PREDICTORS OF POST OPERATIVE HYPOCALCEMIA IN PATIENTS UNDERGOING THYROIDECTOMY

THESIS

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Master of Surgery (MS)

OTORHINOLARYNGOLOGY

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DECLARATION

I, hereby declare that the work reported in the thesis titled **"Predictors of post operative hypocalcemia in patients undergoing thyroidectomy"** embodies the result of an original research work done by me in the Department of Otorhinolaryngology, All India Institute of Medical Sciences, Jodhpur. I further state that no part of the thesis has been submitted, in part or in full, to any other University or Institute for the award of any other degree.

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CERTIFICATE

This is to certify that the thesis titled **"Predictors of post operative hypocalcemia in patients undergoing thyroidectomy"** is the *bona fide* work of **Dr. Jibin C J** carried out under our guidance and supervision, in the Department of Otorhinolaryngology, Department of Biochemistry and Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Jodhpur.

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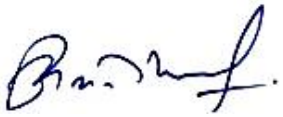

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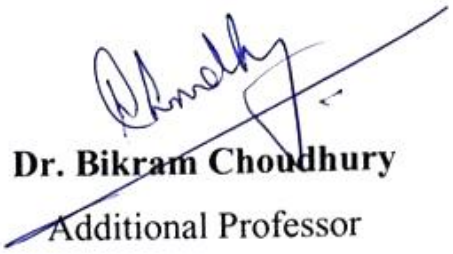

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Dr. Jibin C J

CONTENTS

LIST OF ABBREVATIONS

PTH	Parathyroid hormone
TIRADS	Thyroid imaging reporting and data system
CaSR	Calcium sensing receptors
FNAC	Fine needle aspiration cytology
USG	Ultrasonography
CT	Computed tomography
DTC	Differentiated thyroid carcinoma
ATA	American Thyroid Association
AGES	Age, Grade, Extent and Size
AMES	Age, distant Metastasis, Extent and Size
MACIS	Metastasis, Age, resection Completeness, Invasion and Size
TNM	Tumor, Node, Metastasis

LIST OF ANNEXURES

INTRODUCTION

Thyroid gland is part of the endocrine system which can have wide variety of pathologies. Thyroid swelling has been an age-old health problem in the southern Himalayan slopes. Goiter is mentioned in ancient Hindu medicinal literature. It is mentioned as a health issue in the Atharvaveda, which dates to a time around 2000 B.C. The early Hindu physicians Susruta and Charaka (about 500 B.C.) called neck tumors "Galganda"(1). Significant progress has been made in understanding the molecular mechanisms of thyroid disease during the past few decades. The paradigms for diagnosis and treatment are shifting as a result of these discoveries(2). Since the beginning of civilization, people have been aware of thyroid enlargement-related neck swellings. Byzantine era authors contributed significantly however, not recognized much(3). Hippocrates (first century BC) was aware of thyroid prominences but mistook them for a malformation of the cervical gland(4). Chinese scholar Tshui Chih-Thi described solid goiters as incurable while soft goiters were benign in 85 AD. He also distinguished between the two types of goiters(4). At those times it was considered dreaded surgery due to excessive bleeding with a mortality rate of near 40%. The discovery of anaesthesia and antisepsis led to drastic change in mortality during and after thyroid surgeries, and this was evident by the work of Theodor Billroth, who showed that mortality due to thyroid surgeries has reduced to 8.3% in antiseptic period as compare to 36.1% before that. Theodor Kocher, who is considered the Father of Thyroid surgery did many advancements in thyroid surgeries and in 1890 he adopted classical collar incision aka Kocher's Incision, which is still used (3).

Thyroid cancer incidence has surged by 240% in the last three decades(5). There are many modalities for diagnosing thyroid neoplasms of which USG and USG guided Fine needle aspiration cytology remains the investigation of choice. Ultrasonography has got inter observer variability but with various modalities like TIRADS (Thyroid imaging reporting and data system) scoring(6), the diagnosis of thyroid pathologies is made easy. TIRADS and Bethesda grading systems based on USG and FNAC respectively, are among the most used grading systems and management protocols are also proposed according to these systems. There are different prognostic systems of differentiated thyroid carcinomas. Most popular ones among them are AGES (Age, Grade, Extent and Size), AMES (Age, distant Metastasis, Extent and Size), MACIS (Metastasis, Age, resection Completeness, Invasion and Size), TNM and Dynamic Risk Stratification(7–12) etc. The role of Computed Tomography (CT)

and Magnetic Resonance Imaging (MRI) is limited in DTCs and is reserved for extensive disease with vascular involvement, retrosternal extension, neural involvement, distant metastasis and in suspicion of recurrent disease(13). There are various treatment modalities for thyroid malignancy. Thyroidectomy with or without postoperative radioiodine therapy is most effective. However, the extent of surgery depends on various clinical, radiological and pathological factors. However, many studies have proposed that optimal surgery for DTCs are total thyroidectomy except for micropapillary carcinoma in which hemithyroidectomy or lobectomy with regular follow-up can suffice.

Thyroidectomy is characterized by wide variety of complications of which postoperative hypocalcemia is the most frequent one. Hypocalcemia typically occurs 24-48 hours after surgery with an incidence ranging between 1.2- 40%. It can be permanent (more than 6 months post-surgery) or transient (less than 6 months post-surgery) hypoparathyroidism of which permanent hypoparathyroidism occurs in less than 3% patients (14). Although many studies have looked for risk factors for hypocalcemia following thyroidectomy, the causative factor of the complication have not been completely defined.

The routine protocols for management and prevention of postoperative hypocalcemia like serial calcium and parathyroid hormone (PTH) monitoring prolongs hospital stay and increases the cost. So, if we can find some predictors for the development of postoperative hypocalcemia in the preoperative period itself, early interventions can be done, which can reduce these issues. There have been studies which shows seasonal variation in the development of hypocalcemia (15). Most of the studies discussing risk factors for hypocalcemia are retrospective or are case series and they suggest the need to conduct prospective studies to understand about these risk factors better (15).

Post operative hypocalcemia is the most common complication after thyroidectomy. It can be classified as “biochemical” in the presence of asymptomatic hypocalcemia or “Clinical” when the patient displays symptoms. This prospective study is planned to assess the various factors which may contribute to the development of postoperative hypocalcemia.

REVIEW OF LITERATURE

Thyroidectomy is considered as the most widely used management modality of thyroid nodules. As reported by epidemiological studies, the incidence of thyroid cancer is showing an increasing trend in previous decades (16,17). So, prevention and management of complications of thyroidectomy including the most frequent postoperative hypocalcaemia very important.

The complications following thyroidectomy can range from recurrent laryngeal nerve palsy and hypocalcaemia to vocal cord palsy, local hematoma, granuloma, thyroid storm, seroma etc. Post-thyroidectomy hypocalcaemia may seem harmless at first, but it is a major factor determining the duration of hospital stay and can lead to life threatening events.

DETECTION OF HYPOCALCEMIA

Clinically hypocalcaemia is detected by specific signs and symptoms. The first and most common symptom to develop in a patient with hypocalcaemia is perioral numbness followed by numbness of extremities, muscle cramps and muscle weakness. The most commonly found signs are Chvostek’s sign and Trousseau’s sign. Chvostek’s sign is the twitching of facial muscles in response to tapping over the facial nerve. These facial spasms are caused by hyperexcitability due to hypocalcemia. Trousseau’s sign is the carpopedal spasm induced by ischemia after a sphygmomanometer is inflated to 20 mmHg over the systolic blood pressure for three minutes(18). About a third of hypocalcemia patients lack these symptoms. The Chvostek's sign is positive in 10% of healthy persons(19). Contraction of eyelid muscles is said to be pathognomonic of hypocalcemia. Rarely do people experience unprovoked tetany with carpopedal spasm (main d'Accoucheur). Another sign of hypocalcemia is QT prolongation which can also be seen with hypomagnesaemia and hypokalemia. Psychological symptoms, including emotional instability, anxiety, depression, and less frequently occurring hallucinations and psychosis, can be brought on by hypocalcemia. The signs and symptoms of hypocalcemia can be divided into following categories.

