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 and serious morbidity. Proper identification of parathyroid glands during surgery can be an effective way to prevent this complication.

Methods: The keywords "parathyroid gland," "preserve," "protect," "inadvertent or accidental parathyroidectomy," "surgery," and "dissection" were used to search Medline and Embase databases. A total of 133 articles were selected after preliminary review, of which 80 indexed papers were 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 the thyroid gland, were associated with significantly improved rates of avoidance of inadvertent parathyroidectomy.

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

INTRODUCTION

During thyroid surgery, damage, devascularization, or removal of parathyroid glands (PTGs) can lead to symptoms of hypoparathyroidism, mainly manifesting as hypocalcemia, which may be transient or permanent (1). The 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 postoperative hypocalcemia, confirmed biochemically without clinically symptomatic disease (3). Concurrent neck dissection during thyroid surgery has been identified as an independent predictor of IP and is associated with a fourfold increase in the risk of inadvertent parathyroidectomy (4). Other risk factors associated with IP include malignancy, lymph node (LN) metastasis, and intra-thyroidal location of 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 confirmed by more recent studies that 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 experience IP than in controls (5, 6). The clinical consequences of parathyroid gland removal and damage are summarized in figure 1.

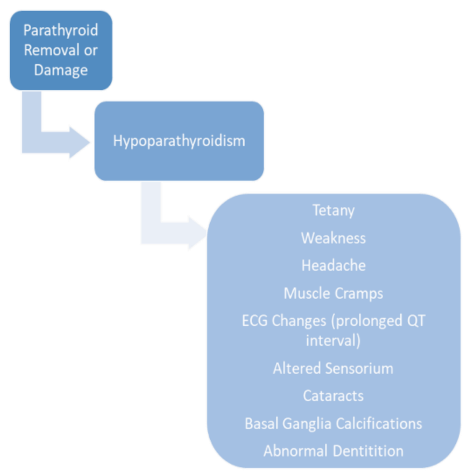

Figure 1: Clinical Consequences of Parathyroid Removal/Damage

Although the exact incidence of IP remains unclear, 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 cases (3). Another study, which reported an incidence of 19.8% for 454 patients, showed that there is a correlation between transient hypoparathyroidism and the number of preserved PTGs, with shorter periods of hypoparathyroidism experienced if more glands were preserved. However, no correlation between the number of glands removed

and the risk of permanent hypoparathyroidism has been reported (7). The preservation of at least one PTG can prevent permanent hypocalcemia postoperatively (8).
Although the incidence of IP is relatively low, it can still lead to severe complications after thyroid surgery (9). Therefore, attempts to preserve PTGs should 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 and provides key recommendations that can be adopted by surgeons to reduce complication rates 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. After a preliminary review, 133 articles were selected, of which 89 were selected for the final review after sifting in concordance with a personal reference list. Finally, 80 indexed papers were reviewed for their relevance. Both original research and review articles were included for review, including all types of thyroid surgery, that is, hemithyroidectomy, total thyroidectomy, and thyroid lobectomy.
The various techniques identified for PTG preservation in the literature are broadly classified into two categories: operative and imaging techniques (figure 2). Evidence for the various techniques and their advantages and disadvantages is systematically presented below.

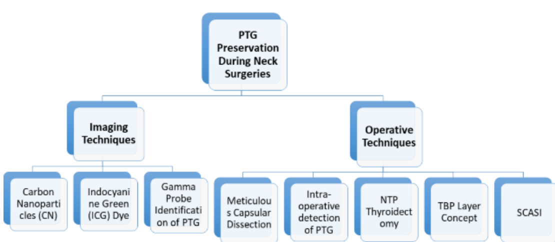

Figure 2: Summary of various PTG preservation techniques NIRL: Near Infrared Light; NTP: No Touch Parathyroid; TBP layer: layer of thymus-blood vessel-inferior parathyroid gland (IPTG); SCASI: Subcapsular Saline Injection.

Imaging Techniques

Various imaging techniques for parathyroid detection and surgical preservation include the following.

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 was not 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.

Some of these techniques are discussed 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 capillary blood (10). Therefore, 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, which can be useful for intraoperative identification and preservation of PTGs.
There is variable evidence to support the use of CNs for parathyroid preservation in routine thyroidectomies. Most clinical trials on CNs have been conducted 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 that reviewed a total of 6504 patients (not counting repetition among studies). The characteristics of the reviews are summarized in Table 1.

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	2408	424

	control group)		
Quality Assessment Method	Jadad Scoring System for RCTs Newcastle-Ottawa-Scale for Non-RCTs	Jadad Scoring System	Jadad Scoring System

Li et al. reported a 23% risk reduction in inadvertent parathyroidectomy with the use of CNs. They also showed a 21% decrease in the risk of postoperative transient hypoparathyroidism and a 38% decrease in the risk of postoperative transient hypocalcemia (11). The study also detailed the injection site for CNs and the dose injected as well as the waiting time and percentage of staining. The most common injection sites in various RCTs and non-RCTs were the upper and lower points of the tumor, followed by 2-4 points around the tumor; the average dose injected was 0.4 ml. The study was limited in that all the studied subjects were Chinese, with no representation from other ethnicities, and the quality assessment scores of the RCTs included in the study were relatively low. The review noted that while the accuracy of neck dissection and anatomical and physiological preservation of PTGs were possible with the use of CNs, further evidence is required to support this claim.

