

## Evaluation of Incidence and Risk factors of Hypocalcemia after Parathyroid Preservation total Thyroidectomy in Patients of Thyrotoxic Goiter

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### Abstract

**Introduction:** Thyrotoxic nodules usually present with diffuse goiter, exophthalmos and rarely pretibial edema. Thyroidectomy is considered to be safe with morbidity of less than 5% as described in literature. The associated complications following thyroidectomy are injury to recurrent laryngeal nerve, postoperative haemorrhage and hypocalcaemia; among which hypocalcemia is the most common, with an incidence of 7-51%. The quality of life is affected significantly by hypocalcemia following thyroidectomy.

**Study Design:** Prospective clinical study.

**Methodology:** Thirty-two patients had undergone total thyroidectomy for thyrotoxicosis. Preoperatively, patients were treated with Methimazole and  $\beta$ -blockers for 4-6 weeks until the T3 and T4 levels were reduced to near normal and were subsequently admitted in ENT ward. Lugol's iodine was administered for 5-7 days as a preoperative preparation before the planned total thyroidectomy with parathyroid preservation.

**Results:** All the patients developed hypothyroidism and were treated with Levothyroxine. 93.6% cases with preserved parathyroid developed temporary hypocalcaemia and needed calcium supplementation for 3 to 8 weeks. Only 6.4% cases had permanent hypocalcemia after six months of surgery and needed lifelong calcium and calcitriol replacement.

**Conclusion:** In conclusion, the most important factor for predicting postoperative hypocalcemia is the number of preserved parathyroid glands and it was found that, to avoid permanent hypocalcemia only two functional parathyroid glands are required. Thus it is imperative for the surgeon to make every attempt at identifying and preserving parathyroid glands and its blood supply.

**Keywords:** Thyrotoxicosis, Hypocalcemia, Total Thyroidectomy.

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### Introduction

Hypocalcemia is the commonest complication after total thyroidectomy, though it is considered to be a safe procedure. Hypocalcaemia may be

temporary in some cases, but can be permanent due to loss of functioning parathyroid glands. The patients need to take long term oral calcium and calcitriol

supplementation which causes significant discomfort<sup>1</sup>. As per literature the incidence of postoperative hypocalcaemia is increased with injury to the parathyroid glands or its blood supply, extensive surgical resection, total thyroidectomy with neck exploration, Graves' disease, thyroid carcinoma, and hemodilution.[2-7] The injury to parathyroid gland is considered to be the most common factor for developing postoperative hypocalcaemia. Proper identification of all parathyroid glands and preservation of their blood supply during the surgery should be attempted to minimize the injury. Identification and preservation of all parathyroid gland is difficult and, in this process, there can be damage to blood supply of the parathyroid glands. Unintentionally removed or de-vascularized parathyroid glands can be auto-transplanted to reduce the incidence of hypocalcemia.[8,9] Postoperative specimen containing parathyroid glands have been reported in a study, that were unintentionally removed with the thyroid gland or the lymph nodes during surgery.[10] Clear cut data does not exist on the numbers of parathyroid glands that need to be preserved *in situ* to prevent postoperative hypocalcaemia. Ability of the surgeon to predict the postoperative hypocalcaemia is very important in the postoperative management. Early detection of the risks for hypocalcemia is the most important determining factor to reduce the hospital stay and avoid unnecessary laboratory examinations. The frequency of postoperative hypoparathyroidism is a significant clinical challenge for the thyroid surgeon because of the absence of well-established preoperative predictors.

### Aims and Objectives

1. To predict the incidence of hypocalcaemia following total thyroidectomy with parathyroid preservation in cases of thyrotoxic nodules.