Neuromuscular irritability

1. Chvostek's sign
2. Trousseau's sign
3. Muscle cramps
4. Muscle weakness
5. Laryngospasm
6. Bronchospasm
7. Paresthesia
8. Tetany
9. Seizure

Mental status

1. Psychosis
2. Fatigue
3. Anxiety
4. Poor memory
5. Reduced concentration
6. Confusion
7. Disorientation

Neurological signs and symptoms

1. Personality disturbances
2. Irritability
3. Impaired intellectual ability
4. Nonspecific EEG changes
5. Increased intracranial pressure

6. Parkinsonism
7. Choreoathetosis
8. Dystonic spasms
9. Extrapyramidal signs due to calcification of basal ganglia
10. Calcification of cerebral cortex or cerebellum

Ectodermal changes

1. Shortened premolar roots
2. Thickened lamina dura
3. Delayed tooth eruption
4. Increased dental caries
5. Atopic eczema
6. Exfoliative dermatitis
7. Psoriasis
8. Impetigo herpetiformis
9. Dry skin
10. Coarse hair
11. Brittle nails
12. Alopecia
13. Enamel hypoplasia

Smooth muscle involvement

1. Abdominal pain
2. Biliary colic
3. Dyspnea

4. Wheezing
5. Dysphagia

Cardiac

1. Prolonged QT interval on EKG
2. Congestive heart failure
3. Cardiomyopathy

Ophthalmologic

1. Subcapsular cataracts
2. Papilledema

THYROIDECTOMY- PROCEDURE RELATED RISK

Different types of thyroidectomy procedures are, total thyroidectomy hemithyroidectomy, subtotal thyroidectomy and thyroid Isthmusectomy (20,21). The newer approaches are Robotic thyroidectomy (22–24), minimally invasive video assisted thyroidectomy and transoral endoscopic thyroidectomy(25–27).

Total thyroidectomy is a procedure in which whole of the thyroid gland including both lobes and isthmus is removed in toto whereas in hemithyroidectomy we are removing one lobe of thyroid along with the isthmus. There is high chance of postoperative hypocalcaemia in total thyroidectomy compared to hemithyroidectomy as all four parathyroid glands are at risk of injury(28). Subtotal thyroidectomy(29,30) is defined as the removal of most of the thyroid gland sparing 2 grams of tissue from the posterior portion bilaterally as this will minimize the risk of parathyroid gland and recurrent laryngeal nerve injury as well as post operative hypothyroidism(28). Candidates for robotic thyroid surgery include patients who have an indication of unilateral thyroid lobectomy. The lateral neck and pectoralis major muscle should be familiar to surgeons thinking about this strategy, as well as substantial competence in head and neck endocrine surgery. Tumours larger than 3 to 5 cm in diameter and/or lesions situated deeper and posteriorly in the tracheoesophageal groove are contraindications. Body habitus and body mass index (BMI) of the patient are additional crucial factors to take into account, as the trans axillary technique is much simpler and quicker to do in patients with low

BMIs (35 kg/mg 2)(22). Currently, benign follicular adenomas with a diameter of less than 4 cm, low-risk papillary carcinomas with a thickness of less than 10 mm, oxyphilic cell tumours with a diameter of less than 4 cm, and Graves' disease as seen on preoperative ultrasonography are all can be considered as indications for endoscopic thyroidectomy. Patients with low-risk, well-differentiated carcinomas can be recommended for the minimally invasive mini-incision technique(31).

After proper preoperative preparations and investigations including ultrasonography of thyroid with TIRADS, Fine needle aspiration cytology from thyroid nodules and thyroid function test, patient is taken for surgery. Superior parathyroid gland is usually found closer to the tubercle of Zuckerkandl which is a pyramidal extension of thyroid gland present at the most posterior side of each lobe(32). Dissection continued further inferiorly and inferior pedicle identified ligated and cut. Care should be taken not to injure the inferior parathyroid gland and recurrent laryngeal nerve which are in close proximity. Each parathyroid glands weighs 35 to 40 mg and measures 3-8mm in all dimensions. It can vary in colour from light yellow to reddish brown(33).

There are wide variety of indications and pathologies for which thyroidectomy is being done which includes Multinodular goitre, thyrotoxicosis, Papillary carcinoma thyroid, Follicular carcinoma, thyroid Medullary carcinoma thyroid, Follicular adenoma thyroid etc. Every thyroid enlargement in neck may not need thyroidectomy. Selecting the appropriate primary operation depending on the indication is also a critical step for maintaining better outcomes. The reason being not only the recurrence of benign or malignant disease after hemithyroidectomy but also the risks in reoperation like high risk of recurrent laryngeal nerve injury. Surgeon should have a clear-cut idea whether the surgery is for benign tumour, malignant tumour or for diagnostic purpose. Nowadays majority of the thyroidectomies are being done in case of benign thyroid nodule for cosmetic reason(34). Colloid nodule or a multinodular goitre is removed when there are compressive symptoms.

Thyroid carcinoma is one of the most common malignancies especially in females. It is most common endocrine malignancy. Thyroid cancers are third fastest increasing malignancy in world. Among thyroid malignancy DTCs comprise of more than 90% of cases. DTCs comprise of papillary and follicular carcinomas. The treatment strategy has changed a lot in last decade for DTCs. There are many modalities for diagnosing thyroid neoplasms of which USG and USG guided Fine needle aspiration cytology remains the investigation of choice.

Thyroid USG is a crucial step in the evaluation of thyroid nodules since it is easily accessible, noninvasive, and affordable. Differentiating benign thyroid nodules that can be managed conservatively from those with suspicious or malignant signs that need additional therapy is the aim of an initial sonographic assessment. Ultrasonography has got inter observer variability but with various modalities like TIRADS (Thyroid imaging reporting and data system) scoring(6), the diagnosis of thyroid pathologies is made easy. TIRADS and Bethesda grading systems based on USG and FNAC(35) respectively, are among the most used grading systems and management protocols are also proposed according to these systems.

SURGICAL FACTORS

Surgical factors which can affect post thyroidectomy hypocalcemia have been studied widely across the world(36,37). Risk factors and management of post-thyroidectomy hypocalcaemia was studied by Dan Nicolae et al (38) in 2019. According to them, during thyroid surgery, gentle manipulation of the parathyroid gland and its blood supply is the key thing to avoid post operative hypocalcaemia. Iatrogenic damage to the parathyroid glands is regarded to be the main culprit in the multifactorial mechanism causing the drop in serum calcium levels following thyroidectomy(39). Del Rio et al (40) states that, Sex (female gender is a strong risk factor), surgical procedure and perioperative changes in serum calcium are the only factors (among all variables examined) that influence early hypocalcemia development and 37.7% patients in this study developed hypocalcemia. The extent of surgery and surgical technique have a great impact on the development of permanent post-thyroidectomy hypoparathyroidism than thyroid pathologies. In total thyroidectomy, peripheral ligation of the inferior thyroid artery at the thyroid capsule should be preferred over central ligation, and also at least 2 parathyroid glands should be identified and preserved during surgery. High-risk procedures, like total thyroidectomy and Graves' disease, require special surgical attention and expertise(41). It was independent of the indication for surgery, extend of surgery and neck dissection.

Many studies have shown that auto transplantation of one or more parathyroid glands are associated with temporary hypocalcemia independent of the type of surgery and neck dissection(42). No correlation was found between parathyroid gland auto transplantation and permanent hypoparathyroidism. Even though we are discussing all these factors and possibilities, the surgeons skill and approach of the surgeon is also an important contributor for development of post-operative hypocalcemia(43).

