NIRL) autofluorescence intraoperatively for parathyroid gland identification and to measure its impact on postoperative hypocalcemia incidence.

STUDY DESIGN: Total thyroidectomies were performed on 170 patients with different thyroid pathologies, block-randomized (1:1) into 2 equal groups. Among controls, traditional overhead white light (WL) was used throughout. In the experimental group, NIRL was used to enhance parathyroid gland recognition before thyroid dissection. The number of parathyroid glands identified was compared after thyroid dissection in controls using WL vs pre-dissection in the experimental using NIRL and with WL vs NIRL before thyroid dissection in the experimental group. Postoperative serum calcium levels and hypocalcemia rates were compared.

RESULTS: The mean number of parathyroid glands identified pre-dissection with NIRL was the same identified post-dissection with WL (3.5 vs 3.6). In the experimental group, converting from WL to NIRL increased the number of glands detected from 2.6 to 3.5 ($p < 0.001$), and revealed at least 1 previously missed gland in 67.1% of patients. Calcium levels $\leq$7.5 mg/dL were one-tenth as common in the NIRL group ($p = 0.005$). The adjusted odds of hypocalcemia developing increased by 15% for every 5-g increase in thyroid gland weight (odds ratio 1.15; 95% CI 1.06 to 1.25). All hypocalcemia resolved within 6 months.

CONCLUSIONS: Using NIRL during thyroidectomy increases intraoperative identification of parathyroid glands, enhances their detection before thyroid dissection, and decreases the incidence of postoperative hypocalcemia. (J Am Coll Surg 2019;228:744–751. © 2019 Published by Elsevier Inc. on behalf of the American College of Surgeons.)

Postoperative hypocalcemia is a frequent complication of total thyroidectomy.[1] The incidence of this complication reported in the literature is between 18% and 59%.[2-6] The most common reason for hypocalcemia is inadvertent damage to parathyroid gland circulation, which, in turn, is secondary to the glands' small size, soft texture, and variable location and number. This damage typically occurs during dissection of the thyroid capsule.[7,8] Consequently, it is preferable for surgeons to accurately identify the position and number of parathyroid glands before commencing resection.

Different techniques have been proposed to aid in parathyroid gland identification.[9-11] Paras and colleagues[12] examined the use of autofluorescence with the Raman technique to differentiate parathyroid glands from other tissues and identified a statistically higher number of parathyroid glands when near-infrared light (NIRL) was used relative to standard white light (WL).[13-15] Variables like patient sex, age,

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and primary diagnosis exerted no influence on the fluorescent intensity of surrounding tissues, including thyroid.[16] However, to our knowledge, few controlled data have been published documenting actual reductions in post-thyroidectomy hypocalcemia incidence when NIRL is used as a parathyroid identification tool, and these were within- rather than between-subject comparisons.[16]

The current randomized controlled trial had 2 primary aims: to compare the effectiveness of using NIRL with WL during total thyroidectomies to identify parathyroid glands earlier in the procedure, and to evaluate the effectiveness of NIRL again relative to WL as a means to reduce the incidence of postoperative hypocalcemia. As a secondary objective, we sought to identify predictors of postoperative hypocalcemia.

METHODS

After receiving IRB approval and in accordance with the Helsinki declaration, a prospective, randomized controlled clinical trial was conducted between January 2017 and August 2017, involving 170 patients who underwent total thyroidectomy. Four trained head and neck surgeons at the Instituto Argentino de Diagnostico y Tratamiento, Buenos Aires, Argentina, performed all procedures. To be eligible for the study, patients had to be 18 years or older, have a clinical indication for total thyroidectomy, have no preoperative hypocalcemia or hypercalcemia or any condition that would predispose them to either, and have provided written consent to participate. Patients who had undergone any previous neck operation, candidates for thyroid lobectomy, and those requiring neck dissection were excluded (Fig. 1).

