Results of a Prospective Multicenter Study Evaluating the Incidence of Postoperative Hypocalcaemia following Total Thyroidectomy

(Original Research Article)

Mohammed O. Bohlala[1], Aisha M. Bojazyah[2], Nagah A. Hussein[3]

[1,2] Department of Surgery, Faculty of Medicine, University Of Derna, Derna, Libya

[1,2] Department of Surgery, Alwahda Teaching Hospital, Derna, Libya

[3] Department Of Medical Care, College Of Medical Technology, Derna, Libya

Corresponding Author: Dr. Aisha Bojazyah, Department of Surgery, Faculty of Medicine, University of Derna, Derna, Libya. E.mail: Aishaelgazwi@yahoo.com

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Abstract

Postoperative hypocalcaemia is a serious complication following a surgery on thyroid gland and is generally thought of to be due to low parathyroid hormone as a result of inhibition of parathyroid gland function. It can either be transient or permanent, in case of which lifelong calcium supplementation is required. Total thyroidectomy may be associated with potential risk of removal of 2,3 or even 4 parathyroid glands, in addition to the risk of circulatory compromise of the parathyroid glands due to manipulation of its vessels intraoperatively. This is a prospective study conducted for duration of 3 years and includes 100 consenting in patients undergoing total thyroidectomy aimed to evaluate the incidence of hypocalcaemia following total thyroidectomy. Data was collected by meticulous history taking, careful clinical examination, appropriate radiological and haematological investigations, including serum calcium. Follow-up of the cases was done for detection of postoperative hypocalcemia and if present was confirmed by assessing ionized calcium. Postoperative hypocalcemia occurred in 8 (8%) patients confirmed by decrease ionized calcium level. The peak age group in which the patients presented was between 40-60 years (46%). The commonest clinical diagnosis was that of solitary thyroid nodule (50%) followed by multinodular goiter (38%). All of the patients who developed postoperative hypocalcaemia were females and none of them developed symptomatic hypocalcaemia. Although uncommon, post-operative hypocalcaemia is seen following total thyroidectomy. In this study, all of the patients who developed postoperative hypocalcaemia became normocalcemic by postoperative day 3. Following total thyroidectomy postoperative hypocalcaemia is transient and usually requires no treatment.

Keywords: Total Thyroidectomy; Incidence; Postoperative complications; Hypocalcemia; Hypoparathyroidism.

Introduction

Hypocalcemia is a common post-operative complication following thyroid surgeries. It can be symptomatic or asymptomatic and it usually occurs in the first few days after the surgery [1,2]. Development of post-operative hypocalcaemia is multifactorial. Factors linked to the development of post-operative hypocalcaemia include surgical technique, iatrogenic parathyroid damage (injury, edema, infarction, ischemia), extent of thyroidectomy, hyperthyroidism, malignancy, patient gender, perioperative serum calcium drop, presence of thyroiditis, diabetes, number of parathyroid glands identified intraoperatively [3,4,5]. In less extensive thyroid surgeries, post-operative hypocalcaemia if present is transient and usually requires no treatment. Acute hypocalcaemia may endanger life. Hence close monitoring in the postoperative period, early identification of signs and symptoms of hypocalcaemia and effective management is crucial in the management of post thyroidectomy hypocalcaemia [6].

Hypocalcaemia can be defined as serum calcium level lower than 8.5 mg/dl and ionized calcium level lower than 4.6 mg/dl. Based on symptoms hypocalcaemia can be further classified into: asymptomatic, moderate hypocalcaemia with numbness, tetany, Chovestek'a sign, Trousseau's sign, and severe hypocalcaemia with ECG changes (U waves, QT prolongation) or bronchospasm. With regard to duration: temporary hypocalcaemia which lasts for less than 6 months duration and permanent hypocalcaemia that lasts for more than 6 months. [1] Asymptomatic hypocalcaemia can be managed by per oral replacement of calcium starting with low dose and titrate according to 24 hours serum calcium assessment. Moderate hypocalcaemia can be treated in general ward with initial high dose of oral calcium along with calcitriol supplementation (0.5 mcg/day) [2]. Patients with severe hypocalcaemia should be treated in intensive care unit with intravenous calcium gluconate (10 ml calcium gluconate is diluted in 100ml normal saline and infused over 15 minutes intravenously) with frequent monitoring of serum calcium levels and continuous cardiac monitoring is done. Once normocalcaemia is achieved, switch over to oral calcium supplementation with Vitamin D. [1]

