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Near Infra Imaging (NIFI), a safe and non-invasive innovation significantly decreasing the post thyroidectomy hypocalcemia

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ABSTRACT

The number of thyroid surgeries especially due to malignant indications has risen in past few decades in India as well as across the globe. The most common complication after Total Thyroidectomy is hypocalcemia from hypoparathyroidism which occurs majorly due to inadvertent removal of parathyroid glands or injury leading to devascularization of Parathyroid Glands. Post surgery hypocalcaemia is assessed by evaluating the value of post-surgery 24-48 hr Serum Calcium level. Majority of times the Post surgery hypocalcaemia is transient, it recovers in few weeks to months, only if it persists for > 6 months it is labelled as permanent hypocalcemia. According to literature incidence of transient and permanent Post surgery hypocalcaemia is 20–35 % and 1–10%, respectively. Post surgery hypocalcaemia can be symptomatic and morbid. It can only be prevented/decreased by early identification and preservation of Parathyroid Glands. The standard methodology is visual analysis of surgical field by operating surgeon. Parathyroid Glands are small in size, with colour similar to brown fat and their position in thyroid bed is also not consistent. They are difficult to identify and success in this method depends on the experience of operating team. This study evaluates the use of Near Infra- Red Imaging during thyroidectomy to preserve the Parathyroid Glands. Based on its inherent autofluorescence, when viewed through Near Infra-Red Imaging, at wavelength of 785 nm, there is a spontaneous and immediate emission of fluorescent light at 820–830 nm from Parathyroid Glands which is 2- to 11-fold enhanced signal over that of the surrounding tissue. The study consists of 7 patients who underwent Total or Completion Thyroid surgeries with use of Near-infrared imaging along with review of literature. None of the seven patients experienced Post surgery hypocalcaemia and in one patient Intrathyroidal Parathyroid Gland was identified with thyroid gland in-situ. The study advocates the use of Near-infrared imaging to make thyroid surgery safer.

Background

Thyroid cancer is increasing across the globe. India is also witnessing this phenomenon. According to Veedu et al the incidence rate of thyroid cancer in India in women increased from 2.4 (95% confidence interval (CI) 2.2-2.7) to 3.9 (95%CI 3.6-4.2) and in men from 0.9 (95%CI 0.8-1.1) to 1.3 (95%CI 1.2-1.5), from 2004 to 2014; a relative increase of 62% and 48% respectively[1]. Surgery in form of Thyroidectomy, especially Total Thyroidectomy is the definitive treatment modality for thyroid cancer. With the rise in Thyroid cancer, the need as well as incidence of thyroidectomy has also increased. Apart from malignancy total thyroidectomy is also the procedure of choice for treating Multinodular Goiter and certain benign thyroid disorders.

The most common complication after Total Thyroidectomy is hypocalcemia from hypoparathyroidism which occurs majorly due to inadvertent removal of parathyroid glands (PGs) or injury leading to devascularization of PG. This is either transient (≤6 months), or permanent (> 6 months). According to literature incidence of transient and permanent hypoparathyroidism post thyroidectomy is 20–35 and 1–10%, respectively[2,3].

According to Benmloud et al.[4] post thyroidectomy hypocalcemia can be symptomatic and even life-threatening. It can increase the length of a hospital stay, require substitutive treatment and prolonged surveillance after discharge, and thus impair quality of life[5], and can even increase mortality risk Parathyroid glands identification and preservation during thyroidectomy is difficult due to small size, similar appearance as compared to surrounding tissue and lack of consistency in its anatomy in thyroid bed[6,7]. Visual inspection of the thyroid bed is the standard procedure to identify and preserve PGs. Experience of surgeon also contributes to the success of PG preservation[8]. We until now, relied upon our experience to identify and preserve PGs by visual inspection especially while dissecting the Infra Thyroid pedicle; while trying to preserve tissue resembling PG. Our methodology is similar to the one suggested by Andre et al.[9] of avoiding active search for PG as it leads to more devascularization.

Recently, we have started using NIFI i.e. Near Infra-red imaging technology to visualize PG. PGs have inherent characteristic autofluorescence (AF) in Near InfraRed (NIR) Spectrum[10]. The signal enhancement is 2 to 11 times then surrounding tissue[11].Near Infra-red imaging has been a great help in identification as well as preservation of PGs.

In this report, we'll be sharing our experience of doing thyroidectomies with support from NIFI including methodology, results and also discussing its salient features as per the available literature.

