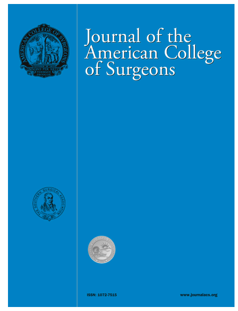

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A Randomized, Controlled Trial Comparing White-Light with Near-Infrared Autofluorescence for Parathyroid Gland Identification during Total Thyroidectomy

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Running title: Prevention of Hypocalcemia using Autofluorescence

Abstract

Background: Parathyroid glands are difficult to identify during total thyroidectomies and accidental resection can lead to problematic post-operative hypocalcemia. Our main goals were to evaluate the effectiveness of using near-infrared light (NIRL) auto-fluorescence intra-operatively 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 prior to thyroid dissection. The number of parathyroid glands identified was compared: after thyroid dissection in controls using WL versus pre-dissection in the experimental using NIRL; and with WL versus NIRL prior to thyroid dissection in the experimental group. Post-operative 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 one previously-missed gland in 67.1% of patients. Calcium levels ≤7.5mg/dl were one-tenth as common in the NIRL group ($p=0.005$). The adjusted odds of developing hypocalcemia increased by 15% for every 5gram increase in thyroid gland weight (OR=1.15; 1.06—1.25). All hypocalcemia resolved within six months.

Conclusions: Using NIRL during thyroidectomy increases the intra-operative identification of parathyroid glands, enhances their detection prior to thyroid dissection, and decreases the incidence of post-operative hypocalcemia.

Keywords: near-infrared light; thyroidectomy; parathyroid; hypocalcemia; imaging

Introduction

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 et al. examined the use of autofluorescence with the Raman technique to differentiate parathyroid glands from other tissues[12] and identified a statistically-greater number of parathyroid glands when near-infrared light (NIRL) was employed, relative to standard white light (WL)[13-15]. Variables like patient gender, age 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 two primary aims: (1) to compare the effectiveness of using near-infrared light (NIRL) versus white light (WL) during total thyroidectomies to identify parathyroid glands earlier in the procedure; and (2) 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 post-operative hypocalcemia.

Materials and Methods

After receiving Institutional Review Board 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 (IADT), Buenos Aires, Argentina, performed all procedures. To be eligible for the study, patients had to be ≥ 18 years old, have a clinical indication for total thyroidectomy, not have pre-operative hypocalcemia or hypercalcemia or any condition that would predispose them to either, and have provided written consent to participate. Patients who had had any previous neck surgery, candidates for thyroid lobectomy, and those requiring neck dissection were excluded (Figure 1).

Patients were block-randomized, by one of the authors, into two 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 non-experimental (NE) group, surgeons only used white light (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 near-infrared light (NIRL) were utilized to illuminate the surgical field. This occurred twice: (1) 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 (2) after thyroid resection. All participating surgeons performed surgeries in both treatment groups.

Outcome measures

The outcome measures of interest were: (1) total number of parathyroid glands identified by the surgeon, using white light versus using NIRL; (2) post-operative serum calcium level; (3) the presence versus absence of post-operative hypocalcemia and symptomatic post-operative hypocalcemia; (4) thyroid gland weight in grams; (5) the need for post-operative hospitalization; (6) mean hospital stay, in days; and (7) the need for calcium replacement.

Equipment

The Fluobeam® 800 system (Fluoptics, Cambridge MA, USA) 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 400nm – 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 5mW/cm^2, that is directed towards 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 only detects 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 (Figure 2). Once all parathyroid glands that could be identified were identified, the surgeon proceeded with thyroid capsule dissection.

All four participating surgeons had been pre-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 intra-operatively. Images were analyzed using IMAGE J software. Parathyroid gland images and parathyroid gland tissue confirmed by the four 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 also was recorded.

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

Each patient's serum calcium level was measured on post-operative day 1, as well as one week and six months post procedure. Hypocalcemia was operationally defined as a serum calcium level below 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 below 7.6 mg/dL and patients whose hypocalcemia was considered symptomatic were treated with intravenously-administrated calcium replacement and monitored closely. Post-operative hypocalcemia was considered persistent if the serum calcium remained below 8.0 mg/dL at the six-month follow-up visit.