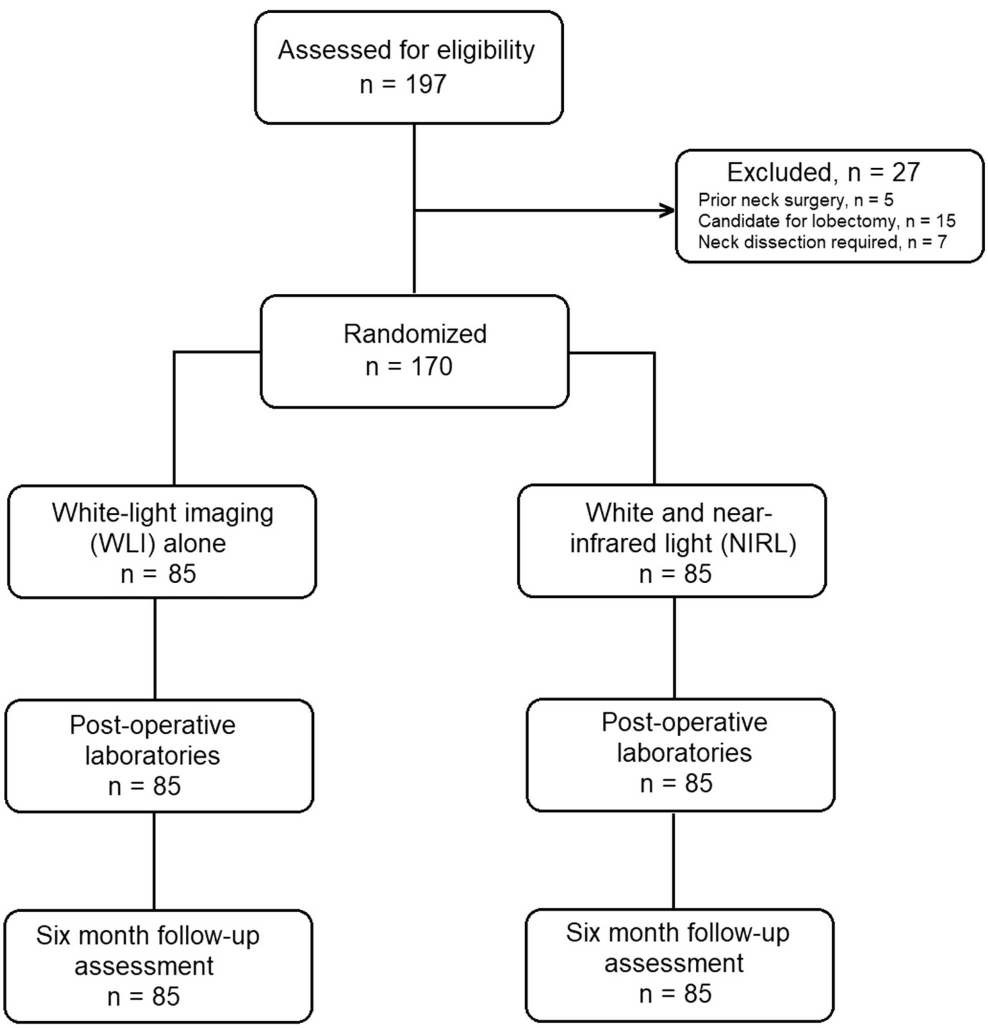

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study.

Patients were block-randomized by one of the authors into 2 groups in a 1:1 ratio using a computer-generated random sequence of odd and even numbers, yielding 85 participants in each group. For patients in the control group, surgeons only used WL and anatomical landmarks throughout the procedure to identify the parathyroid glands. Meanwhile, to identify the parathyroid glands in the experimental (NIRL) group, both WL and NIRL were used to illuminate the surgical field. This occurred twice—after retracting the thyroid gland but before thyroid dissection, the latter involving opening the sternohyoid and sternothyroid muscles and medializing the thyroid gland somewhat, but not yet having dissected the capsule; and after thyroid resection. All participating surgeons performed the operations in both treatment groups.

Outcomes measures

The outcome measures of interest were total number of parathyroid glands identified by the surgeon using WL vs NIRL; postoperative serum calcium level; presence vs absence of postoperative hypocalcemia and symptomatic postoperative hypocalcemia; thyroid gland weight in grams; need for postoperative hospitalization; mean hospital stay in days; and need for calcium replacement.