Various studies regarding serial calcium estimation and analysis postoperatively and the prediction value of post thyroidectomy hypocalcaemia show varying results. But the cost factor of the parathormone estimation may necessitate the use of calcium estimation even in small health care delivery systems. Study conducted by Ancuta Leahu et al shows that patients with positive calcium trend ie, rise of postoperative calcium levels on serial estimation and normocalcaemic pattern excludes hypocalcaemia successfully in 96.2% of patients. The same study shows that the patients with negative calcium trend ie, a serial fall in serum calcium level after thyroid surgeries may result in hypocalcaemia in 51.6% of patients. From these results he concluded that patients with positive calcium trend can be discharged earlier without the fear of hypocalcaemia and patients with negative calcium trends have to be monitored for some more days for hypocalcaemia. [1]

In order to prevent post thyroidectomy hypocalcaemia, the surgeon must have adequate knowledge about surgical anatomy and embryology of thyroid and parathyroid glands. The surgeon must ensure good exposure of the operating field with good light source.[7] Perfect

hemostasis maintained for identification of parathyroids in the operating field with naked eyes. Meticulous dissection should be done throughout the procedure. Prompt recognition of parathyroids by size, colour and location. in addition to careful identify and protect the blood supply to the parathyroids by ligation of inferior thyroid artery at its terminal branch level. Moreover, avoid parathyroid hematoma and excessive suction in the field. In case of accidental injury to parathyroid glands where the perfusion of the gland is doubtful resulting in colour change, immediate parathyroid auto-transplantation in the same side sternocleidomastoid must be performed. Close postoperative follow up and early diagnosis and management also play a crucial role in post thyroidectomy hypocalcaemia. [5]

Methods

Data Collection

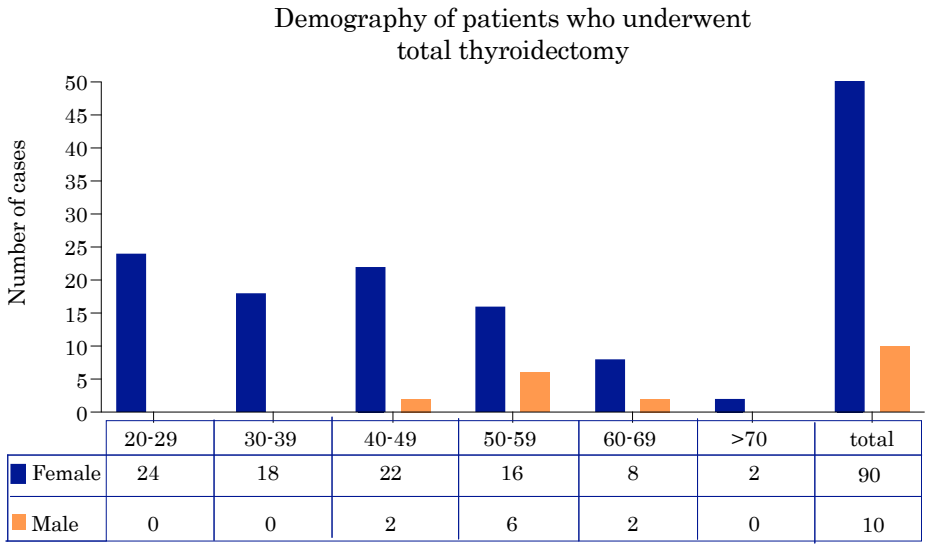
All patients above the age of 20 years admitted in male and female surgery wards of multicentres medical hospitals at the western parts of Libya (Derna, Al-Qubba and Umm Ar Rizam) who underwent total and hemi-thyroidectomy from November 2018 till August 2021. This is a prospective study conducted for a duration of 3 years and includes 100 consenting in-patients undergoing total thyroidectomy.