PARATHYROID GLANDS

Parathyroid glands are endocrine glands which are usually four in number which are small nodular structures located posterior to the thyroid gland(44). These glands produce a peptide called parathyroid hormone (PTH) which plays the major role in calcium homeostasis. They are small, yellowish brown in colour, oval or bean shapes and their colour often becomes more darker with age. It measures 6mm in length and 3-4mm in width. Most of the cases there will be 2 pairs of glands named superior and inferior parathyroid glands. Superior glands are located within 2 cm of the point 1cm above the crossing of recurrent laryngeal nerve and inferior thyroid artery(33). The inferior group of parathyroid glands are located below the inferior thyroid artery or sometimes within 1 cm of the inferior pole of the thyroid gland. These glands are covered by a thin capsule which is fibrous and shows extension into the parenchyma of the gland making it lobular. The inferior thyroid arteries supply the parathyroid glands via its branches supplying both the inferior and superior parathyroid glands in most cases. Sometimes superior parathyroid glands gets blood supply from superior thyroid artery. The gland is composed of parenchymal cells, adipocytes, mast cells and macrophages. These stromal cell and adipocytes increase with age and may reach up to 50% of the gland. The chief cells or principal cells of the gland is concerned with the production of parathyroid hormone. This hormone along with calcitonin and 1,25- Dihydroxy vitamin D3 controls the calcium metabolism of human body.

CALCIUM HOMEOSTASIS

Calcium homeostasis in human body is by a feedback mechanism involving Parathyroid hormone, calcitonin and 1,25-Dihydroxy vitamin D3. Calcium in the extracellular fluid activates the parathyroid cells by binding with the calcium sensing receptors (CaSR), leading to an increase in intracellular calcium(45). This leads to decreased parathyroid hormone release. But when there is hypocalcaemia, the reverse happens and intracellular calcium decreases and PTH release increases. Parathyroid hormone rapidly increases the calcium reabsorption through kidneys and enhances the osteoclastic activity and liberates calcium and phosphates from the skeleton. PTH also increases fibroblast growth factor 23 (FGF23) release from mature osteoblasts and osteocytes. PTH stimulates the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which in turn will increase calcium absorption from the gut. Persistent hypocalcemia and exposure to elevated PTH may also result in 1,25 dihydroxy vitamin D-mediated calcium and phosphorus release from skeleton.

These effects restore the calcium to normal and inhibit further production of PTH and 1,25 dihydroxy vitamin D. When there is hypercalcemia in the ECF, PTH secretion is reduced and 1,25 dihydroxy vitamin D production is reduced from the kidneys. Calcium can directly stimulate CaSR in kidney and cause calciuria. Stimulation of the renal CaSR lead to reduced renal calcium reabsorption, decreased skeletal calcium release, and decreased intestinal calcium absorption, resulting in the normalization of the elevated ECF calcium(45).

CALCIUM

Calcium is the 20^{th} element in the periodic table and it is the 5^{th} most abundant mineral found in earth. In human body its concentrated in bones in the form of hydroxyapatite. An adult human body contains around 1kg of calcium(46,47). Most of the calcium stably incorporated into the bone except a few fractions which is constantly in exchange with the soluble fraction of calcium. Soluble calcium occupies the extracellular fluid with almost equal distribution in interstitial space and serum. Half of the calcium in serum is in the form of free cation and the rest of the calcium is bound to negatively charged amino acid residues on proteins and a few exist in complexes with citrates and lactates(48). Normal serum calcium values range between 8.8 to 10.6 mg/Dl. There are studies showing that preoperative calcium was low in patients who developed post operative hypocalcaemia(49). Most of such studies also compared other parameters like parathyroid hormone levels(50). Serum calcium level reduction > 12% compared to preoperative value was found to have significance in developing post operative hypocalcaemia(51). But this study was done only in patients who were undergoing total thyroidectomy and hemithyroidectomy patients were not included. In a study by Amir et al , preoperative serum calcium value less than 2.27mmol/l was found to have sensitivity of 29-58% in predicting postoperative hypocalcaemia(52). 63% of the patient with preoperative calcium level less than 2.27mmol/l developed symptomatic post thyroidectomy hypocalcaemia. A study found that the post operative calcium less than 0.95mmol/l or lower were associated with symptomatic hypocalcaemia(53). Another study showed that the serum calcium less than 2.10 mmol/l after 24 hours of the procedure has got sensitivity of 99% and positive predictive value of 4% in predicting permanent hypocalcaemia.

PARATHYROID HORMONE

Parathyroid hormone (PTH) is synthesised by the parathyroid glands. It consists of 84-amino-acid polypeptide which plays a pivotal role in calcium and phosphorus metabolism in human

body by exerting its direct effect on kidneys and bones and indirect effect on human gastrointestinal system(54). Parathyroid hormone binds with PTH type 1 receptor for calcium metabolism. It is a G-protein-coupled receptor which is seen in bones, kidneys and breasts. The cells expressing PTH type 1 receptor are osteoblasts, osteoclasts, macrophages and stem cells. PTH regulates the expression of RANK ligands in osteoclasts and osteoblasts. RANK ligand can bind to the surface RANK of osteoclast precursor cells to enhance their differentiation and survival and to mature osteoclasts to promote their activity(54). Yamashita et al studied the effect of preoperative parathyroid hormone on development of hypocalcemia and was found that higher preoperative parathyroid hormone levels is associated with transient postoperative hypocalcemia in patients undergoing thyroidectomy for Grave's disease(55,56). Risk factors and management of post-thyroidectomy hypocalcaemia was studied by Dan Nicolae et al (38) in 2019 and they found that prophylactic calcium and vitamin D supplementation are the best two methods for preventing post thyroidectomy hypocalcaemia. The gentle manipulation of parathyroid glands and preserving their blood supply is the key technique for preventing post thyroidectomy hypocalcaemia. Arer IM et al (57) states that, Serum PTH levels at postoperative 12 and 24 hour can predict early post thyroidectomy hypocalcemia and prophylactic oral calcium supplementation therapy can prevent early post thyroidectomy hypocalcemia with advantage of being cost effective and safe. In this study the incidence of hypocalcemia was 33.9%. Dionigi G et al (14) states that, Pre-operative low calcium, parathormone (PTH), 25-hydroxyvitamin D increases the risk. The calcium drop rate also matters, a decrease of 1 mg/dL calcium over 12 hours after surgery is independently correlated with the risk of symptomatic hypocalcemia. Wang Y H et al(58) Postoperative hypocalcemia and hypoparathyroidism incidence were significantly related to the extent of thyroidectomy, gender, lateral lymph node dissection, operative time, and use of carbon nanoparticles. Carbon nanoparticles was injected in the form of suspension 1ml/50mg which does not enter the blood circulation and hence no side effects. When it is injected into the thyroid tissue it rapidly enters the lymphatics through macrophage phagocytosis and are retained in lymph nodes. Parathyroid glands do not stain black and can be differentiated from black stained thyroid gland and lymph nodes These findings were crucial for guiding surgeons to prevent the occurrence of hypocalcemia and hypoparathyroidism. Edafe O et al (59) states that perioperative PTH, preoperative vitamin D and postoperative changes in calcium are biochemical predictors of post-thyroidectomy hypocalcemia. Clinical predictors include

female sex, Graves' disease, need for parathyroid auto transplantation and inadvertent excision of parathyroid glands.

SEASONAL VARIATION

Seasonal difference in post-thyroidectomy hypocalcemia was studied in McGill university health center Montreal, Canada in 2015 and Marco A Mascarella et al (15) states that, patients operated in winter were 5.6 times more likely to develop hypocalcemia as compared to those in summer. The highest incidence of hypocalcemia occurred in February and lowest rate was observed in August. This study was done in Canadian population in which the serum 25 hydroxy vitamin D peaks in the summer due to increased ultraviolet B exposure and thereby auto-production of vitamin D(60–62). Vitamin D is a pro hormone, a fat-soluble vitamin with a half-life of 15 days and it is produced in the skin on exposure to ultraviolet-B rays. Kordel et al (63) in his cohort study states that, total thyroidectomy performed during August-October was associated with a lower rate of calcium treatment given post-operatively when compared to total thyroidectomy performed during February-April. This would indicate a decreased risk of post-operative hypocalcemia if surgery was carried out after the brighter season. On the effect of low vitamin D on hypocalcemia rates following thyroid surgery, conflicting information is available(64,65). Seasonal change in calcium homeostasis and its effect on post thyroidectomy tetany was studied in 2000 by Yamashita et al and it was found that patients with Grave's disease is more susceptible to calcium and vitamin D deficiency during winter season than summer and thus more prone to development of post operative hypocalcemia.