Equipment

The Fluobeam 800 system (Fluoptics) was used to evaluate parathyroid gland fluorescence. It consists of a filtered camera that has both a WL and NIRL source, as well as a computerized screen that displays fluorescence images in real time. White light has wavelengths limited to the 400 to 700 nm range. Near-infrared light, meanwhile, is emitted by a class 1 laser, which is safe for human eyes, at 750 nm with a power of 5 mW/cm^2, and is directed toward the surgical field. The NIRL is captured by parathyroid tissue that responds by re-emitting light of the same spectrum, but with a longer wavelength (830 nm). A filtered camera that detects only wavelengths between 800 and 900 nm detects this longer parathyroid-emitted wavelength. On the screen, the parathyroid glands appear as small, white, round, well-delineated spots (Fig. 2). Once all parathyroid glands that could be identified were identified, the surgeon proceeded with thyroid capsule dissection.

All 4 participating surgeons had been trained in the use of the Fluobeam system, and all had extensive experience performing thyroidectomy procedures. Data on the number of parathyroid glands identified were recorded intraoperatively. Images were analyzed using IMAGE J software (NIH). Parathyroid gland images and parathyroid gland tissue confirmed by the 4 participating surgeons were compared to identify instances of agreement and disagreement, including the number of glands identified by each method. The time required to use the equipment was also recorded.

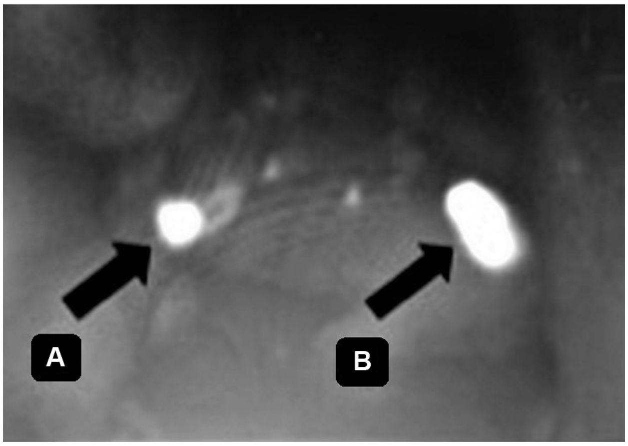

Figure 2. Parathyroid glands visualized under infrared light using the Fluobeam 800 system. (A, B) Parathyroid glands; note that they are small, bright white, roughly circular, and well-delineated.

Postoperatively, the combined weight of all resected thyroid gland tissue was measured and histopathologic analysis performed with frozen sections to identify any unintentionally resected parathyroid tissue.

Each patient's serum calcium level was measured on postoperative day 1, as well as 1 week and 6 months post procedure. Hypocalcemia was operationally defined as a serum calcium level <8.0 mg/dL. Asymptomatic patients with a serum calcium level between 7.6 and 7.9 mg/dL were treated with calcium oral replacement. Patients whose serum calcium level was <7.6 mg/dL and patients whose hypocalcemia was considered symptomatic were treated with intravenously administrated calcium replacement and monitored closely. Postoperative hypocalcemia was considered persistent if the serum calcium remained <8.0 mg/dL at the 6-month follow-up visit.

Statistical analysis

Because the main end point of interest in this study was the incidence of postoperative hypocalcemia, and the primary objective was to compare this incidence among patients in whom NIRL was used vs not used, hypocalcemia incidence was used to estimate our sample size requirement. A baseline estimated incidence of 40% was used, drawing from 4 recently published international studies.[2,4-6] To detect a 50% relative reduction in hypocalcemia, from 40% down to an incidence of 20%, with 95% confidence ($\alpha = 0.05$) and 90% power ($\beta = 0.90$), 79 subjects were necessary in each group. This number was rounded up to 85 per group to account for potential subject loss.

With respect to the number of parathyroid glands visualized, 2 comparisons were performed. The first was to compare the final number of glands identified among controls after thyroid dissection against the number identified before thyroid dissection using NIRL in the experimental group. The second comparison was of the number of parathyroid glands identified using WL vs NIRL in the experimental (NIRL) group before thyroid dissection. Both comparisons were conducted using unpaired Student's *t*-tests.

To compare the 2 treatment groups with respect to the incidence of postoperative hypocalcemia, symptomatic hypocalcemia, hypocalcemia requiring short-term and long-term calcium supplementation, and hospitalization, Pearson's chi-square analysis was performed and odds ratios calculated with 95% confidence intervals. Additional secondary outcomes of interest were postoperative serum calcium level and mean hospital stay (in days), which were also compared between the 2 treatment groups using non-paired Student's *t*-tests, with degrees of freedom adjusted for non-normally distributed data.

