Preventing Inadvertent Parathyroidectomy during Thyroid Surgery - A Literature Narrative

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Significance:

Incidental parathyroid injury is a serious complication of thyroid and neck surgeries, leading to temporary or permanent hypocalcemia. A variety of imaging and operative techniques have been described to prevent this mishap. The use of carbon nanoparticles, and meticulous capsular dissection are the most important ones. This review aims to explore the various techniques for parathyroid preservation and to give key recommendations that can be used by surgeons in different neck surgeries.

Abstract

Background: Accidental parathyroidectomy during thyroid surgery can lead to temporary or permanent hypocalcemia with serious morbidity. Proper identification of parathyroid glands during surgery can be an effective way of preventing this complication.

Methods: The keywords "parathyroid gland", "preserve", "protect", "inadvertent or accidental parathyroidectomy", "surgery", and "dissection" were used to search Medline and Embase databases. 133 articles were chosen after preliminary review, from which 80 indexed papers were finally reviewed for subject relevance.

Results: Imaging techniques such as the use of carbon nanoparticles or indocyanine green angiography, and operative techniques such as meticulous capsular dissection of thyroid gland are linked with significantly improved rates of avoidance of inadvertent parathyroidectomy.

Conclusion: During thyroid surgery, the utilization of imaging techniques and careful operative technique can prevent parathyroid injury. This in turn can prevent complications resulting from hypoparathyroidism such as tetany, ECG changes, and neurological sequalae.

Introduction

During thyroid surgery, any damage, devascularization or removal of the parathyroid glands (PTGs) can lead to symptoms of hypoparathyroidism, mainly manifesting as hypocalcemia, which may be transient or permanent (1). Short term effects of hypocalcemia include paresthesia and neuromuscular instability; long term morbidities are characterized by cataracts, renal failure, seizures, psychiatric derangements, and abnormal dentition (2). Incidental parathyroidectomy (IP) during thyroid surgery has been associated with post-operative hypocalcemia, confirmed biochemically without clinically symptomatic disease (3). Concurrent neck dissection during thyroid surgery has been identified as an independent predictor of IP, associated with a fourfold increase in risk of inadvertent parathyroidectomy (4). Other risk factors associated with IP include malignancy, lymph node (LN) metastasis and intra-thyroidal location of the PTGs (5). Total thyroidectomy, Hashimoto's thyroiditis and extra-thyroidal tumor extension were also identified as risk factors for inadvertent parathyroid removal (6), although this has been contested by more recent studies, which failed to identify age, sex, thyroiditis, malignancy, and thyroid gland size as risk factors (2). There is a higher likelihood of both biochemical and symptomatic hypocalcemia in patients who experienced IP, compared to controls (5, 6). The clinical consequences of parathyroid removal or damage are summarized in figure 1.

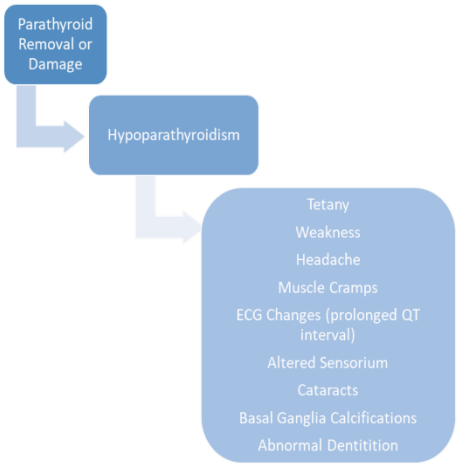

Figure 1: Clinical Consequences of Parathyroid Removal/Damage

While the exact incidence of IP remains undeclared, several studies have reported an incidence of 16% during thyroidectomies (4-6). A retrospective analysis of 281 patients who underwent thyroidectomies reported IP in 25% of the cases (3). Another study, reporting an incidence of 19.8% for 454 patients,

showed that there is a correlation between transient hypoparathyroidism and number of PTGs preserved, with shorter periods of hypoparathyroidism experienced if more glands were preserved. However, no correlation of number of glands removed with risk of permanent hypoparathyroidism was reported (7). Preservation of at least one PTG could prevent permanent hypocalcemia post-operatively (8).