PATIENT AND DISEASE RELATED FACTORS

Transient hypocalcemia was linked to older age in certain research(66), although younger age was linked in other studies(67,68). Development of post operative hypocalcemia was significantly predicted by bone turn over parameters also in those studies. Women with Grave's disease were more likely to develop postoperative hypocalcemia because a higher proportion of women had vitamin D deficiency. Numerous studies revealed that transient hypocalcemia and female sex were related(42).In one study, a multivariable analysis revealed a link between preoperative Graves' disease diagnosis and both temporary and persistent hypocalcemia(41). Other possible factors of transient hypocalcemia found in different studies, multivariable analyses included: longer duration of Graves' disease, preoperative beta-blockade, and heavier thyroid specimens(69). After a complete thyroidectomy, children

with thyroid cancer are at a significant risk of developing hypocalcemia postoperatively. Central compartment neck dissection, which needs to be done selectively, raises the danger even more. Most patients who had hypoparathyroidism at 6 months after surgery recovered their normal parathyroid function by 1 year. After a total thyroidectomy at a pediatric endocrine surgery clinic, children seldom develop permanent hypoparathyroidism(70). Pediatric patients experience more difficulties than adult patients do, most likely as a result of anatomical variations including smaller, more fragile structures and shorter necks.

AIM AND OBJECTIVES

AIM

To identify predictors of post-operative hypocalcemia in patients undergoing thyroidectomy

OBJECTIVES

1. To assess pre and postoperative serum calcium and PTH
2. To assess preoperative Vit D
3. To find out correlation between season in which surgery was performed and postoperative hypocalcemia
4. To correlate with duration of surgery and amount of blood loss

MATERIALS AND METHODOLOGY

Study Design: - Prospective Observational Cohort Study

Inclusion Criteria: Any patient undergoing thyroid surgery for primary thyroid pathology in Department of Otorhinolaryngology, AIIMS, Jodhpur

Exclusion Criteria:

Patients with concomitant primary hyperparathyroidism

Sampling Frame:

According to the studies by Del Rio et al (3) and Arer IM et al(57) the prevalence of postoperative hypocalcemia was 35%. So, based on these studies our sample size would be 47.

Sampling:

All patients presenting to the OPD of the Department of Otorhinolaryngology, for thyroidectomy

MATERIALS AND METHODS

We conducted a Prospective Cohort Study on patients undergoing thyroidectomy surgery in a tertiary care center, by collecting prospective data from November 2020 to August 2022.

All patients undergoing thyroidectomy for primary thyroid pathology were included in this study. Patients with concomitant hyperparathyroidism were excluded from the study. Patients were recruited into study after getting an informed consent. All patients were assessed clinically. Preoperative testing for serum calcium, PTH and Vitamin D were done on the day of surgery. These patients were subjected to surgery as per ATA guidelines(11) and consensus reached in the departmental preoperative clinical discussion. Postoperative testing for PTH was done 24 hours after surgery and serum calcium on day 0 and 1. All patients were assessed clinically for signs and symptoms of hypocalcemia till 48 hours post operatively and this was correlated with the biochemical parameters and the season in which surgery was performed.

SEASON

a) Summer (April-June)
b) Winter (December-March)
c) Monsoon (July-September)
d) Post monsoon (October-November)

Duration and type of season varies with the geographical distribution of the area and seasons of north-western India was studied.

VITAMIN D LEVELS(71)

Deficiency - <10 ng/mL
Insufficiency - 10-30 ng/mL
Sufficiency - 30-100 ng/mL
Toxicity - > 100 ng/mL

PTH LEVELS

(18.5 – 88.0 pg/mL)
Low- Less than 18.5 pg/mL
Normal- 18.5 – 88.0 pg/mL
High- More than 88.0 pg/mL

CALCIUM

Normal range – 8.8-10.6 mg/dL

Vitamin D biochemical analysis was done by chemiluminescence on Siemens ADVIA Centaur. Calcium was done in AU Beckman 680A by CPC method.

Procedure:

1. All 54 patients underwent preoperative testing for serum calcium, PTH and Vitamin D.
2. All patients underwent surgery under general anesthesia as per consensus reached in the departmental preoperative clinical discussion after appropriate counseling and Pre-Anesthetic assessment.
3. Due consent was taken prior to surgery.
4. Duration of surgery and blood loss was noted.

5. Patient was assessed by post-operative serum calcium (Day 0&1) and PTH (after 24 hour).
6. Patient was observed for clinical signs and symptoms of hypocalcemia.

SYMPTOMS

1. Perioral numbness
2. Muscle cramps
3. Muscle weakness

SIGNS

1. **Chvostek's sign-**Twitching of facial muscles in response to tapping over the facial nerve. These facial spasms are caused by hyperexcitability due to hypocalcemia.
2. **Trousseau's sign-** Carpopedal spasm induced by pressure applied to the arm by an inflated sphygmomanometer cuff(18). The patient's hypocalcemia and subsequent neuromuscular excitability will cause spasm of the hand and forearm muscles in the absence of blood flow. The fingers adduct, the DIP and PIP joints extend, and the wrist and metacarpophalangeal joints flex.

TIRADS Grading(6)-Thyroid Imaging Reporting And Data System:-

Table 1.1 TIRADS

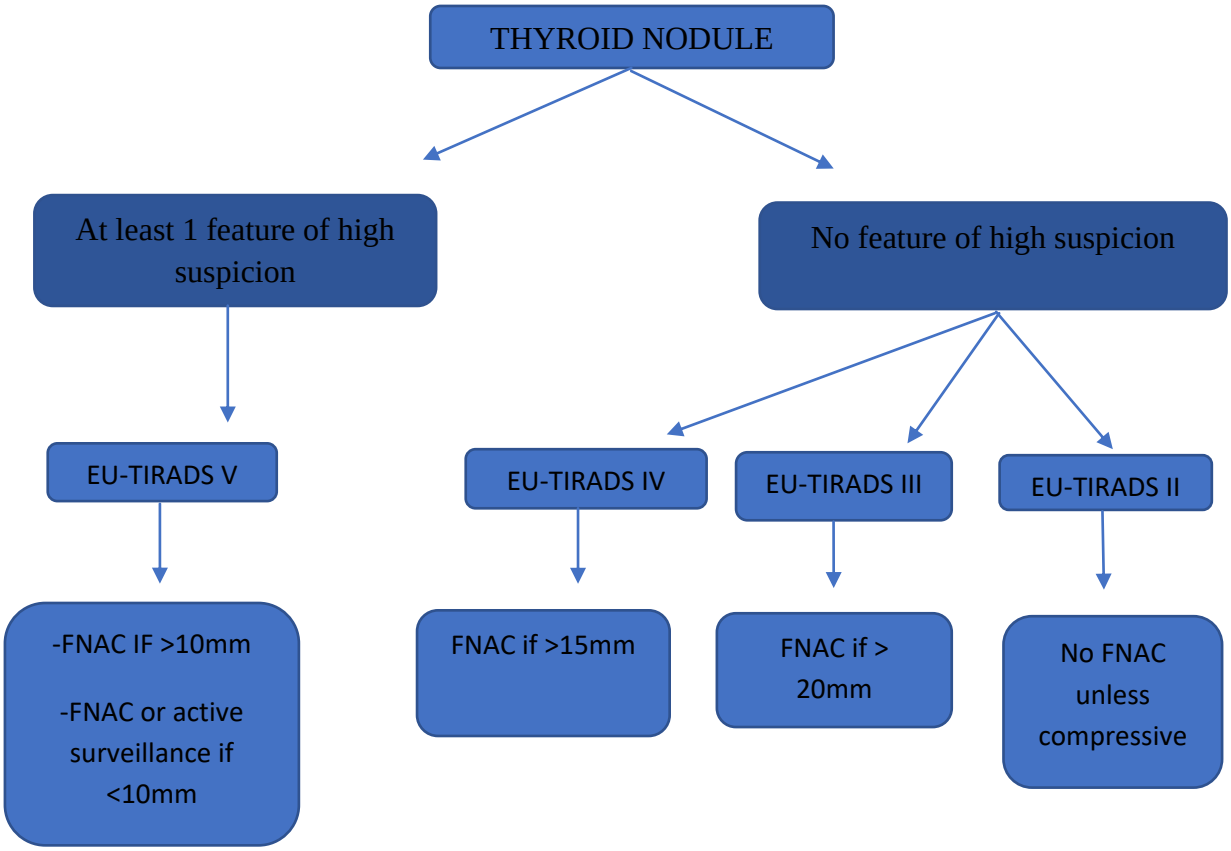
TIRADS GRADING	FEATURES	RISK OF MALIGNANCY
TIRADS I	Normal thyroid gland	
TIRADS II	Benign conditions	0%
TIRADS III	Probably benign nodules	< 5%
TIRADS IV	Suspicious nodules	5-80%
TIRADS V	Probably malignant nodules	>80%
TIRADS VI	Biopsy proven	