For multivariable analysis, simple linear regression and binary logistic regression analysis were conducted to identify covariates associated with the number of parathyroid glands identified and the presence vs absence of postoperative hypocalcemia, respectively.

All analyses were 2-tailed, with $p \leq 0.05$ set as the criterion for statistical significance, depending on the test being performed. All analyses were conducted using SPSS, version 25.0 (SPSS Inc) by a doctoral-level biostatistician.

RESULTS

A total of 170 adults enrolled in the study. All had consented to undergo total thyroidectomy for a variety of primary conditions; the 2 most common were cancer (48.2%) and goiter (38.8%). Seventy-four percent of the patients were female, and the overall mean age was 47.3 years (SD 13.6 years). As summarized in Table 1, the 2 treatment groups (nonexperimental and NIRL) were clinically similar in all baseline characteristics.

The total time that the Fluobeam 800 system was used to evaluate parathyroid gland fluorescence ranged from 3 minutes to 5 minutes (median 4 minutes). No difference was observed in the number of parathyroid glands identified in controls with WL after thyroid dissection (3.6; SD 0.57) and the number identified in the NIRL group using NIRL before thyroid dissection (3.5; SD 0.78; NS) (Table 2). However, in the NIRL group, the number of parathyroid glands visualized before thyroid dissection increased from 2.6 (SD 0.85) to 3.5 (SD 0.78) when WL was toggled to NIRL ($p < 0.001$) (Fig. 3). In addition, either 1 (n = 31) or 2 (n = 26) additional parathyroid glands were identified in two-thirds (67.1%) of NIRL group subjects during the process of toggling from WL to NIRL (Fig. 4).

Table 1. Demographics and Baseline Clinical Characteristics of the Sample, Overall and by Subject Group

Characteristic	All (n = 170)	Controls (n = 85)	NIRL (n = 85)
Age, y, mean (SD)	47.3 (13.6)	45.8 (13.7)	48.7 (13.5)
Sex, n (%)			
Female	126 (74.1)	59 (69.4)	67 (78.8)
Male	44 (25.9)	26 (30.6)	18 (21.2)
Primary diagnosis, n (%)			
Thyroid cancer	82 (48.2)	44 (51.8)	38 (44.7)
Goiter	66 (38.8)	29 (34.1)	37 (43.5)
Follicular adenoma	16 (9.4)	7 (8.2)	9 (10.6)
Hyperthyroidism	5 (2.9)	4 (4.7)	1 (1.2)
Hurthle cell cancer	1 (0.6)	1 (1.2)	0 (0.0)

NIRL, near-infrared light.

In 4 patients, autotransplantation of parathyroid glands was needed when parathyroid tissue was recognized with NIRL on the thyroid gland surface after the thyroidectomy had been performed. Parathyroid tissue was confirmed by frozen section before re-implantation. On simple linear regression analysis, none of the evaluated covariates exerted a statistically significant influence on the number of parathyroid glands visualized using either method.

Postoperatively, the incidence of hypocalcemia was 8.2% (n = 7) in the NIRL group vs 16.5% (n = 14) among controls, a 50% relative reduction in the NIRL group that nonetheless just failed to achieve borderline statistical significance (chi-square 2.66, degrees of freedom [df] 1; $p < 0.103$) (Table 2). However, more severe hypocalcemia, defined as a serum calcium level ≤7.5 mg/dL, was observed in just 1.2% in the NIRL visualization group vs 11.8% in the WL group, a difference that was highly significant (chi-square 7.87, df 2; $p = 0.005$) (Fig. 5). In the NIRL group, the minimum calcium level recorded postoperatively was 7.5 mg/dL. Conversely, in the WL group, 6 patients had a serum calcium level <7.5 mg/dL; the lowest recorded level was 6.8 mg/dL. Overall mean postoperative serum calcium level was also significantly higher in those in the NIRL group ($p = 0.009$). On the other hand, symptomatic hypocalcemia developed in only 1 and 2 subjects in the WL and NIRL groups, respectively (chi square 0.34, df 1; $p = 0.56$), and long-term calcium replacement, beyond hospitalization, was deemed necessary in just 1 subject per group (odds ratio 1.00; $p = 1.00$).