Data were collected by meticulous history taking, careful clinical examination, and appropriate radiological and haematological investigations, including serum calcium level. Follow-up of the cases was done for detection of post-operative hypocalcaemia and if present was confirmed by assessing ionized calcium and parathormone levels. Patients with pre-existing hypocalcaemia and primary parathyroid pathology were excluded from this study.

Results

The present prospective study was done on 100 patients who fit into the inclusion and exclusion criteria and had undergone total thyroidectomy at three Medical centers across eastern part of Libya from November 2018 till August 2021.

In this study the youngest patient was 20 years old whereas the oldest patient was 75 years old. The average age was 42.1 years (Figure 1).



	20-29	30-39	40-49	50-59	60-69	>70	total
Female	24	18	22	16	8	2	90
Male	0	0	2	6	2	0	10

Figure 1: Age Distribution of the Patients in Years.

Out of the 100 patients, studied 90 were female whereas 10 were males with a female to male ratio of 9:1 (Figure 2).

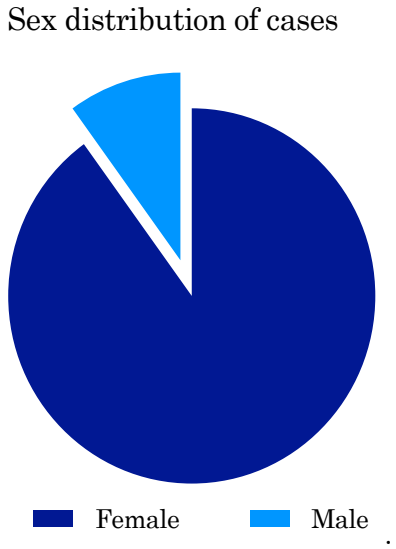


Figure 2: Sex Distribution of the Patients in Years.

Half of the patients had a clinical diagnosis of solitary thyroid nodule while the next most common diagnosis was that of multinodular goitre with 38%. Patients with toxic goitre, colloid goitre and Grave's disease made up 4% each of the cohort (Figure 3).

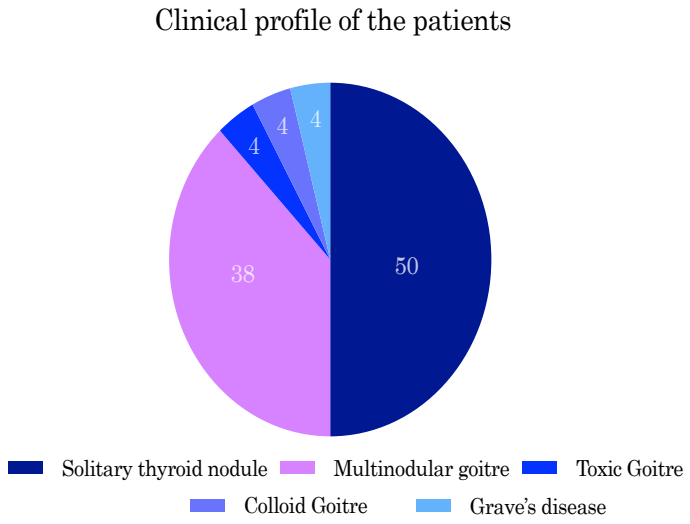


Figure 3: The Clinical Profile of Patients Who Underwent Total Thyroidectomy.

Majority of the patients (86%) had presented with a swelling in the anterior aspect of the neck, the next most common presentation was that of a swelling in the anterior aspect of the neck associated with pain (9%) (Figure4).

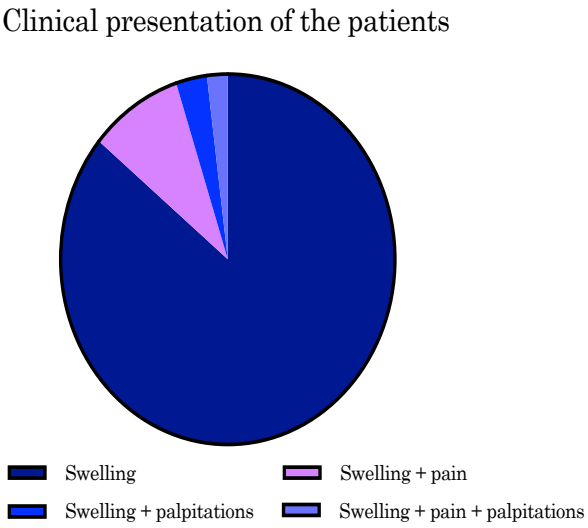


Figure 4: The Clinical Profile of Patients Who Underwent Total Thyroidectomy.