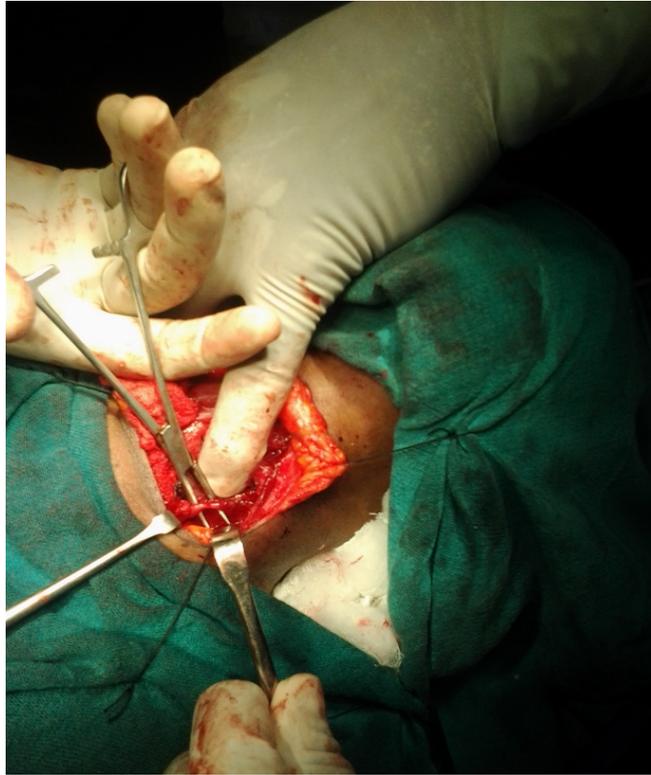
2. To find out the risk factors for postoperative hypocalcaemia associated with total thyroidectomy.

### Materials and Methods

This study was conducted in Fakir Mohan Medical College, Balasore in collaboration with Kalinga Institute of Medical Science, Bhubaneswar from June 2015 to June 2019. This study was a prospective clinical study. Thirty-two patients with thyrotoxicosis attending endocrinology OPD with symptoms of diffuse goitre, palpitation, proptosis, pretibial myxedema were selected for surgery. All these patients were treated with thionamides (Methimazole or Carbimazole) and  $\beta$ -blocker (Propranolol) for more than 6 months. Those patients, who were not responding to thionamide treatment after 6 months of therapy, were considered for total thyroidectomy. These 32 cases were admitted to ENT ward for preoperative preparation with high dose of Methimazole (up to 40 mg daily in divided doses), Propranolol (up to 120 mg daily in divided doses) and oral Lugol's Iodine solution. The Lugol's Iodine was given in form of drops, with each drop containing 8 mg of iodine. Three drops of Lugol's iodine were given 3 times a day as per protocol published by Roy et al.[11] Serial measurements of serum FT4 was done until a near normal level was achieved. After attaining a euthyroid state, they were taken up for total thyroidectomy under general anaesthesia. Collar incision was made from one sternocleidomastoid muscle to the other at the level of 2 fingers above xiphisternum. Sub-platysmal flaps were elevated superiorly up to the hyoid and inferiorly 2 centimetres below the lower pole of the thyroid. Under microscope, the inferior thyroid arteries were identified along with its parathyroid branch (Figure-1). The inferior thyroid artery was ligated by subcapsular dissection and parathyroid branch was preserved. Superior and middle thyroid pedicles were identified and subcapsular dissection was done on both sides. Both the thyroid lobes along with

isthmus were separated from trachea. One side parathyroid gland (2 in no.) along with their blood supply were preserved. The specimen of total thyroidectomy was delivered, suction drain kept and wound closed in layers (Figure:-2). Serum calcium

was measured on the first postoperative day for the detection of any hypocalcaemia. The patients who developed postoperative hypocalcaemia were managed with calcium gluconate injection.