While the incidence of IP is relatively low, it can still lead to severe complications after thyroid surgery (9). Attempts to preserve the PTGs should therefore be made to prevent the occurrence of hypoparathyroidism. This review attempts to cover the major methods and techniques that have been used for parathyroid preservation till date and will provide key recommendations that can be adopted by surgeons to reduce complication rate arising from inadvertent parathyroid damage or removal.

REVIEW OF LITERATURE

The keywords "parathyroid gland", "preserve", "protect", "inadvertent or accidental parathyroidectomy", "surgery", and "dissection" were used to search Medline and Embase databases. 133 articles were chosen after preliminary review, from which 89 were selected for final review after sifting in concordance with a personal reference list. 80 indexed papers were finally reviewed for subject relevance. Both original research and review articles were included for review, with all types of thyroid surgery i.e., hemithyroidectomy, total thyroidectomy, and thyroid lobectomy under consideration.

The various techniques identified for PTG preservation in the literature were broadly classified into two categories: operative techniques and imaging techniques (Figure 2). Evidence for the various techniques, and their pros and cons are systematically presented below.

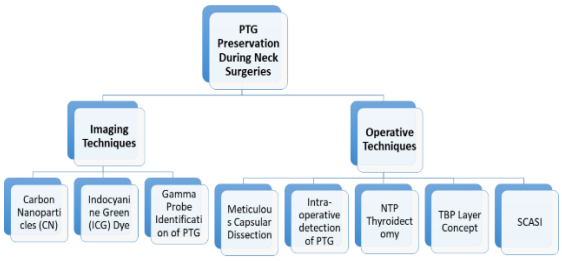

Figure 2: Summary of Various Techniques for PTG Preservation. NIRL: Near Infrared Light; NTP: No Touch Parathyroid; TBP layer: layer of thymus-blood vessel-inferior parathyroid gland (IPTG); SCASI: Subcapsular Saline Injection.

Imaging Techniques

Various imaging techniques for parathyroid detection and surgical preservation include:

1. Carbon Nanoparticles (CNs)
2. Indocyanine Green (ICG) Angiography
3. Mitoxantrone Hydrochloride: the use of mitoxantrone hydrochloride, a chemotherapy agent, for detection of PTGs is under trials, and remains a novel technique with applications in the future. This technique will not be mentioned in detail in this review.
4. Gamma Probe Identification (GPI) of Sestamibi-labeled normal PTGs: this last technique has been largely abandoned in favor of more advanced techniques, and will not be discussed in detail in this review.

We discuss some of these techniques in detail below:

1. Carbon Nanoparticles (CNs)

CNs are strong lymphatic tracers, composed of polymeric carbon granules with an average diameter of 150 nm, able to cross lymphatic vessels without entering into capillary blood (10). For this reason, they are used to distinguish PTGs from cervical LNs, both of which appear similar to the naked eye. The position of PTGs on the back of the thyroid gland can be extremely variable; they can be found in any location, including being embedded with the thyroid, thymus, or carotid sheath. CNs stain cervical LNs and the surrounding thyroid tissue black but do not stain PTGs, due to which they can be useful in intra-operative identification and preservation of PTGs.

Table 1: Characteristics of Systematic Reviews regarding Efficacy of CNs

Authors	Li., et al	Wang., et al	Su., et al
Year of Publication	2015	2017	2018
Number of Included Trials/Studies	15 (11 RCTs, 4 Non-RCTs)	47 RCTs	8 RCTs
Number of Patients in CN Group	586	2197	420
Number of Patients in Control Group	162 (methylene blue group) 307 (blank control group)	2408	424
Quality Assessment Method	Jadad Scoring System for RCTs Newcastle-Ottawa-Scale for Non-RCTs	Jadad Scoring System	Jadad Scoring System

There is variable evidence to support the use of CNs in routine thyroidectomies for parathyroid preservation. Most of the clinical trials regarding CNs have been done in China, with very few corresponding studies from the rest of the world. This review focuses on the results of three meta-analyses and systematic reviews, which review a total of 6504 patients (not counting repetition among studies). The characteristics of the reviews are summarized in table 1.