All 100 cases had undergone total thyroidectomy. Most of the patients (86%) had a hospital stay of less than 2 days.

4 patients had an extended postoperative stay of 3-5 days due to other complications like surgical site infection and hematoma formation (Figure 5).

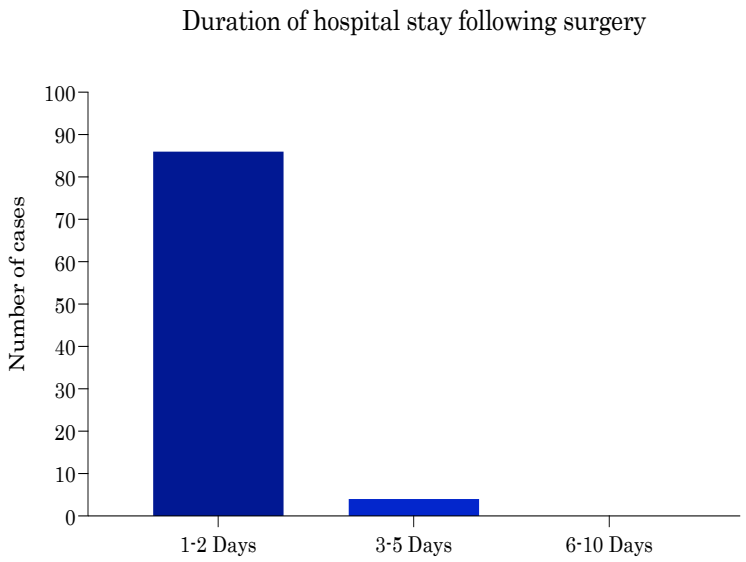


Figure 5: Duration of Hospital Stay following Surgery.

Two of the patients who had hypocalcaemia belonged to the age group of 50-59 years were operated for recurrence (Figure 6).

Out of the 8 patients who had post-operative hypocalcaemia, 6 had undergone total thyroidectomy and had a clinical diagnosis of multinodular goitre and 2 had undergone total thyroidectomy with a clinical diagnosis of papillary thyroid cancer (Figure 7).

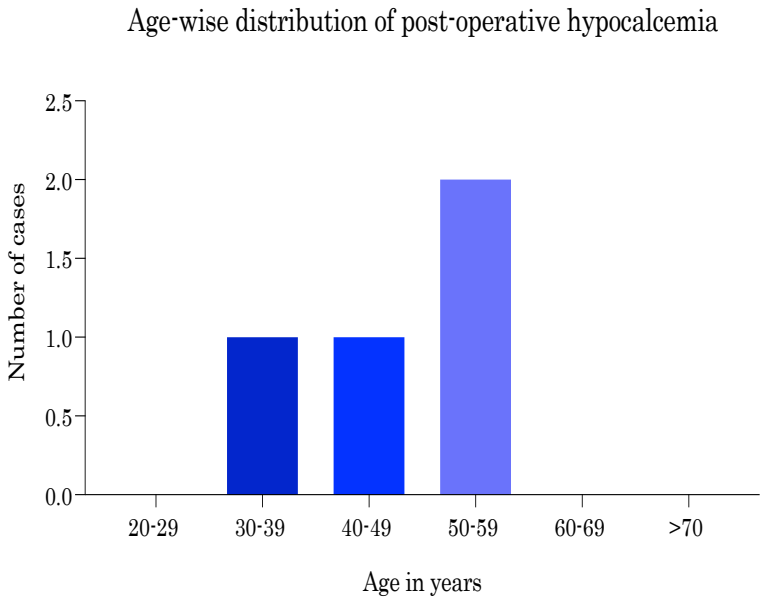


Figure 6: Age Distribution of the Patients in Years.