Table 2. Outcomes, Comparing Patients in the White Light Only and White Light Plus Near-Infrared Light Group

Outcome	White light (n = 85)	Near-infrared light (n = 85)	Test statistic		p Value
			Student's *t*-test (df)	Chi-square (df)	
PT glands detected, pre-dissection, mean (SD)	NA	2.6 (0.85)	NA	NA	NA
PT glands detected, post-dissection, mean (SD)	3.6 (0.57)	3.5 (0.78)	1.01 (168)	—	0.32
Thyroid gland weight, g, mean	25.5	24.6	1.38 (168)	—	0.17
Postoperative serum calcium, mg/dL, mean	8.39	8.65	2.65 (168)	—	0.009*
Postoperative serum calcium <8.0 mg/dL, %	16.5	8.2	—	—	0.103
Postoperative serum calcium <7.6 mg/dL, %	11.8	1.2	—	7.87 (1)	0.005*
Symptomatic postoperative hypocalcemia, %	1.2	2.4	—	0.34	0.56
Long-term treatment for hypocalcemia, %	1.2	1.2	—	0.00	1.00
Postoperative hospitalization required, %	14.1	7.1	—	2.24 (1)	0.14
Length of hospital stay, d, mean	0.26	0.11	1.75 (143.9)†	—	0.08

*Significant.
†Degrees of freedom adjusted for non-normality of data.
df, degrees of freedom; NA, not applicable; PT, parathyroid.

Six (7%) patients in the NIRL group required hospitalization vs 12 (14%) controls (chi-square 2.24, df 1; p = 0.14), and the mean days of hospitalization were 0.11 vs 0.26 in the 2 groups, respectively (t = 1.75, adjusted df = 143.9; p = 0.08); neither difference was statistically significant. No patient experienced permanent hypocalcemia, with serum calcium levels ≥8.0 mg/dL in all patients by 6 months of follow-up. No patient was lost to follow-up.

On binary regression analysis, the only covariable that was statistically predictive of postoperative hypocalcemia was thyroid gland weight (p = 0.013), with a mean 15.1% increased rate of hypocalcemia for every 5.0-g increase in thyroid weight (adjusted odds ratio 1.15; 95% CI 1.06 to 1.25; p = 0.004). Thyroid weight also was the only predictor we identified that was predictive of a postoperative serum calcium level ≤7.5 mg/dL (p = 0.010).

DISCUSSION

To our knowledge, this is the first randomized controlled study in which NIRL was evaluated by several surgeons as an intraoperative tool to enhance post-thyroidectomy outcomes. White light has long been used to aid in the identification of parathyroid glands during total thyroidectomies. However, its use sometimes falls short, resulting in inadvertent damage or resection of parathyroid tissue, altered regulation of serum calcium levels, and potential lifelong morbidity.[17] To solve this problem, many researchers and medical practitioners have proposed using a fluorescence guidance system consisting of NIRL and IV administration of a fluorescent dye. Among the dyes used has been methylene blue,[18] which has been shown to enhance parathyroid gland visibility intraoperatively; however, it also can be a source of side effects.[19] To

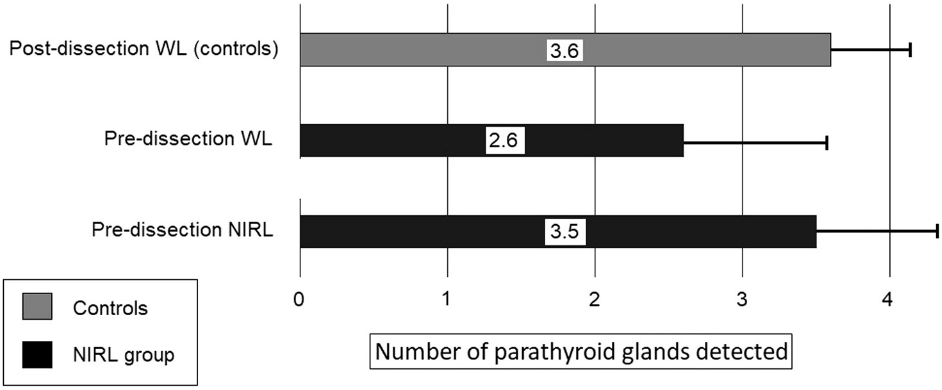

Figure 3. Mean number of parathyroid glands detected after thyroid dissection with white light (WL), and before thyroid dissection with WL and near-infrared light (NIRL). Note how there is virtually no difference in the number detected pre-dissection under NIRL and post-dissection with WL. However, toggling from WL to NIRL pre-dissection resulted in increased gland detection of roughly 0.9 glands per subject.