Statistical analysis

Since the main outcome of interest in this study was the incidence of post-operative hypocalcemia, and the primary objective was to compare this incidence among patients in whom NIRL was used versus not used, hypocalcemia incidence was used to estimate our sample size requirement. A baseline estimated incidence of 40% was used, drawing from four 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 (α= 0.05) and 90% power (β= 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, two comparisons were performed. The first was to compare the final number of glands identified among controls after thyroid dissection against the number identified prior to 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 prior to thyroid dissection. Both comparisons were conducted using unpaired Student's t tests.

To compare the two treatment groups with respect to the incidence of post-operative hypocalcemia, symptomatic hypocalcemia, hypocalcemia requiring short-term and long-term calcium supplementation, and hospitalization, Pearson $\chi 2$ analysis was performed. Further secondary outcomes of interest were post-operative serum calcium level and mean hospital stay (in days), which also were compared between the two 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 versus absence of post-operative hypocalcemia, respectively.

All analyses were two-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, 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 two most common being 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 two treatment groups (NE 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; standard deviation, SD = 0.57) and the number identified in the NIRL group using NIRL prior to thyroid dissection (3.5; SD = 0.78) (NS) (Table 2). However, in the NIRL group, the number of parathyroid glands visualized prior to thyroid dissection increased from 2.6 (SD = 0.85) to 3.5 (SD = 0.78) when WL was toggled to NIRL ($p < 0.001$) (Figure 3). In addition, either one (n = 31) or two (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 (Figure 4).

In four patients, auto-transplantation 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.

Post-operatively, the incidence of hypocalcemia was 8.2% (n = 7) in the NIRL group versus 16.5% (n = 14) among controls, a 50% relative reduction in the NIRL group that nonetheless just failed to achieve borderline statistical significance ($\chi 2 = 2.66$, 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 versus 11.8% in the white light group, a difference that was highly significant ($\chi 2 = 7.87$, df = 2, $p = 0.005$) (Figure 5). In the NIRL group, the minimum calcium level recorded post-operatively was 7.5mg/dl. Conversely, in the white-light group, six patients had a serum calcium level below 7.5mg/dl, the lowest recorded level being 6.8mg/dl. The overall mean post-operative serum calcium level also was significantly higher in those in the NIRL group ($p = 0.009$). On the other hand, only one and two subjects in the WL and NIRL groups developed symptomatic hypocalcemia ($\chi2 =$; $p = 0.57$), respectively; and long-term calcium replacement, beyond hospitalization, was deemed necessary in just one subject per group (OR = 1.00, $p = 1.00$).

Six patients (7%) in the NIRL group required hospitalization, versus twelve (14%) controls ($\chi2 = 2.24$, df = 1, $p = 0.14$), while the mean days of hospitalization were 0.11 vs. 0.26 in the two groups, respectively ($t = 1.75$, adjusted df = 143.9, $p = 0.08$), neither difference statistically significant. No patient experienced permanent hypocalcemia, with serum calcium levels ≥ 8.0 mg/dL in all patients by six months of follow-up. No patient was lost to follow-up.

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

Discussion

To our knowledge, this is the first randomized, controlled study in which near-infrared light was evaluated, by several surgeons, as an intra-operative 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 the intravenous 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 avoid this, others have used indocyanine green (ICG) [20, 21]. However, while some reports have been encouraging, the intravenous administration of ICG confirms the perfusion, but not the location of parathyroid tissue, since ICG also is taken up in relatively-high concentrations by thyroid tissue, rendering specific visualization of parathyroid tissue difficult [22]. Others have proposed utilizing parathyroid glands' own unique auto-fluorescent properties for intra-operative visualization[12, 13]. Shinden et al. 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 et al. reported that they were able to benefit from the intrinsic fluorophores of parathyroid tissue[24] to pre-operatively identify all 16 parathyroid glands they sought in their patients[25]. Falco et al. also have reported that parathyroid visualization increased when NIRL, rather than WL, was employed ($p = 0.026$)[16]; in their study, consistent with our own, co-variates like patient gender, 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].