The systematic review by Wang. et al of 47 RCTs included 4605 patients: the largest meta-analysis conducted to date on the role of CNs in PTG preservation and LN dissection. They reported a 22% lower rate of accidental PTG removal, as well as a decline of 31% in transient and 24% in permanent postoperative hypoparathyroidism. The risk of transient post-operative hypocalcemia was also 30% lower in the CN group; however, no significant risk reduction in rate of permanent hypocalcemia was reported (10). The review not only supported the evidence obtained from previous RCTs but also negated the results of some studies underweighting the role of CNs in PTG preservation. The study was limited by possible publication bias for RCTs with negative findings, as well as by the relatively low-quality assessment scores for the included RCTs (average 2.25).

Su. et al in 2018 reported the results of a meta-analysis and systematic review carried out for 8 RCTs with a total of 844 patients. The included RCTs were of relatively high-quality compared to previous studies, with 2 RCTs scoring 4 and 4 RCTs scoring 3 on the Jadad Scoring System. The most common procedure performed was central neck dissection (CND), mostly for papillary thyroid cancers (PTCs). Significant lowering of the risks of inadvertent parathyroidectomy (OR=0.24), transient hypoparathyroidism (OR=0.39) and postoperative hypocalcemia (OR=0.39) were reported by the study. However, the study failed to demonstrate a significant reduction in risk of permanent hypoparathyroidism with CN use: this can be attributed to the fact that preservation of only one PTG is sufficient to prevent this complication (12). While the study, like other meta-analyses published before, recommends the use of CNs for complete neck dissection and PTG preservation during thyroid surgery, it also stressed on the need of more RCTs, particularly in non-Chinese populations to assess the efficacy, feasibility, and safety of using CNs routinely during neck surgeries.

2. Indocyanine Green (ICG) Angiography

While ICG angiography has had a documented role in various surgical procedures, its practical value in endocrine surgeries in the neck is relatively novel. Although no large scale RCTs have been conducted so far in this regard, results from prospective studies and individual cases show a promising role for ICG angiography for intraoperative PTG preservation.

The working premise of ICG dye is as follows: once the dye is injected intravenously, it rapidly binds plasma lipoproteins, and emits fluorescence when excited by near infrared light (NIRL) at a wavelength of around 800 nms (13). Using fluorescence imaging systems, an image of the PTGs can then be projected within a few minutes, which can be used by the operating surgeon to avoid damaging the PTGs. A trial of ICG with 26 patients demonstrated normal post-operative levels of parathyroid hormone (PTH) in 24 of the 26 patients; transient hypoparathyroidism was reported for 2 patients with poorly vascularized PTGs, with recovery soon after (14). Another study with 22 patients who underwent bilateral axillo-breast approach (BABA) robotic thyroidectomy reported significantly reduced rates of IP with use of ICG Angiography (15). A systematic review on the use of various optical technologies during thyroidectomy or parathyroidectomy also reported ICG as the most common technique for intraoperative visualization of PTG and assessing its vascularity but concluded that large scale RCTs correlating the efficacy of these techniques with post-operative PTH levels should be carried out before their routine introduction into clinical practice (16).