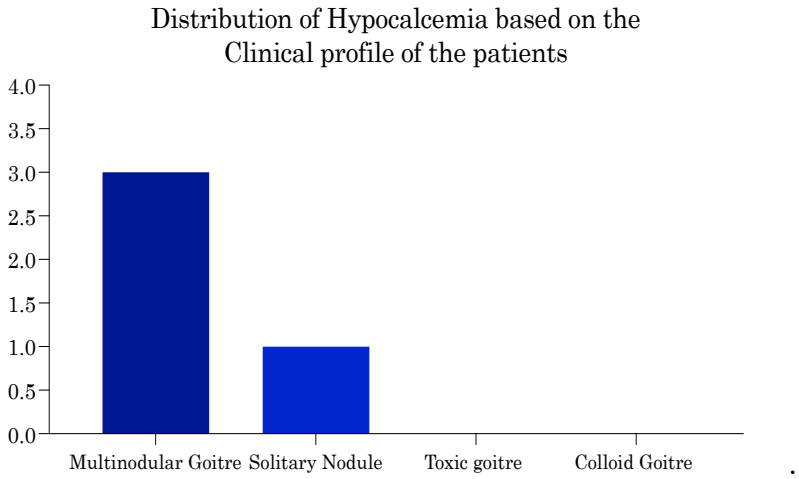


Figure 7: Distribution of Hypocalcemia Based on the Clinical Profile of the Patients

. ***Trend of Hypocalcaemia in the Postoperative Period***

Out of the total 100 patients,8 female patients developed post-operative hypocalcaemia as determined by the corrected calcium levels done on post- operative day 0. This was confirmed by ionized calcium and parathormone levels, which were also found to be low. All 8 of the patients were asymptomatic and their corrected calcium levels normalized by post-operative day 3. None of the patients were treated for their hypocalcaemia (Figure 8). In all of the patients who were diagnosed to have postoperative hypocalcaemia on the basis of corrected calcium levels done on postoperative day 0, both ionized calcium and parathormone were also decreased.

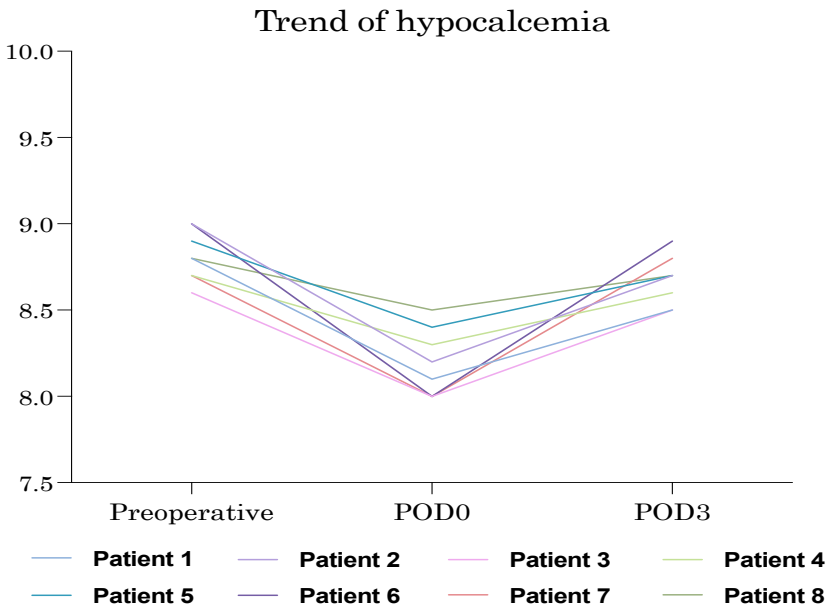


Figure 8: Trend of Hypocalcaemia Based on the Operative Day.

Discussion

Post-thyroidectomy hypocalcaemia is one of the most common complications[2]. According to the literature, post-thyroidectomy hypocalcaemia occurs in 50–68% of patients[3,4]. In our study, Post-thyroidectomy hypocalcaemia developed in 8% of the patients. This study includes patients with both benign and malignant thyroid conditions. In a study done by Liu et al there was a similar mean age of 46 years in a cohort of patients with benign thyroid diseases[5]. Most of the patients in this study were female with a female to male ratio of 9:1. This is similar to some studies, like that done by Limonard et al[6], but is slightly different than other series, mostly Western in which the male ratio is slightly higher, but with a female preponderance nonetheless[7,8]. The effects of female gonadal hormones and X chromosome inactivation on thyroid gland and immune system greatly contribute to the female predilection of autoimmune thyroid disease. The former mainly include prolactin and estrogen. The direct actions of estrogen on the thyroid tissue contribute to the development of thyroid goiter, nodule and cancer in women[9]. The clinical diagnosis of the patients who presented were solitary nodule thyroid (50%), multinodular goitre (38%), toxic goitre (4%), colloid goitre (4%) and Grave's disease (4%). This in contrast to most other studies done, in which multinodular goitre had a higher prevalence.[10,11,12] This could be explained due to the fact that these studies were done in a predominantly western cohort consisting of Caucasian patients.