In the current study, we discovered, first, that surgeons were able to identify as many parathyroid glands using NIRL prior to thyroid dissection as they were able to identify under WL after the thyroidectomy was completed; and, second, that using NIRL prior to thyroid dissection was significantly more effective at identifying parathyroid glands than using WL, with NIRL revealing at least one otherwise-missed gland in two out of every three patients, and a mean 1.0 missed gland per patient overall. We also observed that the incidence of hypocalcemia post-operatively, among patients in whom NIRL was used, was half that observed among those on whom surgeons only employed white light, 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, since enhanced, earlier identification of these small glands, prior to, 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, since virtually as many parathyroid glands were observed prior to thyroidectomy with NIRL as after thyroidectomy when WL was employed, 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 post-operative serum calcium level of 7.5 mg/dl or less, from ten subjects in the white-light group to just a single patient in the NIRL group ($p = 0.005$); and in zero calcium levels below 7.5mg/dl in the NIRL group versus six in their white-light counter-parts ($p = 0.009$). The mean post-operative 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 et al., who identified a hypocalcemia incidence rate of 5.2% among patients in whom NIRL was used, versus 20.9% in those for whom it was not, a difference that also was statistically significant, at $p < 0.001$.[28] That study is marred, however, by a design that had all the procedures performed using NIRL performed by the same surgeon, while all procedures performed on controls were performed by a second surgeon, raising the issue of operator bias. One design advantage of our study over theirs is that we had four surgeons who all performed procedures with and without NIRL and in both patient groups.

Another interesting finding we made which, to our knowledge, others have not even evaluated, is the direct and highly-significant correlation we detected between thyroid weight and the rate of post-operative hypocalcemia, such that every 5 gram 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 post-operative 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 six months post-operatively, 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 sub-group 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 two reasons: the representativeness of the subjects, and the level of experience and proficiency with NIRL of the operators. Clearly, further similar studies must be performed at other centers, or possibly one or more multi-center 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 two comparisons of greatest interest: the differences between the number of parathyroid glands detected with versus without near-infra-red light ($p < 0.001$), and the percentage of patients in the two treatment arms whose post-operative serum calcium level was < 7.6 mg/dL ($p < 0.005$), both would have remained statistically significant, even with a Bonferroni-adjusted p (0.05/9 comparisons = 0.0055).

Conclusions

In a randomized, controlled study of 170 thyroidectomy patients, using NIRL intra-operatively was found to increase the intra-operative identification of parathyroid glands, and allow for their localization earlier in the procedure, prior to versus after thyroid dissection, relative to using white light alone. Our data also indicate that using near-infrared light has the potential to decrease the incidence of more severe post-operative hypocalcemia. Further randomized trials with larger patient populations are needed to verify these findings and gain new insights into how to further enhance thyroidectomy-patient outcomes.

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

Patient characteristics	**All (170)**	**Controls (85)**	**NIRL (85)**
Age, 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.

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

Outcome	**White light (n = 85)**	**Near-infrared light (n = 85)**	**Test statistic t or χ2 (df)**	**p Value**
PT glands detected, pre-dissection, mean (SD)	n/a	2.6 (0.85)	n/a	n/a
PT glands detected, post-dissection, mean (SD)	3.6 (0.57)	3.5 (0.78)	t = 1.01 (168)	0.32
Thyroid gland weight, mean	25.5 g	24.6 g	t = 1.38 (168)	0.17
Postoperative serum calcium, mean	8.39 mg/dL	8.65 mg/dL	t = 2.65 (168)	0.009*
Postoperative serum calcium < 8.0 mg/dL, %	16.5%	8.2%	$\chi2$ = 2.66 (1)	0.103
Postoperative serum calcium < 7.6 mg/dL, %	11.8%	1.2%	$\chi2$ = 7.87 (1)	0.005*
Symptomatic postoperative hypocalcemia, %	1.2%	2.4%	$\chi2$ = 0.34	0.56
Long-term treatment for hypocalcemia, %	1.2%	1.2%	$\chi2$ = 0.00	1.00
Post-op hospitalization required, %	14.1%	7.1%	$\chi2$ = 2.24 (1)	0.14
Length of hospital stay (days), mean	0.26	0.11	t = 1.75 (143.9) †	0.08

*Significant.