EU-TIRADS- European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults(72). The search for echogenic signs of high suspicion forms the basis of the EU-TIRADS grading system.

Table 1.2 EU-TIRADS

CATEGORY	USG FEATURES	MALIGNANCY RISK %
EU-TIRADS I Normal	No nodules	None
EU-TIRADS II Benign	Pure cyst Entirely spongiform	0%
EU-TIRADS III Low risk	Ovoid Smooth Isoechoic/hyperechoic No features of high suspicion	2-4%
EU-TIRADS IV Intermediate risk	Ovoid Smooth Mildly hypoechoic No features of high suspicion	6-17%
EU-TIRADS V High risk	At least 1 of the following features of high suspicion - Irregular shape - Irregular margins - Microcalcifications - Marked hypo echogenicity (and solid)	26-87%

Figure 1.1 Evaluation of thyroid nodule



BETHESDA System for Cytological grading of FNAC:

Table 1.3 BETHESDA Grading

BETHESDA GRADING	DESCRIPTION	RISK OF MALIGNANCY
I	Non diagnostic	1-4%
II	Benign	0-3%
III	Follicular lesion of undetermined significance	5-15%
IV	Follicular Neoplasm	15-30%
V	Suspicious for malignancy	60-75%
VI	Malignant	97-99%

Figure 2.1 Incision marked

Figure 2.2 Subplatysmal flap Elevation

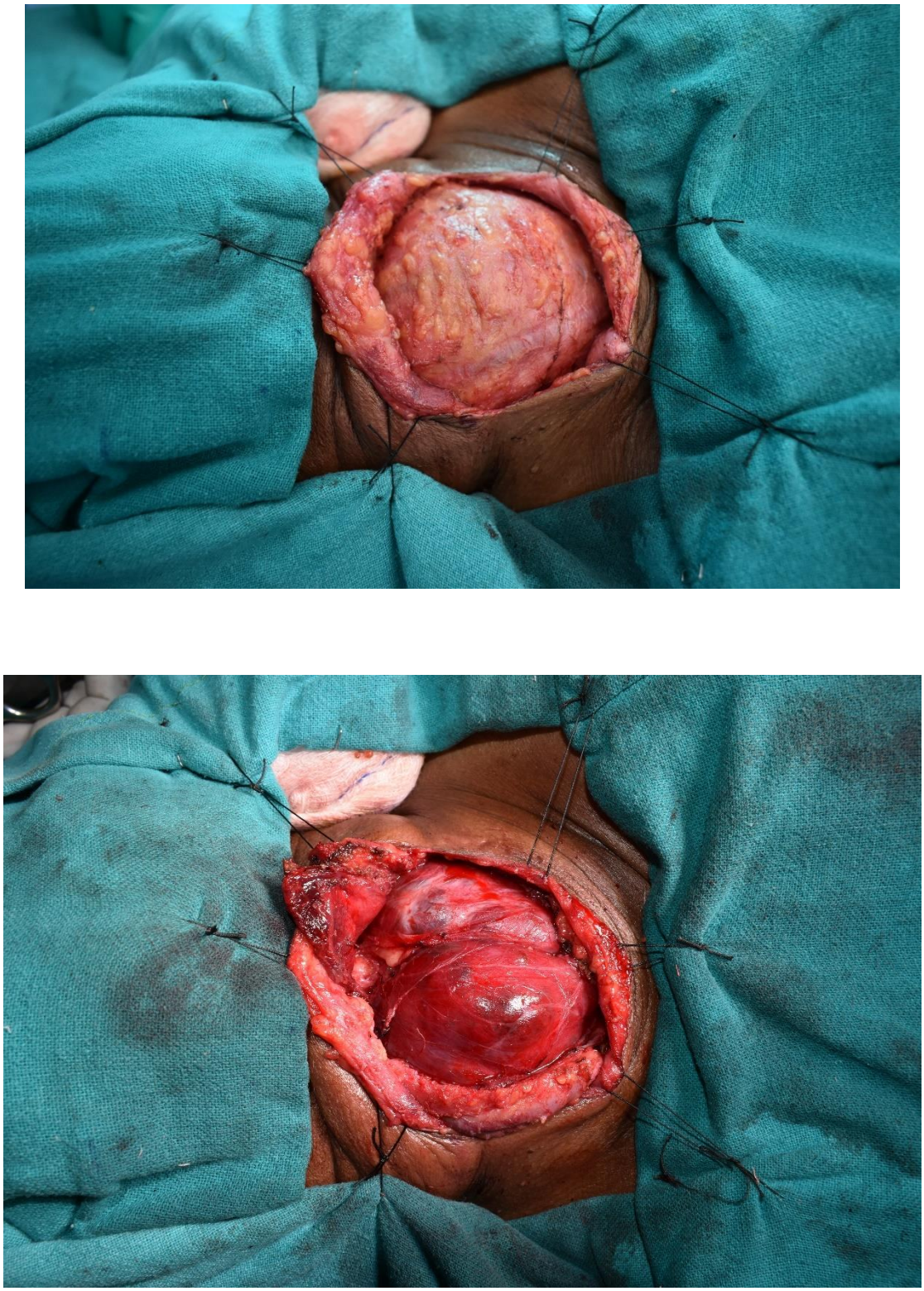
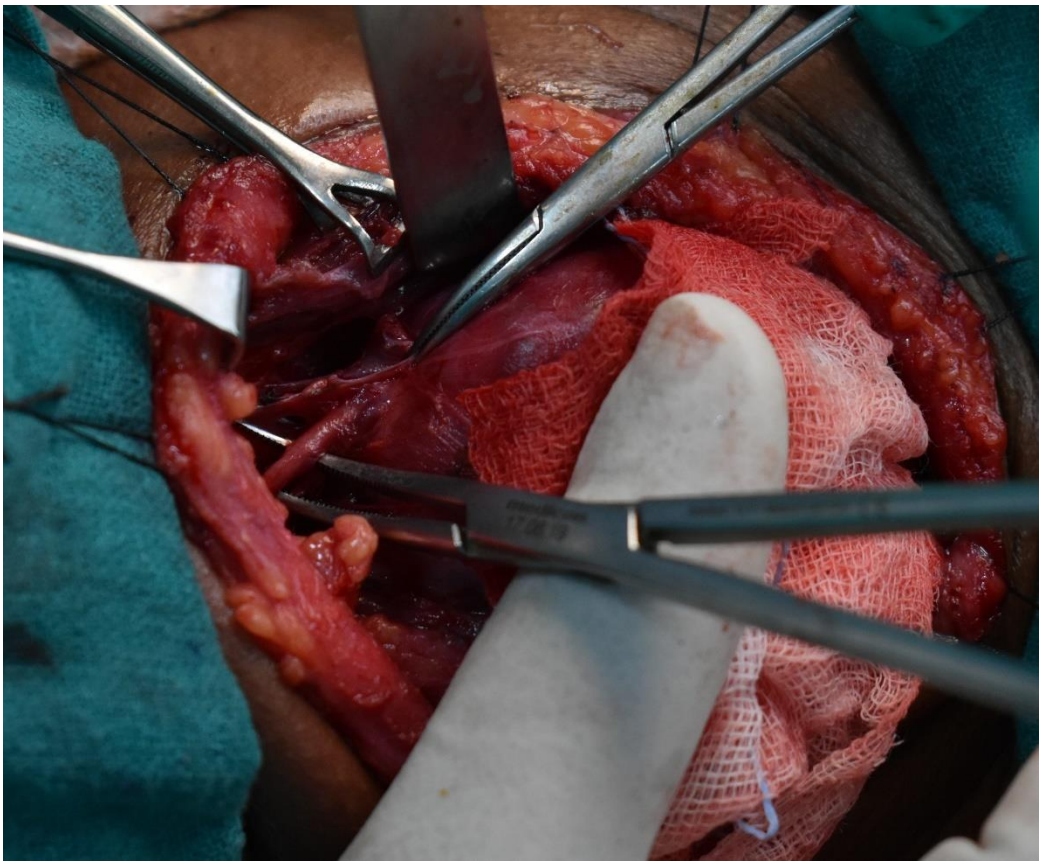