Operative Techniques

Various operative techniques to preserve PTGs during neck surgeries were identified by the literature search:

- Meticulous capsular dissection of thyroid gland
- Intraoperative detection of PTGs
- TBP layer concept for preserving IPTG
- No Touch Parathyroid (NTP) thyroidectomy technique
- Subcapsular Saline Injection (SCASI)
- Use of ultrasound scalpel for PTG preservation
- Improved Miccoli surgery for PTG protection

Detailed discussion of some of the operative techniques is presented below:

1. Meticulous Capsular Dissection of Thyroid Gland

The earliest report of meticulous capsular dissection comes from Thompson, who in 1973 advocated dissection in the plane between the thyroid capsule and the thyroid artery to achieve total extracapsular lobectomy without damage to the parathyroid, the external branch of the superior laryngeal nerve (SLN), or the recurrent laryngeal nerve (RLN) (17). During total thyroidectomy, the goal is to mobilize and laterally retract the superior and inferior PTGs along with their

vascular pedicle, before ligating the vascular branches of thyroid arteries lying on the thyroid capsule (18). Failure to achieve this, either due to high location of the glands on the lateral surface of thyroid or due to damage to the vascular pedicle can lead to injury to the glands, and may result in the loss of their viability.

Method Used	Accuracy	Sensitivity	Specificity	Kappa Value	AUC Area
Clinician Diagnosis	94.4 %	100 %	88.9 %	0.889	0.944
Cytological Examination after Diff-Quik Staining	85%	100 %	66.7 %	0.688	0.914
Rapid PTH assay	60%	100 %	11.1 %	0.121	0.554

Dzodic and Santrac recently presented some practical tips for in situ preservation of the PTGs, based on meticulous capsular dissection and preservation of important vascular structures in the area. Some of the major points identified by their study are briefly outlined in figure 3.

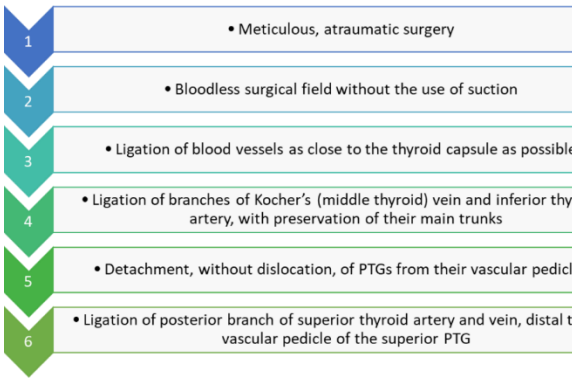

Figure 3: Essential Steps in Meticulous Capsular Dissection for Preservation of PTGs (19)

They also recommend visual identification of viability of PTGs at the end of every operation, and prompt management of venous stasis or arterial ischemia if noted (19). In settings with less experienced surgeons or with low-cost facilities available, the use of methylene blue dye, especially in cases of CND, can help distinguish PTGs from LNs, thereby aiding their identification. With this technique, the authors report a prevalence of permanent hypoparathyroidism of less than 0.5%.

While meticulous capsular dissection appears to be a good practical technique, it should be assessed by more retrospective and prospective studies undertaken on total thyroidectomies and CNDs.

2. Intraoperative Detection of PTGs

Intraoperative detection of the PTGs can be done by various means, including by the clinician, by rapid cytological examination, or by rapid-intraoperative PTH (rIO-PTH) assays. These techniques have varying accuracies, sensitivities, and specificities, accounting for the frequency of their use in clinical practice. A clinical trial by Wei et al, comparing the identification of PTGs during LN dissection for 21 patients, by clinicians, rIO-PTH and rapid cytological detection showed the following results (table 2).

Table 2: Sensitivity and Consistency Analysis of Various Techniques of Intraoperative PTG Detection (20)

This study shows relatively low consistency values for PTH assay and cytological examination compared to clinician diagnosis. However, a larger, more recent trial with 86 patients by the same authors gives slightly contrasting results, with clinical eyeballing falling behind PTH analysis, and frozen section pathology being considered the golden standard test for PTG detection (21). Table 3 outlines the results from this study so as to be compared against the previous one.

Table 3: Sensitivity and Consistency Analysis of Various Techniques of Intraoperative PTG Detection (21)

The relative discrepancy between the two studies does not preclude the fact that intraoperative cytological detection and PTH assay are good techniques for quick identification of PTGs during thyroid surgery, and can be used as adjuncts to other techniques for PTG preservation. However, there is a need for further studies regarding this aspect.