†Degrees of freedom adjusted for non-normality of data

df, degrees of freedom; n/a, not applicable; PT, parathyroid.

FIGURE LEGENDS

Figure 1. CONSORT flow diagram for the study.

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

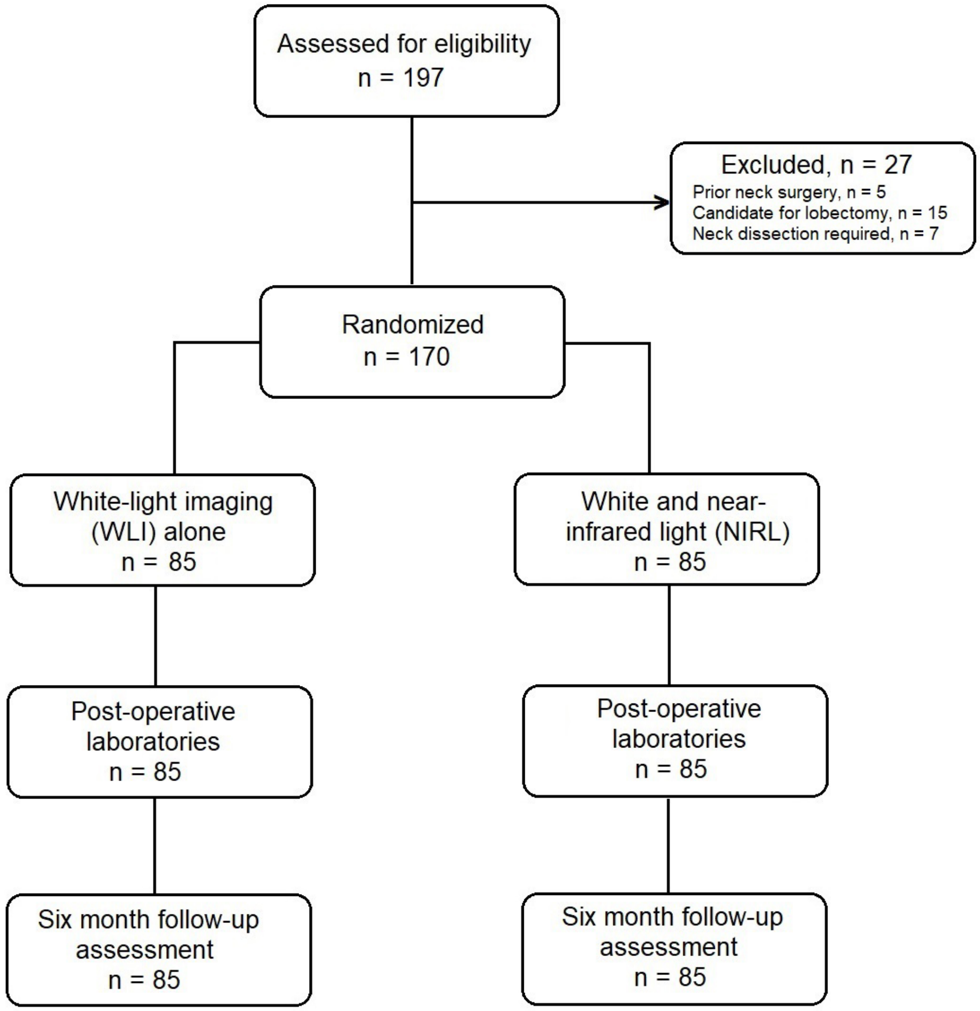
Figure 3. Mean number of parathyroid glands detected after thyroid dissection with white light (WL), and prior to thyroid dissection with white light and near-infrared light (NIRL). Note how there is virtually no difference in the number detected pre-dissection under NIRL and post-dissection with WL.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