Materials & Methods

The study includes 7 patients who underwent Total or completion thyroidectomy between the May 2022 to December 2022 at CK Birla Hospital, New Delhi. NIFI imaging developed by Irillic India was used to identify PGs during thyroidectomy. The institute's Ethical Review Board (ERB) approved its use for Thyroid surgery.

The procedure was performed as per the clinical pathway discussed and approved in clinical governance council of the hospital.

The clinical pathway included:

1. Preoperative assessment: It includes necessary radiology, cytology, thyroid profile,tumor markers (if required), and investigations prescribed/ required by anaesthesia team.

2. Intraoperative steps: As with every surgical procedure, the patient is positioned, draped and prepped.

- Lower neck crease incision is given and skin flaps are raised & secured.
- Strap muscles are retracted / incised to expose the thyroid gland.
- Superior pedicle is dissected and ligated, thyroid gland is mobilized off the thyroid bed by incising thyroid capsule.
- Identification of PG / PGs was done with support of NIFI followed by visual inspection of thyroid

bed, meticulous dissection and ligation of branches from inferior thyroid pedicle is done with attempt to preserve the identified PG.

- Recurrent Laryngeal Nerve (RLN) is identified in the Tracheoesophageal (TE) grove and dissected till Berry's ligament mobilizing the gland off the trachea.
- Similar steps are repeated on contralateral side if Total thyroidectomy is being done and the specimen is removed en-mass.
- Straps are closed and neck wound is closed over suction drain.

3. Post operative care: The patient is asked to remain in In Patent Department (IPD) for next 48 hrs and observed for any bleeding, hematoma, respiratory distress, voice change and difficulty in breathing & swallowing; drain output, vitals are noted and Complete blood count (CBC), Serum electrolytes with Serum Calcium are advised after 24hrs. Majority of patients are discharged from IPD after 48 hrs.

Description of NIFI

Parathyroid tissue, when excited with light in the range of 760-790nm, emits Fluorescent light in the wavelength 800-900nm. The intensity of the fluorescence signal from the PG is significantly higher than that of the thyroid and surrounding tissue making it easier to identify the gland through an imaging device sensitive to the near infra-red range of wavelength. In this study we used, the Irillic nm fluorescent imaging system (Irillic Pvt Ltd., Bangalore) works on the principle of Near-infrared imaging (NIFI). The non-contact hand held probe makes it convenient to visualize PG autofluorescence from a distance of 20 to 25 cm. Additionally, ICG can be injected to check the vascularity to the parathyroid glands prior to closure.

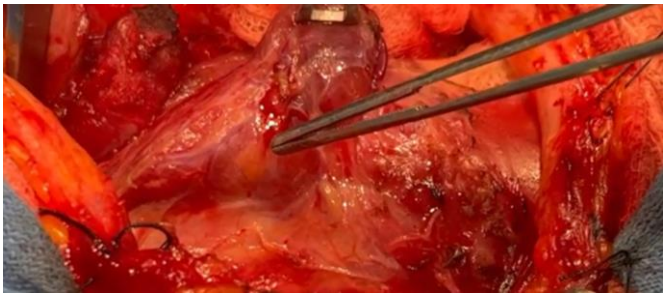
In Six patients PGs were identified and preserved during the dissection of thyroid bed. In one patient intrathyroidal PG was identified during dissection of Left lobe of Thyroid. The PG retained autofluorescence in the specimen also. It was harvested from the thyroid specimen, minced into smaller pieces and re-implanted in Sternocleidomastoid muscle.

Fig 1 shows the naked eye view of thyroid bed and when the same field is viewed through NIFI, in Fig 2 PG is identified.

1. Naked eye view of Thyroid Bed (Thyroid gland retracted by finger and pointed by the forcep, white tissue is trachea)

2. When viewed through NIFI, PG can be identified

In Fig 3 intrathyroidal PG is suspected which is confirmed when viewed through NIFI in Fig 4.



3. Suspected Intrathyroid PG

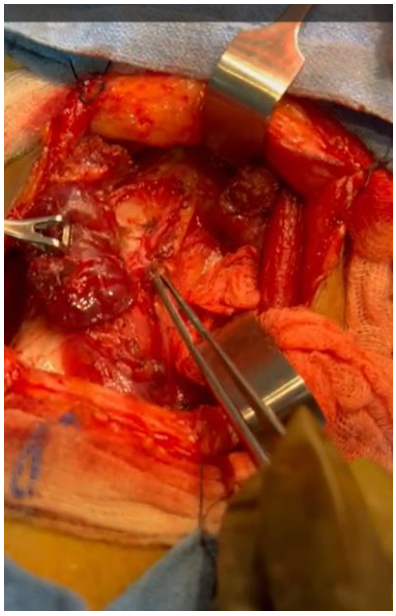
4. Confirmed through NIFI

In Fig 5 and Fig 6 the PG tissue isolated from the thyroid specimen in Fig 3 and Fig 4 is being confirmed before re-implantation.