3. TBP Layer Concept

The TBP Layer (layer of thymus-blood vessel-IPTG) is a new concept introduced by Wang et al for the in situ preservation of PTGs during CND. This concept considers the thymus, the IPTG and the blood vessels connecting them as a single layer, which is covering the common carotid artery, the trachea, and the paratracheal nodes between them. Identification, exposure and retraction of this layer instead of directly exposing the common carotid artery is helpful in preserving the IPTGs, as well as the RLN (22). The study by Wang et al, conducted for 487 patients (181 study group; 306 control group) who underwent total thyroidectomy with ipsilateral or bilateral CND, showed an increase in the preservation rate of IPTG to up to 77.9% on the right side and 76.3% on the left side from 52% and 37.9% respectively, compared to controls. The majority of the IPTGs were either preserved in situ or devascularized and autotransplanted. There was also a statistically significant decrease in the incidence of transient hypoparathyroidism. Therefore, it was concluded that the TBP layer concept can aid in IPTG preservation while ensuring complete LN dissection during thyroid surgeries (23).

4. No Touch Parathyroid (NTP) Thyroidectomy Technique

This technique relies on identification and separation of the PTGs from the thyroid in the beginning of extracapsular thyroidectomy to avoid trauma or manipulation of the PTGs and to preserve their vascularity. The authors could only identify one propensity matched analysis for this technique, conducted for 50 patients with benign goiters, in which the NTP technique was associated with similar operative times and lesser frequency of hypoparathyroid complications (24). The efficacy and clinical value of this technique remain to be systematically assessed.

5. Subcapsular Saline Injection (SCASI)

SCASI is another novel technique for preservation of PTGs. It was first assessed by a recent clinical trial of 196 patients, equally divided between two groups. In this technique, after division of the upper pole of the thyroid gland, the subcapsular layer of the gland around the cricoid cartilage is injected with 2-3 ml of normal saline (0.9%), and the inflated layer is then dissected along the margins of the thyroid gland. This helps in identification and eventual preservation of the superior PTGs. The technique was linked to a decrease in both temporary hypoparathyroidism (19.4% in SCASI vs 35.7% in non-SCASI group) and permanent hypothyroidism (0% vs 4.1%). The study was limited by retrospective design, and low sample size, outlining the need for further prospective RCTs for this technique (25). Similar results were reported by another retrospective non-randomized trial on the role of SCASI for PTG preservation during BABA robotic thyroidectomies (26).

Method Used	Accuracy	Sensitivity	Specificity	Kappa Value	AUC Area
Clinician Eyeballing	63.3%	100%	13.9%	0.156	0.569 ± 0.045
Cytological Examination after Diff-Quik Staining	91.7%	93.6%	89.0%	0.829	0.908 ± 0.027
Rapid PTH assay	92.3%	93.8%	90.3%	0.842	0.918 ± 0.025

CONCLUSION AND RECOMMENDATIONS

Based on our review of literature, there is no single technique universally acceptable for parathyroid preservation during neck surgeries. Different imaging and operative techniques have variable practical applications, and while some techniques such as Carbon Nanoparticles (CNs) appear promising, they cannot be easily applied in lower middle income countries (LMICs). It therefore appears important that prospective, large scale RCTs be carried out for the major techniques, including CNs, Indocyanine Green (ICG) dye angiography, meticulous capsular dissection, surgery based on layer-of-thymus-blood vessels-inferior PTG (TBP), and Subcapsular Saline Injection (SCASI). The key recommendations that can be derived from this literature review can be presented as follows:

1. For thyroid lobectomies, meticulous capsular dissection can effectively lead to PTG preservation.
2. For central neck dissection (CND), surgery based on the TBP Layer Concept has good prognostic value (22).
3. CNs need to be introduced in clinical practice for neck surgeries, and they can be used as adjuncts alongside the operative techniques listed above as well.

More research in the form of prospective trials needs to be carried out in order to develop uniform guidelines to aid PTG preservation during surgery.

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Disclosure: None

Human/Animal Rights: No human or animal rights are violated during this study.

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