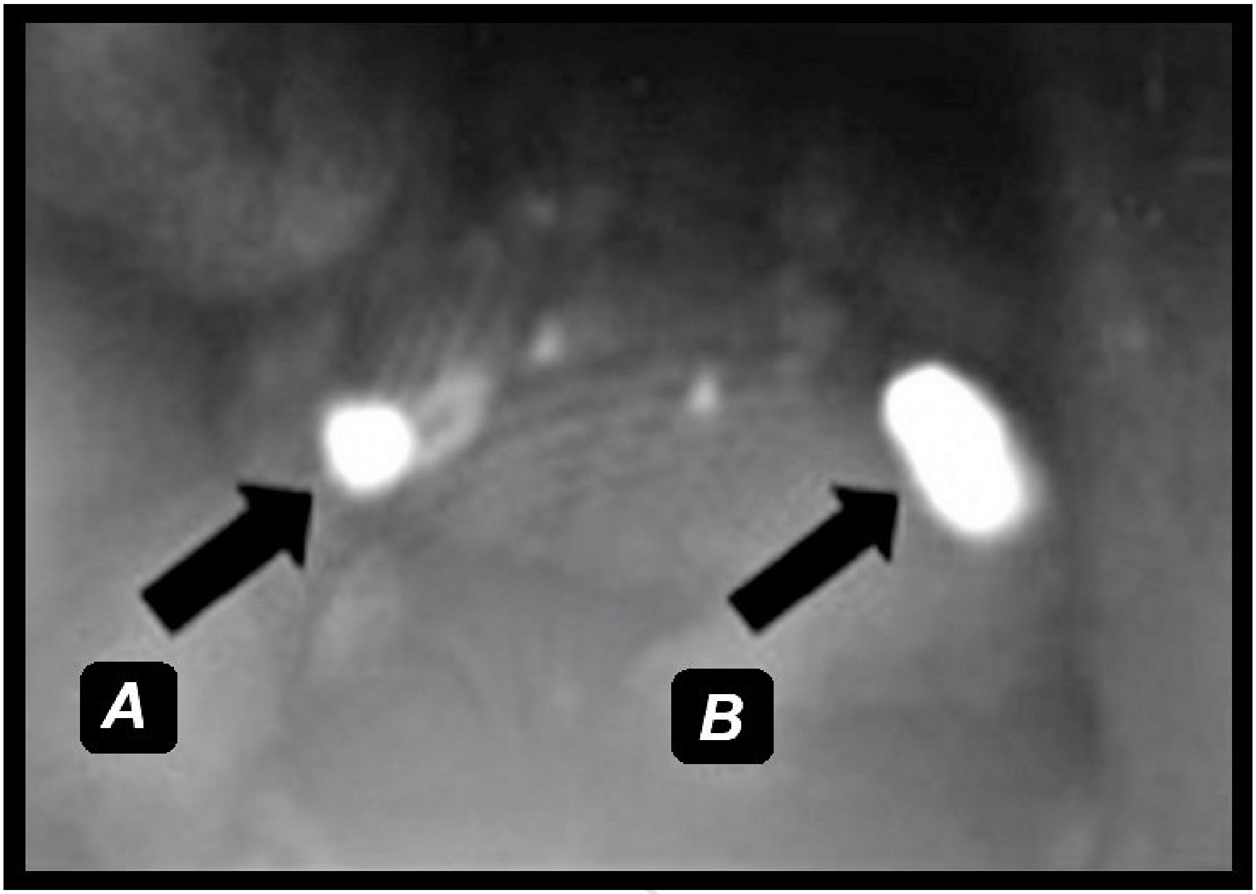
Figure 4. Number of parathyroid glands detected by subject group and light source. Prior to thyroid dissection in the active intervention group, toggling from white light (WL) to near-infrared light (NIRL), resulted in the detection of either one (n = 28) or two (n = 28) more glands in 56 of 85 subjects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

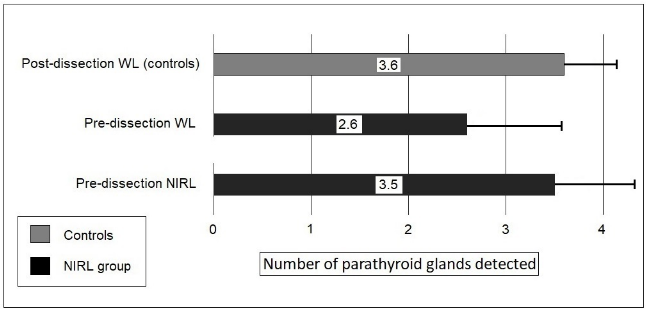
Figure 5. Postoperative day 1 serum calcium levels in patients undergoing thyroidectomy under white light (n = 85) vs near-infrared light (n = 85). In the white-light group, 10 patients had a postoperative serum calcium level under 7.6 mg/dL, vs just 1 such patient in the near-infrared light group.