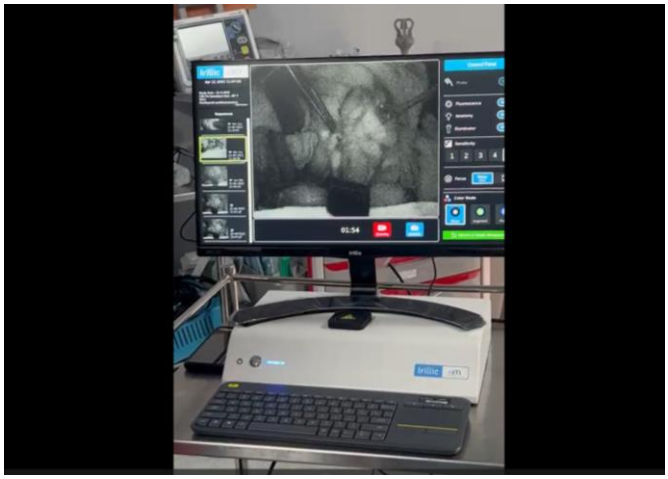
5. Removed Parathyroid Glands getting Confirmed through NIFI

6. Removed PG's when viewed through NIFI

Fig 7 and Fig 8 describes the advantage of NIFI in differentiating PG from lymph node in Paratracheal area i.e. level VI.



7. Differentiating PG from Level VI LN



8. Corresponding NIFI image

Results

There were six (85%) females and one (15%) male with a mean age of 48.2 years (range 24–58 years). The final histopathology suggested follicular variant of papillary thyroid carcinoma (PTC) in three patients; Classical PTC in one patient; follicular adenoma in one patient and multinodular goiter in two patients

The Serum Calcium levels of all the patients after 24 hrs was > 7.5 mg/dl. No patients developed symptoms of hypocalcemia in postoperative period or required external calcium or Vitamin D supplementation.

Table 1

Patient ID	Sex	Age	Operation	Diagnosis	Histopathological features	Tumor size	Postperative Serum Calcium mg/dl/ (mmol/L)
1,	48	F	TTE	PTC	Follicular variant	0.7cm	8.9(2.22)
2.	58	F	TTE	PTC	Follicular variant	1.3cm	9.6(2.4)
3.	50	M	CTE	MNG	N/A	13cm	9.7(2.42)
4.	50	F	TTE	MNG	N/A		8.9(2.22)
5.	51	F	CTE	Follicular neoplasm	Follicular Adenoma	5cm	8.8(2.2)
6.	24	F	CTE	PTC	Follicular variant	1.2cm	9.1(2.27)
7.	57	F	CTE, CCND	PTC	Classical variant	Microsc-opic Foci	7.6(1.9)

F-Female, M-Male, TTE-Total thyroidectomy, CTE-Completion thyroidectomy, PTC-Papillary thyroid carcinoma, MNG-Multinodular goiter, N/A- Not applicable, CCND-Central compartment neck dissection

Discussion

There has been steady increase in thyroid surgeries in the last few decades across the globe. According to Loyo et al, 'Surgical cases in United States increased from 364,288 in 1993 through 2000 to 507,356 in 2001 through 2008, with an increase in thyroid cancer surgical cases from 28% to 34%'[12].

When to evaluate for PSH

Postoperative/post-surgery hypocalcemia (PSH) due to inadvertent removal, injury or devascularization of Parathyroid gland/glands remains the most common complication after thyroidectomy, especially Total Thyroidectomy. PSH is documented in the serum calcium, levels recorded 24–48 h after surgery[7,13-14].

The British Association of Endocrine and Thyroid Surgeons (BAETS), defines postoperative hypocalcaemia as day one postoperative calcium of less than 2.1 mmol/L[15]. The review by Wu et al describes cut-off range for post operative hypocalcemia from 1.8 to 2.12 mmol/L[16].

Asari et al. documented decrease in serum calcium levels after surgery below 1.9 mmol/L to be of concern regardless of the presence of hypocalcemia symptoms[17]. We have considered value of serum calcium 24 hrs post-surgery as cut off for evaluating PSH. In all our patients the 24 -48hr Serum Calcium value was above 1.89 mmol/L with the mean value of 2.2 mmol/L.