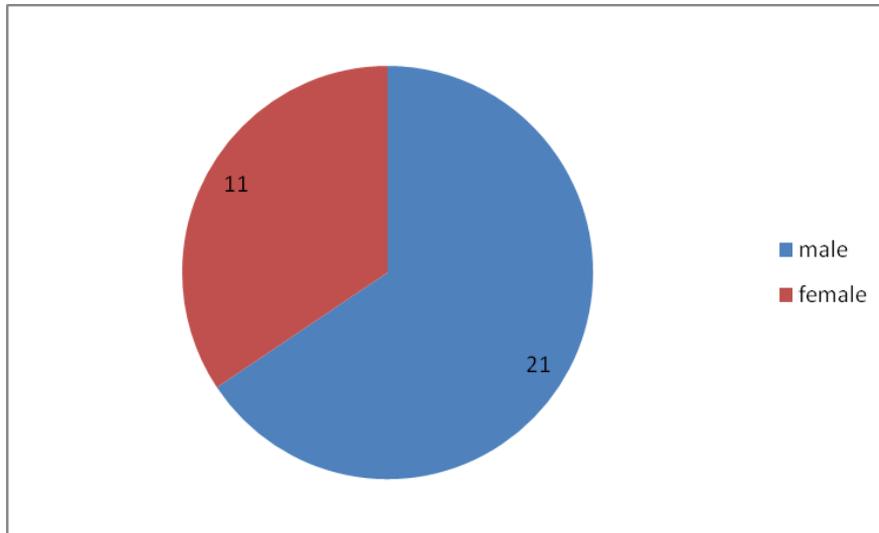
**Figure 1: Inferior thyroid pedicle**



**Figure 2: total thyroidectomy specimen**

**Results:**

There were 21 females and 11 male patients in this study with male to female ratio of 1:1.9. The age range in the study population was 14.5 to 65 years with mean age of 35.25 (Figure-3, Table-1).



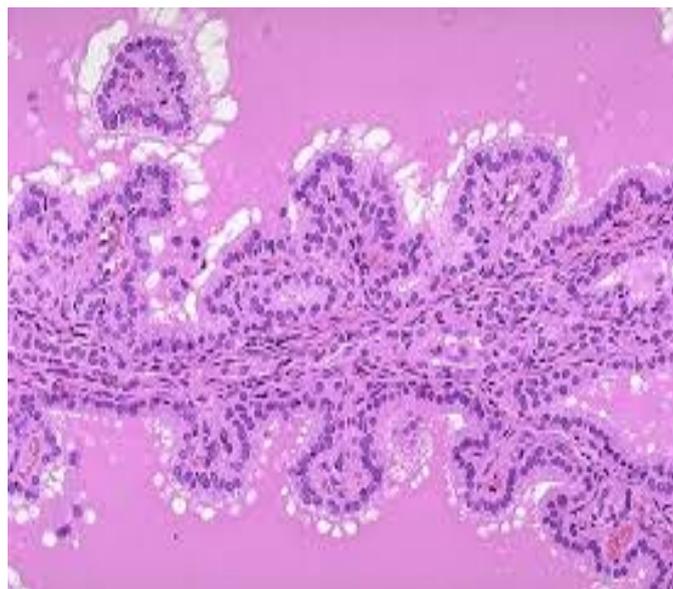
**Figure 3: Sex distribution**

**Table 1: Age Group and Sex**

Age group	Male	Female
10- 20 years	0	6
0 Ears	2	8
>30 years	9	7

**Histopathology**

Minimal to moderate lymphocytic infiltration was observed in 25 of total 32 resected specimens. (Figure-4).



**Figure 4: Post operative histopathology**

In this study, we had preserved parathyroid glands in all the cases except in one case because of harboring multifocal micropapillary carcinoma. Temporary hypocalcaemia developed in 93.6% cases of parathyroid preservation thyroidectomy, and needed calcium and calcitriol supplementation for a period of 3 to 8 weeks. Two patients developed permanent hypocalcaemia despite parathyroid preservation. (Table-2).

**Table 2: Hypocalcaemia and calcium supplement**

No of cases	Temporary/ Permanent hypocalcaemia	Duration of calcium supplement	Serum calcium after 1 year
16	Temporary	3 weeks	Normal
13	Temporary	8 weeks	Normal
2	Permanent		Persistence hypocalcaemia

## Discussion

Definitive therapy in the form of total thyroidectomy has increased in the recent years for thyrotoxic patients with diffuse goitre that are responding poorly to medical therapy and are unlikely to achieve remission. This has been facilitated by the initial presentation of thyrotoxicosis with very high levels of thyroid hormones, high titre of anti-thyroid receptor antibody (TRAb), larger goitre size and availability of experienced thyroid surgeons. The technical advancement and better knowledge of thyroid anatomy result in thyroidectomy being performed safely[11]. However, postoperative complications are inevitable even with experienced surgeons. The factors responsible for development of hypocalcaemia after thyroidectomy are largely unknown, and are likely to be multifactorial. The possible etiological factors include surgical technique, iatrogenic damage to the parathyroid (injury, edema, infarction, ischemia), extent of thyroidectomy, Graves' disease, concomitant presence of malignancy, nodularity of the thyroid gland, patient gender, degree of postoperative drop in serum calcium and iPTH level, presence of thyroiditis, proper intraoperative identification of the numbers of parathyroids, and presence of diabetes. Postoperative bleeding, injury to recurrent laryngeal nerves and parathyroid stunning are the commonly observed complications following total thyroidectomy[12-14] Even with very careful dissection, parathyroid

insufficiency or stunning is common in cases of total thyroidectomy with parathyroid glands preservation because of the difficulty in identifying the normal parathyroid glands and in preserving their blood supply.