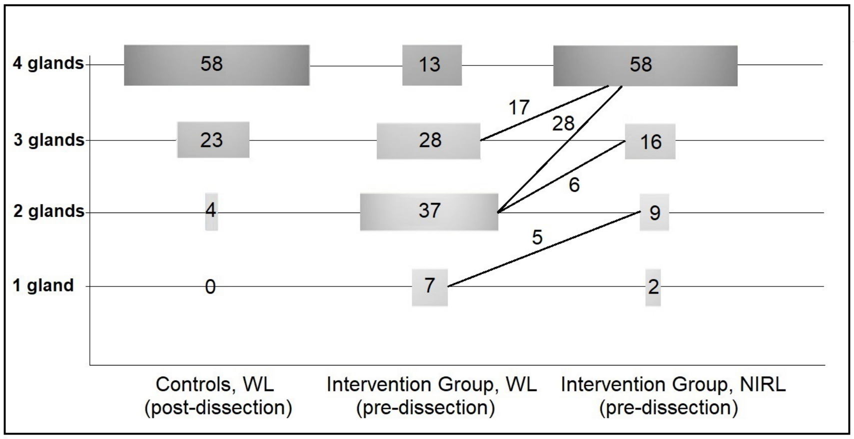
Precis

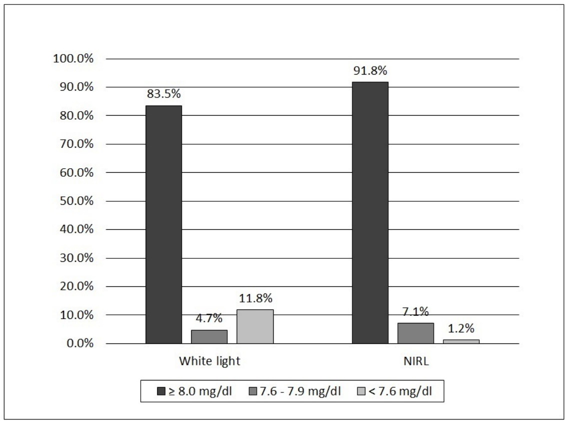
In a randomized controlled trial with 170 patients, patients whose thyroidectomy was performed under near-infrared light had their parathyroid glands detected earlier intraoperatively, prior to thyroid dissection vs afterward, and were only one-tenth as likely to have a postoperative day 1 serum calcium level ≤ 7.5mg/dL.


Assessed for eligibility
n = 197
Excluded, n = 27
Prior neck surgery, n = 5
Candidate for lobectomy, n = 15
Neck dissection required, n = 7
Randomized
n = 170
White-light imaging
(WLI) alone
n = 85
White and near-
infrared light (NIRL)
n = 85
Post-operative
laboratories
n = 85
Post-operative
laboratories
n = 85
Six month follow-up
assessment
n = 85
Six month follow-up
assessment
n = 85


A
B


Post-dissection WL (controls)
3.6
Pre-dissection WL
2.6
Pre-dissection NIRL
3.5
0
1
2
3
4
Controls
NIRL group
Number of parathyroid glands detected


4 glands
3 glands
2 glands
1 gland
58
13
58
23
28
16
4
37
9
0
7
2
17
28
6
5
Controls, WL
(post-dissection)
Intervention Group, WL
(pre-dissection)
Intervention Group, NIRL
(pre-dissection)


100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
83.5%
4.7%
11.8%
91.8%
7.1%
1.2%
White light
NIRL
≥ 8.0 mg/dl
7.6 - 7.9 mg/dl
< 7.6 mg/dl