In this study out of the total cohort of 50 patients, 4 patients (8%) developed post-operative hypocalcemia on post-operative day 0, as evidenced by the fall in corrected calcium levels. This was further confirmed by assessing ionized calcium and parathormone levels, both of which were low. By the third post-operative day calcium levels normalized. None of these patients were symptomatic and did not receive calcium correction in any form. In a study done by John et. al. in 1966 a similar trend was observed with a serum calcium falling by the first post-operative day and subsequently normalizing[13]. Hypocalcaemia is a common complication after thyroid surgery. It usually occurs in first days after surgery and it can be symptomatic or asymptomatic. The frequency of transient hyperparathyroidism after thyroid surgery is between 6.9 and 49%. The studies showing lesser incidence of post-operative hypocalcaemia included more patients who had undergone less extensive thyroid surgery whereas those studies which showed higher incidence of hypocalcaemia had included patients who had undergone more extensive thyroid surgery.[14,15,16,17,18,19] Variability of incidence rates of post-operative hypocalcaemia could also be explained due to different authors applying differing definitions of hypocalcaemia and lack of a single standard definition.

Post-operative hypocalcaemia after thyroid surgery is not properly understood although it is thought to be multifactorial. These factors include surgical technique followed and iatrogenic damage to the parathyroid which can be due to direct injury, edema, infarction or ischemia.

Other factors which can lead to hypocalcaemia include extent of thyroidectomy, hyperthyroidism, malignancy, patient gender, perioperative serum calcium drop, presence of thyroiditis and number of identified parathyroid glands intraoperatively. Post-operative hypocalcaemia may be attributed to temporary hypoparathyroidism caused by reversible ischemia to the parathyroid glands or hypothermia to the glands. Most authors believe that post thyroidectomy hypoparathyroidism occurs because of ischemia secondary to ligation of inferior thyroid artery. This is a logical inference, as the blood supply to parathyroid glands comes mainly from this vessel.[20,21,22] post-operative hypocalcaemia may also result from non-specific hemodilution that occurs due to stress of surgery.[23,24,25] Some studies have shown that a release of calcitonin in the immediate post-operative period could explain the causation of transient hypocalcaemia, whereas a few other studies have refuted this. It has been suggested that when subtotal thyroidectomy is done in patients with hyperthyroidism, post-operative hypocalcaemia may result due to sudden reversal of negative bone and calcium balance (hungry bone syndrome).[26] But all of the patients who undergo thyroid surgery are rendered euthyroid hence their osteodystrophy would have been corrected, hence going against the above hypothesis. However in this study we were unable to fully study the relationship between hyperthyroidism and post-operative hypocalcaemia.

Another suggested cause of post-operative hypocalcaemia includes unilateral absence of parathyroid glands or the presence of one gland on one side, with inadvertent removal of the parathyroid glands present on the other side. This is seen in Lobdell-DiGeorge syndrome which can present with approximately 38 anomalous combinations. But this is a rare case and the hypocalcaemia in this case would either be transient or permanent hypocalcaemia depending upon whether the intact lobe has a single or no parathyroids.[27] Most studies underline the significance of expertise and surgeon's experience. Hypocalcaemia in the post-operative period was more commonly seen in the female gender.[13,15,28,29] Although other studies showed that gender has no significant effect on the incidence of hypocalcaemia.[19,30,31] In our study all of the patients who developed hypocalcaemia were female.