Figure 2.3 Exposing the Thyroid gland



Figur2.4 Identification of superior pedicle

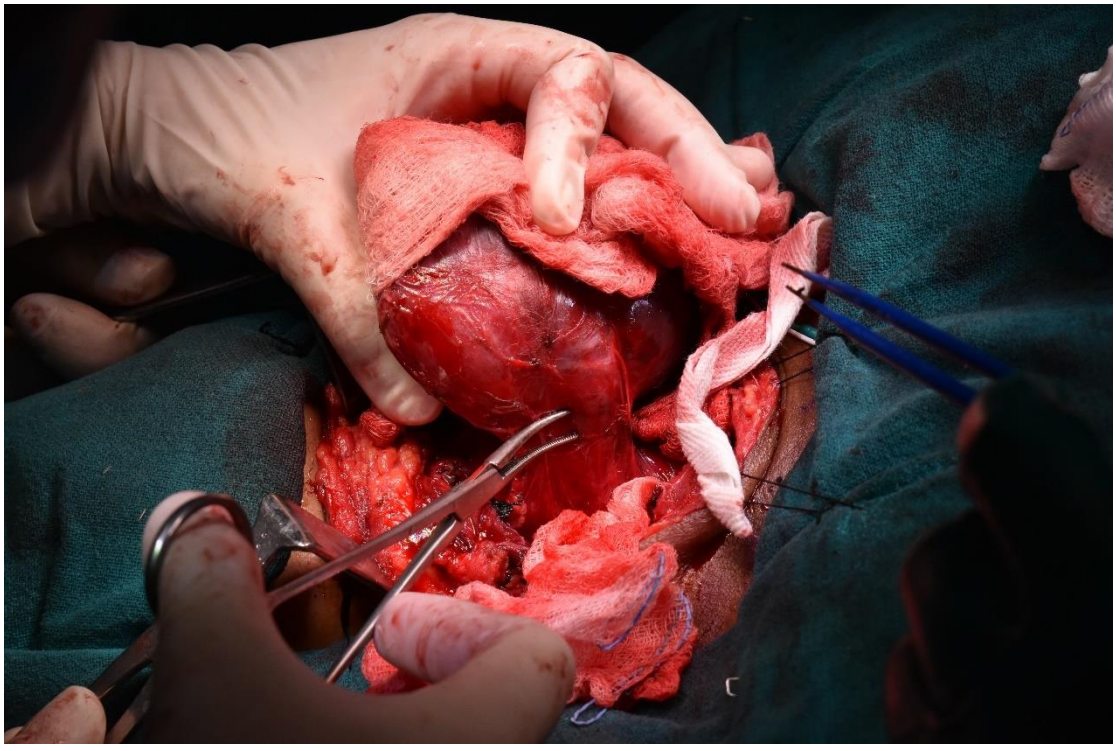


Figure 2.5 Tubercle of Zuckerkandl

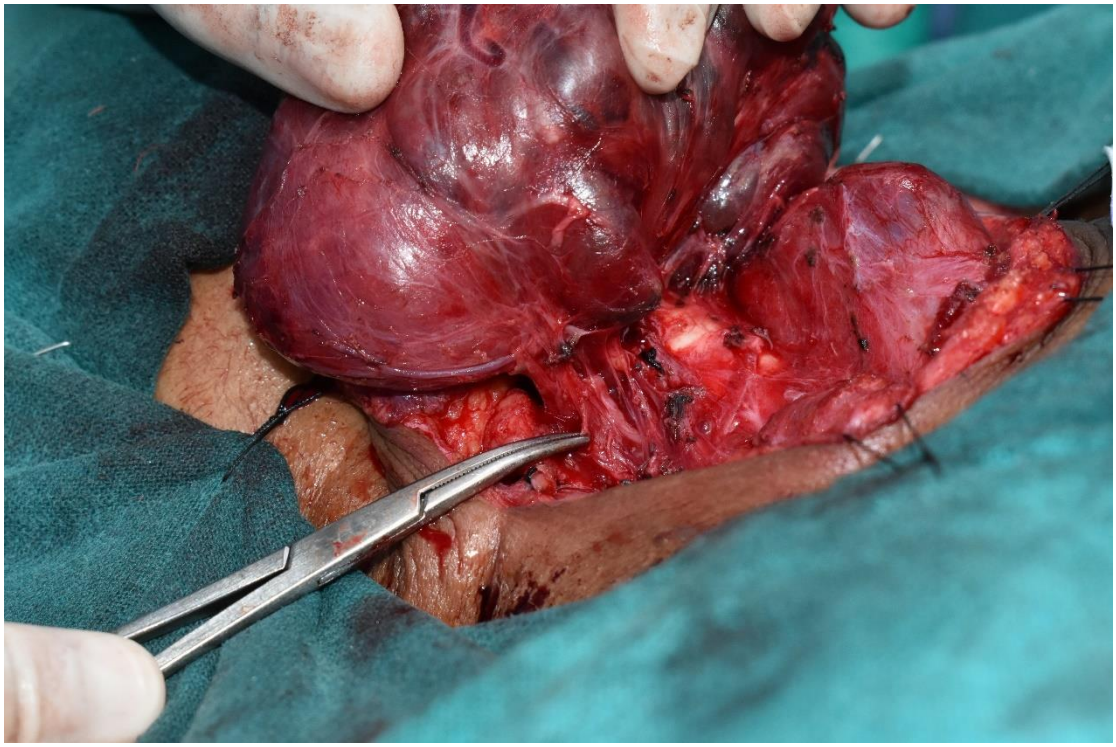


Figure 2.6 Recurrent laryngeal nerve

Figure 2.7 Chvostek's sign

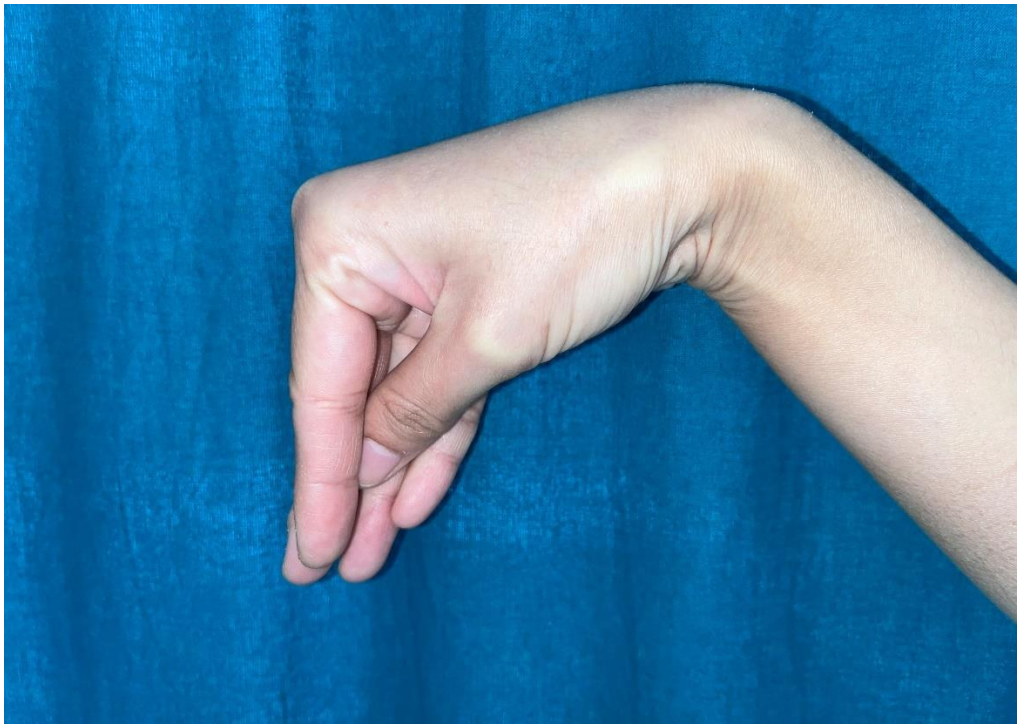


Figure 2.8 Trousseau's sign

STATISTICAL ANALYSIS

Data was entered in Microsoft excel and analysed using SPSSv26 (IBM Corp. released 2021 IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Quantitative variables were described using the chi- square test. Nominal Variables were described using proportions and analysed using Fischer Exact test. A p-value of <0.05 s considered as significant.

Ethical approval and consent to participate

Ethical approval was obtained from AIIMS Jodhpur; Institutional Ethical Committee certificate reference No. AIIMS/IEC/2021/3373, dated- 12/03/2021 attached in annexure “F”. All patients were informed about the purpose of the study and the benefits of patients in the study. After inclusion in the study, informed consent was obtained from all the participants. The patient's information sheet was given to all patients, and their role in the study was explained before administering screening tools. They were assured of the complete confidentiality of the information and were explained the option of withdrawing from the study at any point in time if they desired to do so. All the data collected were kept confidential. There were no adverse events reported during the course of the study.