Categorization of PSH

The acute form of hypocalcemia is generally transient and recovers over few months. It is generally defined as permanent or Late hypocalcaemia if calcium and/or vitamin D supplements are needed to maintain normocalcaemia at 6 months or more following surgery[15]. The American Association of Clinical Endocrinologist (AACE) and American College of Endocrinology (ACE) makes this distinction between temporary and permanent PSH at 12 months[18].

Persistent PSH may manifest as multiple calcinosis, cataracts, tetany, gastrointestinal diseases, leading to decrease in quality of life, and in some patients disability[19-22]. A large Scandinavian cohort study, also observed an increased risk of mortality with permanent PSH[23].

The incidence of transient PSH post thyroidectomy ranges from 18 to 39%[24-27]. The fifth BAETS audit report suggested temporary and late hypocalcaemia rate

of 23.6% (95% CI, 22.7–24.5%) and 6.5% (95% CI, 5.8–7.2%) respectively in patients who had total thyroidectomy [15]. Studies by Duclos A, et al[28] et al reported transient or definitive post thyroidectomy hypoparathyroidism as 20–35 and 1–10%. A recent observational study from India reported Hypocalcemia in 15 patients out of their 34 patients in the post-op period[29].

Factors affecting PSH

Certain factors like female gender, extent of thyroid surgery, surgeon experience, Vit D3 and Magnesium levels also influence development of PSH. In a study by Paolo Del Rio[30] et al 42% (701/1669) of patients developing PSH were females, in men PSH identified was 21.4% (94/439). The reasons speculated are 'smaller operative field' in females[31] and the prevalence of vitamin D deficiency[32]. Del Rio et al[30] also noticed, greater hypocalcemia incidence in patient undergoing total thyroidectomy (38.8%) than in patient undergoing lobectomy group (13.8%). Gonzalez-Sanchez et al[33] suggested significantly lower PSH at 6 months in surgeons operating around 40 cases per year. Magnesium plays a significant role in secretion of PTH and Vitamin D is an independent risk factor of PSH[34-37].

Preventing PSH through NIFI

A. NEED FOR NIFI: Post Surgery Hypocalcemia after thyroid surgery can be prevented by early identification and preservation of PGs. The standard methodology is visual analysis of surgical field by operating surgeon. PGs are small in size, with colour similar to brown fat and their position in thyroid bed is also not consistent. They are difficult to identify and success in this method depends on the experience of operating team[38-40].

B. BASIS OF NIFI: The inherent characteristic of autofluorescence (AF) in parathyroid gland was discovered in 2008[41]. Fluorescence is a property of certain substances and molecules to absorb light at a given wavelength, which briefly raises the energy of the molecule to a higher excited state. The molecule then emits light at a higher wavelength with lower energy, which can be detected and measured[42,43]. When viewed through Near Infra-Red Imaging (NIFI), at wavelength of 785 nm, there is a spontaneous and immediate emission of fluorescent light at 820–830 nm from PGs which is 2- to 11-fold enhanced signal over that of the surrounding tissue[44-47]. This detection of autofluorescence is a dye-free technique that allows noninvasive, real-time identification and precise localization of PGs. The intrinsic fluorophore responsible for this optical effect in PGs is still unknown; however, evidence suggests that it could be a calcium-sensing or a vitamin D receptor[44,48]. De Leeuw F, Breuskin I, Abbaci M et al demonstrated that NIFI images were reliable, they corresponded to the PGs in 76% to 100% of the cases[39,48-52]. McWade et al. and others have reported excellent PG detection rates through NIFI, with a specificity of more than 80%[44,47,51,52]

C. BENEFITS OF NIFI: The meta-analysis by Barbieri et al. found that NIFI reduced short and medium-term hypocalcemia[53]. Wei Liu et al[54] analysed 2899 patient data pooled from eight studies, they showed that the incidence of transient hypocalcemia was 7.11% (60/844) in the NIFI group and 22.40% (458/2045) in the N–E(naked-eye) (group ($p<0.0001$).Benmiloud et al[55], conducted randomized clinical trial with a 6-month follow-up at 3 referral hospitals in France. The temporary postoperative hypocalcemia rate was 9.1% (11 of 121 patients) in the NIFI group and 21.7% (26 of 120 patients) in the control group (between-group difference, 12.6% [95% CI, 5.0%-20.1%]; $P=.007$). In their study, they reported 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 device). This led to decrease in inadvertent resection of PGs resulting in decrease in auto transplantation. In Near-infrared imaging group all the 4 auto transplanted PGs were identified before the removal of thyroid specimen, they had to be removed because it was not possible to keep them in situ during dissection. Kahramghil et al. also