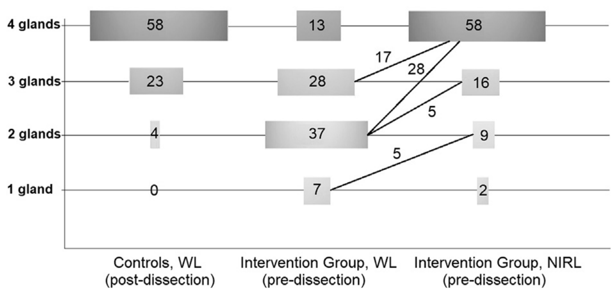

Figure 4. Number of parathyroid glands detected by subject group and light source. Before thyroid dissection in the active intervention group, toggling from white light (WL) to near-infrared light (NIRL) resulted in the detection of either 1 (n = 28) or 2 (n = 28) more glands in 56 of 85 subjects (66%).

avoid this, others have used indocyanine green.[20,21] However, although some reports have been encouraging, IV administration of indocyanine green confirms the perfusion but not the location of parathyroid tissue because indocyanine green is also taken up in relatively high concentrations by thyroid tissue, rendering specific visualization of parathyroid tissue difficult.[22]

Others have proposed using parathyroid glands' own unique autofluorescent properties for intraoperative visualization.[12,13] Shinden and colleagues[23] demonstrated empirically that when surgeons use a photodynamic eye system, they can distinguish parathyroid glands from the intrinsic fluorescence of neighboring tissues because parathyroid glands exhibit a higher level of intrinsic fluorescence than surrounding lymph nodes, thyroid tissue, and fat.[23] Again without administering any dye, Kim and colleagues[24] reported that they were able to benefit from the intrinsic fluorophores of parathyroid tissue to preoperatively identify all 16 parathyroid glands they sought in their patients.[25] Falco and colleagues[16] have also reported that parathyroid visualization increased when NIRL, rather than WL, was used ($p = 0.026$); in their study, consistent with our own, covariates like patient sex, age, and primary diagnosis exerted no influence on the intensity of fluorescence in tissues surrounding the parathyroid glands, including the thyroid glands and other adjacent tissues.[16]

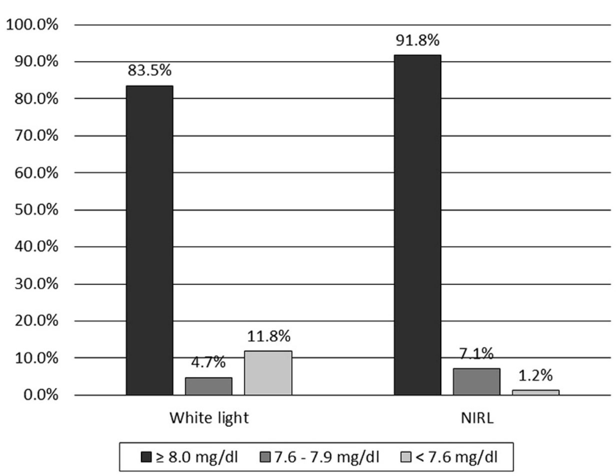

Figure 5. Postoperative day 1 serum calcium levels in patients undergoing thyroidectomy under white light (n = 85) vs near-infrared light (NIRL) (n = 85). In the white-light group, 10 patients had a postoperative serum calcium level <7.6 mg/dL, vs just 1 such patient in the NIRL group.

In the current study, we discovered, first, that surgeons were able to identify as many parathyroid glands using NIRL before thyroid dissection as they were able to identify under WL after the thyroidectomy was completed; and, second, that using NIRL before thyroid dissection was significantly more effective at identifying parathyroid glands than using WL, with NIRL revealing at least 1 otherwise-missed gland in 2 of every 3 patients, and a mean of 1.0 missed gland per patient overall. We also observed that the incidence of hypocalcemia postoperatively among patients in whom NIRL was used was half that observed among those for whom surgeons used WL only, and that the incidence of more severe levels of hypocalcemia was even more markedly reduced.