RESULTS

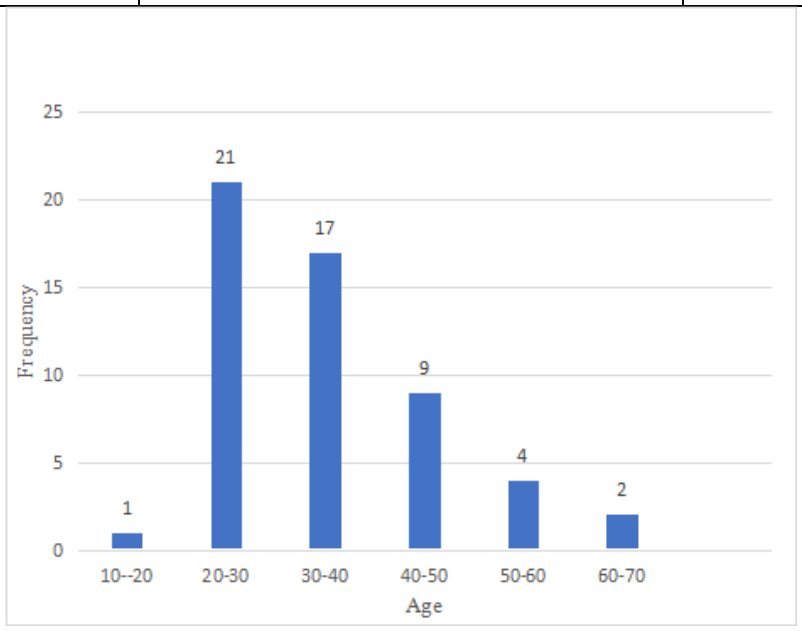
A total of 54 patients who got operated in the Department of Otorhinolaryngology, AIIMS, Jodhpur, fulfilling the inclusion criteria were studied. All patients were included in study after due informed consent.

AGE

All 54 patients who were included in this study were above the age of 10 years and below 70 years. 38.8% of the patients were in their third decade of life and 31.5% of the patient were between 30-40 years. Only 6 patients were above the age of 60 years and only one patient was below 20 years.

Table 2.1 Table showing Age group

Age group	Number of patients	Percentage
10-20	1	1.9
20-30	21	38.8
30-40	17	31.5
40-50	9	16.7
50-60	4	7.4
60-70	2	3.7
Total	54	100.0



Frequency- Number of patients

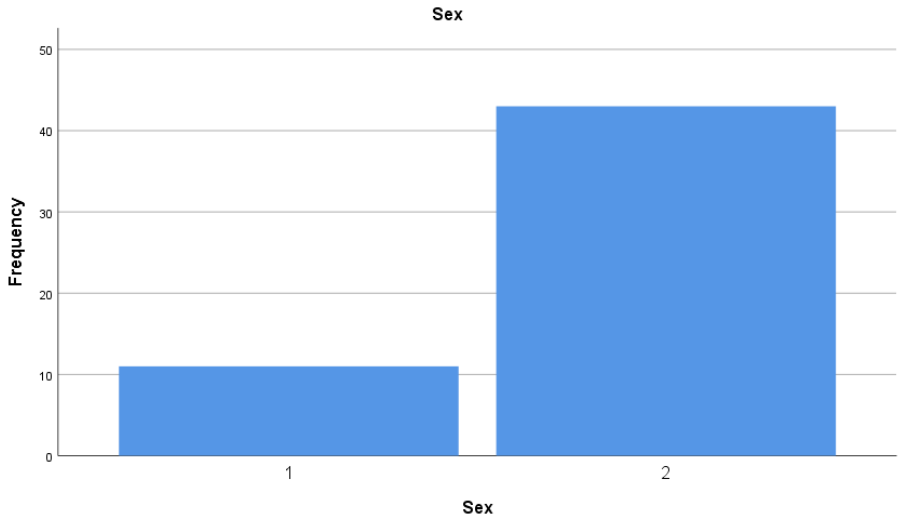
Figure 3.1 Bar diagram showing Age group

SEX

Around 80% of the patients were females and 20 % were males in our study

Table 2.2 Table showing Gender distribution

Gender	Number of patients	Percentage
1-Male	11	20.4
2-Female	43	79.6
Total	54	100.0



Frequency- Number of patients

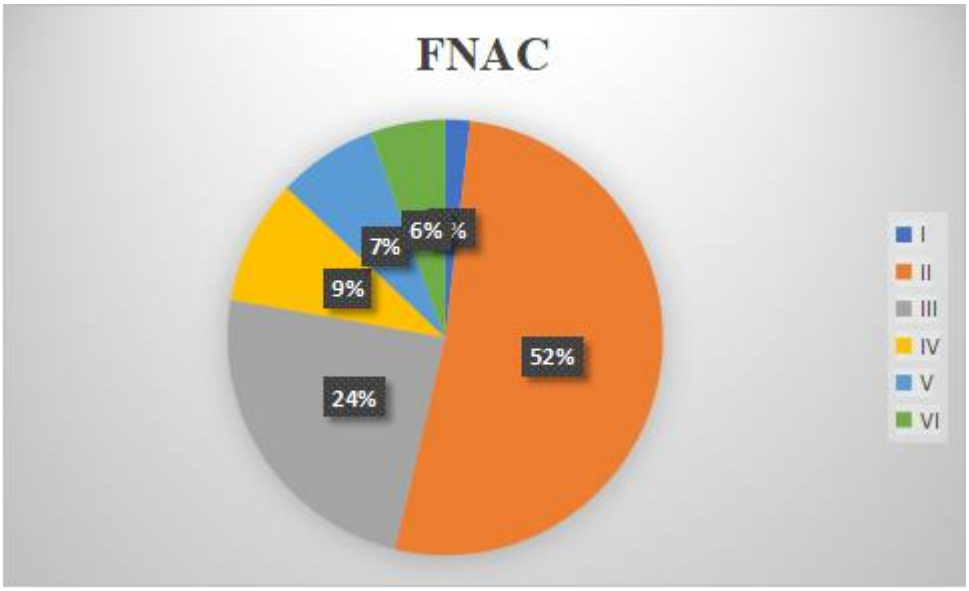
Figure 3.2 Bar diagram of Gender distribution