In this study, the incidence of transient and permanent hypocalcemia in was 9.2%, and 0.5%, respectively, which is comparable to previous reports of patients who had thyroidectomy[11,15,16] The patients with postoperative hypocalcaemia received oral calcium and calcitriol to achieve a calcium level close to the lower limit of normal range to mitigate symptoms of hypocalcaemia. With subsequent follow-ups, 30 patients out of a total 32 (93.6%) regained normal serum calcium level over a period of 3-8 weeks after stopping calcium and calcitriol supplementation and were labelled as transient hypoparathyroidism. The probable explanation for this transient hypoparathyroidism is parathyroid stunning or relative ischemia and has been described in case of parathyroid injury, extensive lymph node dissection, parathyroid devascularization, and Graves' disease[17-18] The reported incidences of postoperative hypocalcaemia are more common in cases of total thyroidectomy for Graves' disease[4,7] In this present study, 32 patients were being treated for Graves' disease at the time of operation. The incidence of permanent hypocalcemia in our study was 6.4% which are lower than earlier reports which was 9.37%. was 9.37% among patients with Graves' disease;

but there was no correlation between the presence of Graves' disease and the development of hypocalcemia.

In the present study, the risk factor for developing postoperative permanent hypocalcemia in one case was involvement of parathyroid by multifocal micropapillary thyroid carcinoma. In the other case, permanent hypocalcaemia may be explained by accidental devascularisation of the parathyroid glands during surgery, as dissection may increase the risk of injury to the inferior parathyroid glands and their blood supply. The surgery under operating microscope, result in parathyroid glands and their blood supply can be separated from the thyroid gland and the central node group within the fat by meticulous dissection. There is some sort of advantage, by carefully dissecting the overlying fascia, between the parathyroid glands and their blood supply within the thymic tissue and the central node group within the fat.

During total thyroidectomy, the anteriorly located or intrathyroidal parathyroid glands are difficult to preserve successfully. The implantation of parathyroid glands into muscles, that are removed intentionally may also fail to survive in all cases. Discoloration tend in parathyroid due to direct trauma should not be preserved. Parathyroid glands with unintentional injury to their blood supply may be implanted or removed, as there is description of successfully preventing hypoparathyroidism with at least two functional parathyroid glands, and no additional advantage of having more than two identified and preserved parathyroid glands<sup>4</sup>. In our study of 32 cases, we were able to identify the parathyroid glands and their blood supply in all. Intraoperative identification of the parathyroid glands in our study varied from two to four. We were able to preserve at least 2 glands with intact blood supply in 31 cases. Further, Attie and Khafif have suggested that hypocalcaemia can be avoided by at least two functional parathyroid glands.[11] In a study of 83

patients, attempting parathyroid preservation thyroidectomy, 1.7 glands could be preserved successfully, whereas in our study we could preserve 2 glands in all cases. The incidence of permanent hypoparathyroidism in their study was 9.37% while it was 6.4% in our study.

In literature, opinions differ regarding the relationship between development of postoperative hypocalcemia and patient age, but it was also observed that there was no significant difference in mean age between patients who developed transient hypocalcaemia and those who did not.[19]

Several studies have tried to explore the reason behind the higher prevalence of post-thyroidectomy hypocalcaemia in females but the exact mechanisms are still elusive. In one study, the differential sex steroid effect on PTH secretion, genetic variability in cell-signalling pathways as well as possible iatrogenic surgical damage due to anatomic differences providing a relatively diminutive operative field have been ascribed to the higher incidences postoperative hypocalcaemia in females.[19]

There are only few studies in literature that have investigated the relationship between diabetes and postoperative hypocalcaemia. Statistically significant correlation was noted in some studies with presence of diabetes and recovery of parathyroid function following thyroidectomy. Though the proposed hypothesis emphasizes on presence of small vessel disease and impact on angiogenesis for the vulnerability to parathyroid gland to hypoxia in diabetic subjects, the exact mechanism is unclear[21,22]. This hypothesis was not confirmed in this another study, and no significant difference ( $p = 0.399$ ) was observed on development of more frequent hypocalcaemia among diabetics than nondiabetics.