The importance of more sensitive detection of parathyroid tissue during thyroidectomies is largely a patient-safety issue because enhanced, earlier identification of these small glands before rather than after thyroid dissection should reduce the incidence of postoperative hypocalcemia from the accidental parathyroid devascularization or resection that often occurs during total thyroidectomy procedures.[26,27] In our trial, because virtually as many parathyroid glands were observed before thyroidectomy with NIRL as after thyroidectomy when WL was used, less dissection was required in the former group, logically reducing the surgical risk of disrupting parathyroid circulation and likely saving considerable time. This apparent increased safety was reflected in non-statistically significant halving of the rate of hypocalcemia; but also a dramatic reduction in the number of patients who had a postoperative serum calcium level of ≤7.5 mg/dL, from 10 subjects in the WL group to just a single patient in the NIRL group ($p = 0.005$); and in zero calcium levels <7.5 mg/dL in the NIRL group vs 6 in their WL counterparts ($p = 0.009$). The mean postoperative serum calcium level also was statistically higher in our NIRL patients ($p < 0.009$).

Our results closely mirror those of another recently published study by Benmiloud and colleagues,[28] who identified a hypocalcemia incidence rate of 5.2% among patients for whom NIRL was used vs 20.9% in those for whom it was not, a difference that also was statistically significant ($p < 0.001$). That study is marred, however, by a design that had all of the procedures performed using NIRL done by the same surgeon, while all of the procedures performed on controls were done by a second surgeon, which raises the issue of operator bias. One design advantage of our study compared with theirs is that we had 4 surgeons who all performed procedures with and without NIRL and in both patient groups.

Another interesting finding we made that, to our knowledge, others have not even evaluated, is the direct and highly significant correlation we detected between thyroid weight and the rate of postoperative hypocalcemia, such that every 5-g increase in thyroid weight increased the likelihood of hypocalcemia by approximately 15%. This association also held for more severe hypocalcemia. This suggests that future investigators assessing interventions to decrease post-thyroidectomy hypocalcemia rates should both measure thyroid weight and consider it a potential predictor of postoperative calcium levels.

Our study has strengths and weaknesses. Its greatest strengths are almost unquestionably its unique focus on questions not previous asked and its design as a prospective randomized controlled study involving several surgeons performing both procedures. We also followed patients for 6 months postoperatively, with zero loss to follow-up, to see if low serum calcium levels normalized; which occurred in all instances; and we included patients with a broad range of thyroid pathologies. One of the study's greatest weaknesses is that the sample (85 patients per group) was too small to allow for subgroup analyses. Also because the sample was relatively small, and because all procedures were performed at a single center, it is possible that our results might not be generalizable to all other centers for the following reasons: representativeness of the subjects and level of experience and proficiency with NIRL of the operators. Clearly, additional similar studies must be performed at other centers, or possibly one or more multicenter studies, to address these generalizability concerns. Finally, and again related to the size of the sample, we did not perform Bonferroni-style adjustments to compensate for the potential of false-positive results that can arise in studies with multiple comparisons. This being said, the 2 comparisons of greatest interest, that is, the differences between the number of parathyroid glands detected with vs without NIRL ($p < 0.001$) and the percentage of patients in the 2 treatment arms whose postoperative serum calcium level was <7.6 mg/dL ($p < 0.005$), both would have remained statistically significant even with a Bonferroni-adjusted p value (0.05/9 comparisons = 0.0055).

CONCLUSIONS

In a randomized controlled study of 170 thyroidectomy patients, using NIRL intraoperatively was found to increase the intraoperative identification of parathyroid glands, and allow for their localization earlier in the procedure, before vs after thyroid dissection, relative to using WL alone. Our data also indicate that using NIRL has the potential to decrease the incidence of more severe postoperative hypocalcemia. Additional randomized trials with larger patient populations are needed to verify these findings and gain new insights into how to enhance thyroidectomy patient outcomes.

Author Contributions

Study conception and design: Dip, Falco, White, Rosenthal

Acquisition of data: Dip, Falco, Verna, Prunello, Loccisano, Quadri, Rosenthal

Analysis and interpretation of data: Dip, Falco, White, Rosenthal

Drafting of manuscript: Dip, Falco, White, Rosenthal

Critical revision: Dip, Falco, Verna, Prunello, Loccisano, Quadri, White, Rosenthal

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