According to literature gender has been identified as a significant risk factor for hypocalcaemia. Many previous studies tried to explain the higher prevalence of post-operative hypocalcaemia in females; they suggested that the disparity could be due to the effects of sex steroids on PTH secretion, genetic variation among cell-signaling pathways or anatomic differences that can cause more frequent iatrogenic damages because of a more diminutive operative field.[32] Some studies identified low preoperative level of serum calcium as a risk factor for the development of transient hypocalcaemia.[33,34,35,36] Whereas in this study, no such difference has been identified between mean preoperative serum calcium level in early hypocalcaemia group and in normocalcemic group.

In this study, hyperthyroidism did not appear to be significantly related to the development of post-operative transient hypocalcaemia. This is corroborated by the studies done by Ozemir et

al in 2016 and Noureldine et al in 2014.[37,38] On the other hand in a few other studies hyperthyroidisms has been linked to the development of post-operative hypocalcaemia.[39,40,41] This could be due to the larger size of thyroid gland in thyrotoxicosis which makes operating on it a much more challenging prospect. In this study all the 8 the hypocalcaemia patients who had undergone total thyroidectomy had substantially large multinodular goitres. The extent of thyroidectomy and the surgical technique followed are invariably linked to parathyroid injury, edema, infarction, ischemia or incidental parathyroidectomy.[14,41,42] Trying to identify the recurrent laryngeal nerve and dissection around the parathyroid glands lead to edematous venous congestion. Another cause of venous congestion is ligation of thyroid veins. Eventually venous stasis reduces parathyroid function and may lead to transient hypocalcaemia.[20] In this study the incidence of transient hypocalcaemia was much lower than other studies since the cohort consisted only of patients who had undergone less extensive thyroid surgery. The importance of intra operative identification of all 4 parathyroid glands is controversial. Some authors recommend routine physical identification and preservation of as many of parathyroid glands as possible.[40] Other authors have questioned this strategy.[21,33,43,44,45] To avoid potential injury to the parathyroid glands, every surgeon must be thoroughly aware of their anatomic complexity that contributes to difficulty of identification and possible injury. Strict adherence to capsular dissection represents the optimum method for safe preservation of parathyroid glands without necessitating their systemic identification. Distal ligation of all terminal branches of the superior and inferior thyroid arteries, close to the thyroid capsule, enables reliable separation of all tissues carrying parathyroid gland away from the thyroid surface. Continued dissection in this tissue, with the aim to identify all parathyroid glands may increase the risk of their mechanical injury or devascularization.

In this study all of the patients who developed post-operative hypocalcaemia showed a fall in parathormone levels. Similar trend was seen in the studies conducted previously.[41,42,43] Graff et al have suggested in their study that a single early post-operative intact parathormone measurement may be the most cost effective screening tool for hypocalcaemia and combined with the serum calcium measurement on post-operative day 0 increases the specificity of detecting post-operative hypocalcaemia.[42]

Thyroid surgery may compromise the parathyroid function either by direct trauma or by impairment of blood flow. This in turns leads to fall in the serum parathormone levels, which leads to hypocalcaemia. Detection of hypocalcaemia was based on clinical observation of signs and symptoms connected to the fall in calcium levels that are usually seen hours after surgery. But now with advent of newer specific immunoassays that can accurately determine the circulating levels of parathormone, post-operative measurement of parathormone levels can be used as an early predictor of post- operative hypocalcaemia. Parathormone has a very short half-life of 3-5 minutes hence a drop in parathormone levels can be observed immediately after the surgery.

Conclusion

Development of postoperative hypocalcaemia is multifactorial. Factors linked to the development of post operative hypocalcaemia include surgical technique, iatrogenic parathyroid damage (injury, edema, infarction, ischemia), extent of thyroidectomy, hyperthyroidism, malignancy, patient gender, perioperative serum calcium drop, presence of thyroiditis, diabetes, number of parathyroid glands identified intraoperatively. The incidence of benign thyroid disorders is higher in females than in males. The peak age group in which the patients presented was between 40-60 years. The commonest clinical diagnosis was that of solitary thyroid nodule followed by multinodular goitre. All the patients who developed post-operative hypocalcaemia were female. None of the patients were symptomatic. By the post-operative day 3, calcium levels had normalized. The overall incidence rate of postoperative hypocalcaemia in patient who had undergone total thyroidectomy was found to be 8%.

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