The systematic review by Wang et al. of 47 RCTs included 4605 patients, which is 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 31% decline in transient and 24% decline in permanent postoperative hypoparathyroidism. The risk of transient postoperative hypocalcemia was also 30% lower in the CN group; however, no significant reduction in the risk 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 of eight RCTs with a total of 844 patients. The included RCTs were of relatively high quality compared to previous studies, with two RCTs scoring 4 and four RCTs scoring 3 on the Jadad Scoring System. The most common procedure performed was central neck dissection (CND), mostly for papillary thyroid cancer (PTCs). A significant reduction in the risk of inadvertent parathyroidectomy (OR=0.24), transient hypoparathyroidism (OR=0.39), and postoperative hypocalcemia (OR=0.39) was reported in this study. However, this study failed to demonstrate a significant reduction in the risk of permanent hypoparathyroidism with CN use, which 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 previously, recommends the use of CNs for complete neck dissection and PTG preservation during thyroid surgery, it also stressed the need for 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 a documented role in various surgical procedures, its practical value in endocrine surgeries of the neck is relatively novel. Although no large-scale RCTs have been conducted thus 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 injected intravenously, it rapidly binds plasma lipoproteins and emits fluorescence when excited by near-infrared light (NIRL) at a wavelength of approximately 800 nm (13). Using fluorescence imaging systems, an image of the PTGs can 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 postoperative levels of parathyroid hormone (PTH) in 24 of the 26 patients; transient hypoparathyroidism was reported in 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 the use of ICG Angiography (15). A systematic review on the use of various optical technologies during thyroidectomy or parathyroidectomy also reported that ICG is the most common technique for intraoperative visualization of PTG and assessment of its vascularity, but concluded that large-scale RCTs correlating the efficacy of these techniques with postoperative 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 have been identified in 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

A detailed discussion of some operative techniques is presented below.

1. Meticulous Capsular Dissection of Thyroid Gland

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

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

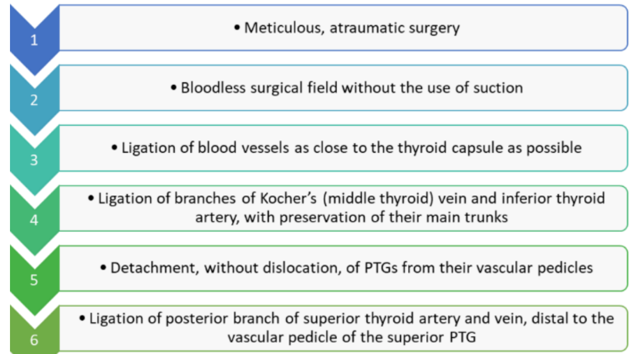

Figure 3: Essential Steps in Meticulous Capsular Dissection for Preservation of PTGs (19)

They also recommend visual identification of the viability of PTGs at the end of every operation and prompt management of venous stasis or arterial ischemia (19). In settings with less experienced surgeons or 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 reported a prevalence of permanent hypoparathyroidism of less than 0.5%.

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

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

This study showed relatively low consistency values for the PTH assay and cytological examination compared to clinician diagnosis. However, a larger, more recent trial with 86 patients by the same authors reported slightly contrasting results, with clinical eyeballing falling behind PTH analysis, and frozen section pathology is considered the gold standard test for PTG detection (21). Table 3 outlines the results of this study for comparison with the previous one.

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

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

The relative discrepancy between the two studies does not preclude the fact that intraoperative cytological detection and PTH assay are good techniques for the quick identification of PTGs during thyroid surgery and can be used as adjuncts to other techniques for PTG preservation. However, further studies are needed on 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 in situ preservation of PTGs during CND. This concept considers the thymus, IPTG, and the blood vessels connecting them as a single layer that covers the common carotid artery, trachea, and paratracheal nodes between them. Identification, exposure, and retraction of this layer instead of directly exposing the common carotid artery are helpful in preserving the IPTGs as well as the RLN (22). Wang et al. conducted a study of 487 patients (181 study group; 306 control group) who underwent total thyroidectomy with ipsilateral or bilateral CND and showed an increase in the preservation rate of IPTG 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 IPTGs were preserved in situ, devascularized, or autotransplanted. There was also a significant decrease in the incidence of transient hypoparathyroidism. Therefore, it was concluded that the TBP layer concept can aid IPTG preservation while ensuring complete LN dissection during thyroid surgeries (23).

4. No Touch Parathyroid (NTP) Thyroidectomy Technique

This technique relies on the identification and separation of PTGs from the thyroid at 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 a lower 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 preserving the PTGs. It was first assessed in a recent clinical trial of 196 patients, equally divided between the 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 aids in the identification and eventual preservation of superior PTGs. The technique was linked to a decrease in both temporary hypoparathyroidism (19.4% in the SCASI group vs. 35.7% in the non-SCASI group) and permanent hypothyroidism (0% vs. 4.1%). This study was limited by its retrospective design and small sample size, outlining the need for further prospective RCTs for this technique (25). Similar results were reported in another retrospective non-randomized trial on the role of SCASI in PTG preservation during BABA robotic thyroidectomies (26).

CONCLUSION AND RECOMMENDATIONS

Based on our review of the literature, no single technique is universally acceptable for parathyroid preservation during neck surgery. Different imaging and operative techniques have various practical applications, and while some techniques such as Carbon Nanoparticles (CNs) appear promising, they cannot be easily applied in lower-middle-income countries (LMICs). Therefore, it is important that prospective, large-scale RCTs be carried out for 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 derived from this literature review are as follows.

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

More research in the form of prospective trials is needed to develop uniform guidelines to aid in PTG preservation during surgery.

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Disclosure: None

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

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