showed that 37% to 67% of PGs were perceived by NIFI more quickly than with a naked eye, and a study by Kim et al, found that up to 93% of PGs could be detected by NIFI before the naked eye detected them. In our experience, we were able to sight PGs using NIFI before they became visible to naked eye. This resulted in better preservation of PG, none of our seven patients experienced PSH. Also, in the case no 1, the intrathyroid PG was identified with the thyroid gland still in situ; Fig 3 and Fig 4. We had to remove it with the thyroid specimen as there was no way possible to preserve blood supply without compromising completion of thyroid resection. This early identification of PG led to successful auto transplantation due to substantial decrease in ischemia time leading to early revival of Parathyroid function; Fig 5 and Fig 6.

Other methods tried for preventing PSH

A. INDOCYANINE GREEN (ICG): Indocyanine Green is an amphiphilic tricarbocyanine dye that travels through the circulatory system, has a half-life of approximately 3– 5 min, and is excreted in 15–20 min by the biliary system[56]. ICG is excited at 780–805 nm and emits a maximum NIR signal at 830–835 nm[57,58]. Due to Its fluorescence property it has been considered in parathyroid preservation and prevention of hypocalcemia. The procedure is known as 'ICG Fluorescence guided surgery', the vascular structures in the neck accumulate ICG and show fluorescence when viewed through Infra-Red Camera. The non specificity of ICG sometimes makes even the most experienced surgeon to confuse the PGs with other anatomical structures, such as the thyroid, thymus nodules, or lymph nodes[59]. We prefer to use PGs inherent autoflouresecnce feature as a method for their early detection; ICG may be used for assessing the vascularity of the preserved PG. ICG has been proposed to be the most suitable agent for the intraoperative assessment of the PG vascularization[60-65]. In our case series we haven't used ICG, it may be helpful in cases requiring extensive central neck dissection and in recurrent cases.

B. METHYLENE BLUE (MB) & 5-AMINOLEVULINIC ACID (5-ALA): Certain other methods such as administration of methylene blue(MB)[66] or 5-aminolevulinic acid (5- ALA)[67-69]. have been tried for parathyroid identification. MB administration did not become a common practice due to the lack of specificity[70]. It is also potentially toxic, causing serious adverse neurological events. Therefore, no prospective randomized study has been performed with MB, and the literature has discouraged its use[71-73]. ALA, a metabolic-targeting contrast agent, is the precursor of the fluorescent molecule porphyrin, which is an intermediate in the heme synthesis pathway. ALA uptake increases as the number of mitochondria in PG cells increases[74]. ALA administration causes photobleaching and many other phototoxic effects on both the skin and eyes. Additionally, the fluorescent signal is absent in some pathological PG[75,76] .

Conclusion

The rising number of thyroidectomy procedures over the last few decades have resulted in more patients suffering from post thyroidectomy hypocalcemia due to inadvertent removal or devascularization of parathyroid gland. Visual identification and preservation of parathyroid gland/glands is the standard methodology for preventing this complication. In best of the hands and institutes dedicated for thyroidectomies still one-fourth of the patients suffer from hypocalcemia after the surgery. Near Infra-red Imaging (NIFI) utilizing the inherent characteristic of autofluorescence of parathyroid gland when viewed from Infra-red camera have been shown to augment the standard methodology of PG indentification and preservation leading to substantial decrease in post surgery hypocalcemia. Our experience of 7 patients along with review of literature leads us to advocate NIFI during thyroid surgery to make it safer.

Conflict of Interest:

None.

Funding:

None.

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None.

Abbrevations:

1. Parathyroid glands (PGs).
2. Post surgery hypocalcaemia (PSH).
3. Near Infra-Red Imaging (NIFI).
4. Autofluorescence (AF).
5. Ethical Review Board (ERB).
6. Recurrent Laryngeal Nerve (RLN).
7. Tracheoesophageal (TE).
8. Complete blood count (CBC).
9. In Patent Department (IPD).
10. British Association of Endocrine and Thyroid Surgeons (BAETS).
11. American Association of Clinical Endocrinologist (AACE).
12. American College of Endocrinology (ACE).
13. Indocyanine green (ICG).
14. Methylene Blue (MB)
15. 5-aminolevulinic acid (5-ALA)

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