Another controversy revolves around the systematic examination of all four parathyroid glands during thyroidectomy.

Some of the published studies suggest physical identification of all four glands and to preserve as many as possible[23-25]. In one series, a higher level of postoperative PTH was found with a higher number of intraoperative parathyroid gland identification, but statistically significant correlation was not observed with the incidence of postoperative hypocalcaemia ( $p = 0.63$ ). However every surgeon must be aware of the anatomic complexity contributing to difficulty in identification which may prevent unfavourable outcome following thyroidectomy. Strict adherence to capsular dissection is the optimum method for safe preservation of parathyroid gland and may obviate the need of intraoperative systematic identification. It includes the distal ligation of all terminal branches of the superior and inferior thyroid arteries close to the thyroid capsule and enables reliable separation of all tissues carrying parathyroid gland away from the thyroid surface. The aim is to identify all parathyroid glands with meticulous capsular dissection to avoid risk of mechanical injury or devascularisation of the parathyroid glands[22].

There are differences in opinions regarding the definitions of temporary and permanent postoperative hypocalcaemia. Differences in the occurrence of postoperative hypocalcaemia may be accounted by the incidence of accidental parathyroid injury during thyroidectomy, the extent of the procedure and the final pathologic diagnoses from the pathologic specimens. The definitions of temporary and permanent postoperative hypocalcemia are based on biochemical as well as clinical evaluation. Incidence of biochemical hypocalcemia (3-56%) is higher than that of clinical definition (4-39%) with a partial overlap[26-28]. In this study, IP was associated with an increased incidence of temporary/permanent hypocalcemia, regardless of whether the biochemical or clinical definition was used. The standard definition of permanent postoperative hypocalcaemia was derived from a study

that included 99 thyroidectomy cases in which the recovery of parathyroid postoperatively was noted maximum within a period of six months.[28]

There are several limitations in our study that include the sample size, which was relatively small. The levels of initial thyroid hormones were not available in all cases and the titre of TRAb was not measured in all patients. Postoperative PTH estimation was not done in all cases, so also the assessment of Vitamin D status. Different sizes of the goitres and presence of varying degrees of thyroiditis noted in surgical specimen as well as the presence of multifocal micropapillary thyroid carcinoma in one case might have a bearing on the overall incidence of postoperative hypocalcemia.

There were several limitations in our study. The definition of permanent hypocalcemia varied between the included studies described in literature. This study had subgroup analyses of different follow-up durations, the effect of other definitions, including continued calcium supplementation and serum calcium and serum parathormone levels, was not discussed due to insufficient sample size. Also due to confounders and heterogeneity was noted in our analysis. It was also seen that surgery volume might be a confounder because experienced high-volume surgeons might dissect more expertly and have greater anatomical knowledge of the parathyroid gland. It was proposed that, thyroid pathology experts at higher-volume centers are better at identifying incidental parathyroidectomy. In one of the study that included cases that received intraoperative parathyroid gland transplantation, and this a known factor affecting postoperative hypocalcemia. The effect of lymph node dissection and reoperation could also not be eliminated because is no recognized standard for reporting this regard, but some low-quality studies did not report data in a standardized fashion, which might also have caused the heterogeneity and

publication bias found in our analysis. The authors proposed to have a multicenter research is might be necessary to address this issue. The sensitivity analysis, subgroup analysis, and a random-effects model were used to address this, but the interpretation of our results was based on a sufficient understanding of these limitations

### Conclusion

The number of preserved parathyroid glands is the most important factor for predicting the incidence of postoperative permanent hypocalcemia following total thyroidectomy for thyrotoxic goiters. Preservation of at least two functional parathyroids can prevent the development of permanent postoperative hypocalcaemia. Thus every effort should be made by the surgeon to preserve as many as parathyroid glands with intact blood supply during total thyroidectomy.

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