Table 2.3 Showing TIRADS staging

TIRADS	Number of patients	Percentage
I	3	5.6
II	14	25.9
III	21	38.9
IV	12	22.2
V	4	7.4
Total	54	100.0

Table 2.4 Showing BETHESDA category

BETHESDA	Number of patients	Percentage
I	1	1.9
II	28	51.8
III	13	24
IV	5	9.3
V	4	7.4
VI	3	5.6
Total	54	100.0



BETHESDA I,II,III,IV,V,VI

Figure 3.3 Pie diagram showing FNAC

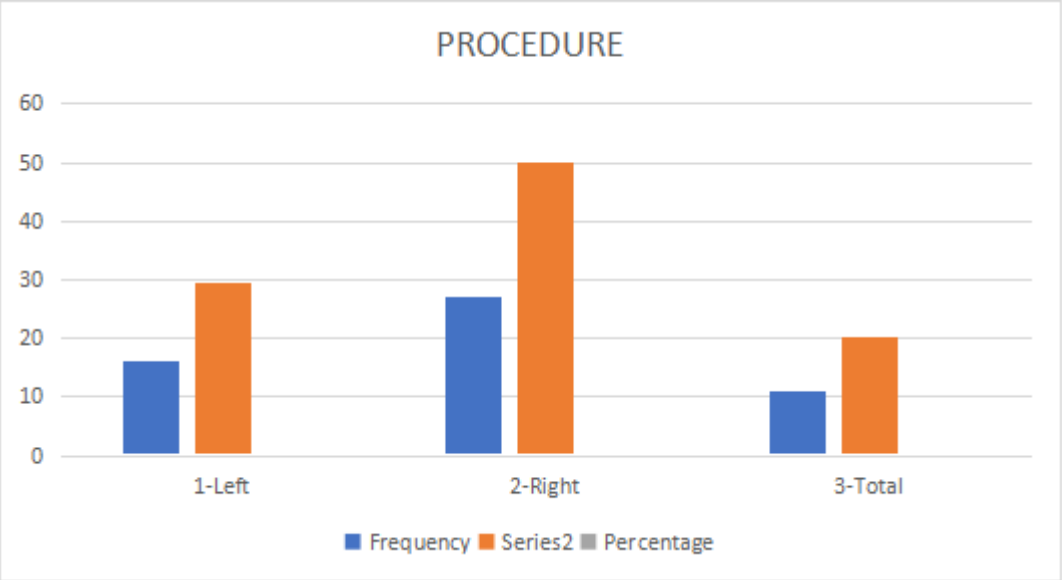
All patients underwent ultrasonography and fine needle aspiration cytology from the thyroid lesions. 52 % of the patients were having BETHESDA category 2 lesion which stands for benign thyroid neoplasm. Only 3 patients were proven malignancy preoperatively whereas 14 patients were found to have thyroid malignancy on histopathology reports post operatively. Around 40% of the nodules were TIRADS III grade in ultrasonography and only 4 patients were TIRADS V.

PROCEDURE

Out of 54 patients who got operated, 16 patients underwent left hemithyroidectomy, 27 underwent right hemithyroidectomy and 11 patients underwent total thyroidectomy.

Table 2.5 Showing Type of surgery

Procedure	Number of patients	Percentage
1-Left	16	29.6
2-Right	27	50.0
3-Total	11	20.4
Total	54	100.0



Frequency- Number of patients

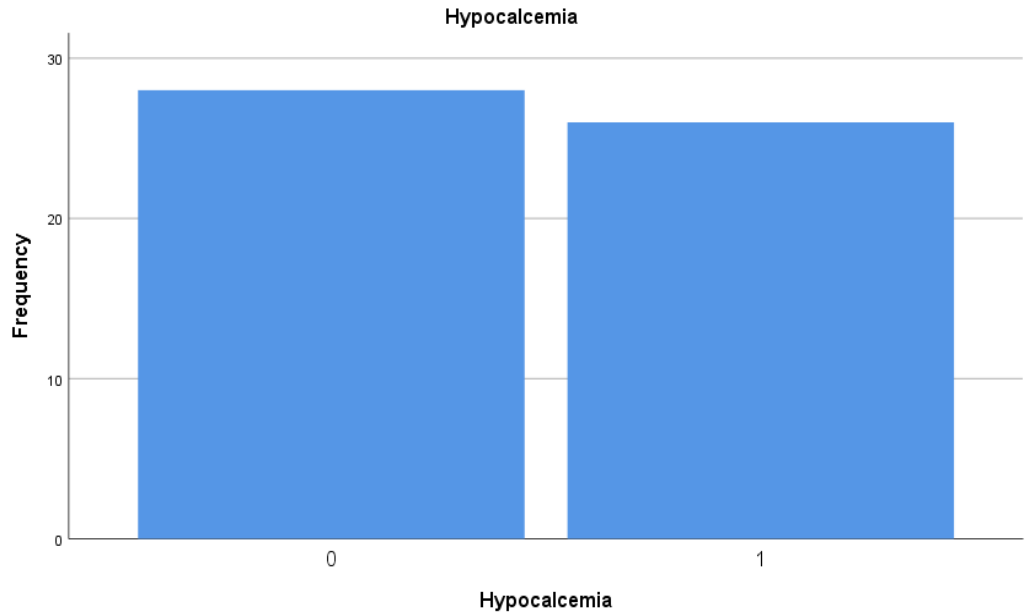
Figure 3.4 Bar diagram of Type of surgery

Hypocalcemia

Out of 54 patients, 26(48.1%) patients developed symptomatic as well as biochemical hypocalcemia and rest 28(51.9%) were asymptomatic with normal calcium levels.

Table 2.6 Frequency of Hypocalcemia

Hypocalcemia	Number of patients	Percentage
0-No	28	51.9
1-Yes	26	48.1
Total	54	100.0



Frequency- Number of patients

Figure 3.5 Bar diagram of Hypocalcemia

SEASON

Most of the patients (61%) were operated in the winter season and only 7 patients(13%) were operated in post monsoon season

Table 2.7 Seasonal variation

SEASON	Number of patients	Percentage
1-Summer	11	20.4
2-Winter	33	61.1
3-Monsoon	3	5.6
4-Post monsoon	7	13.0
Total	54	100.0

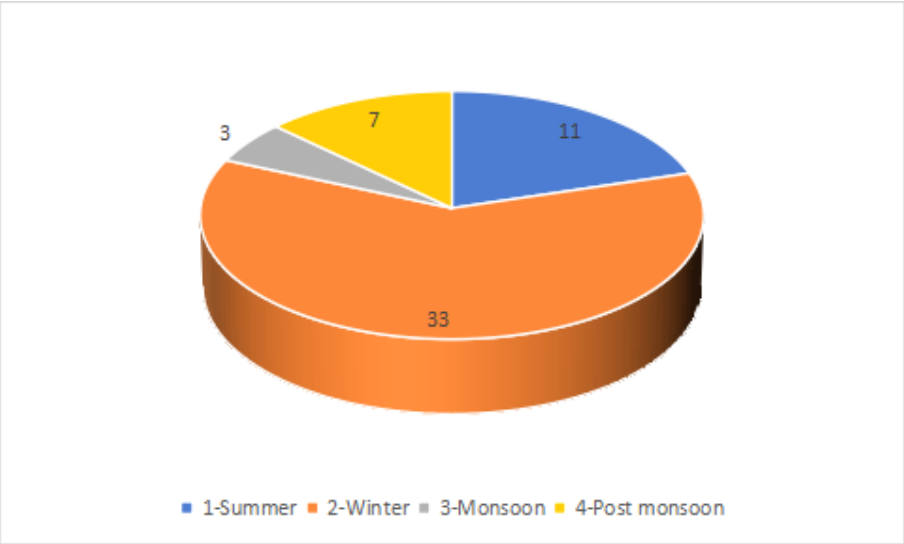


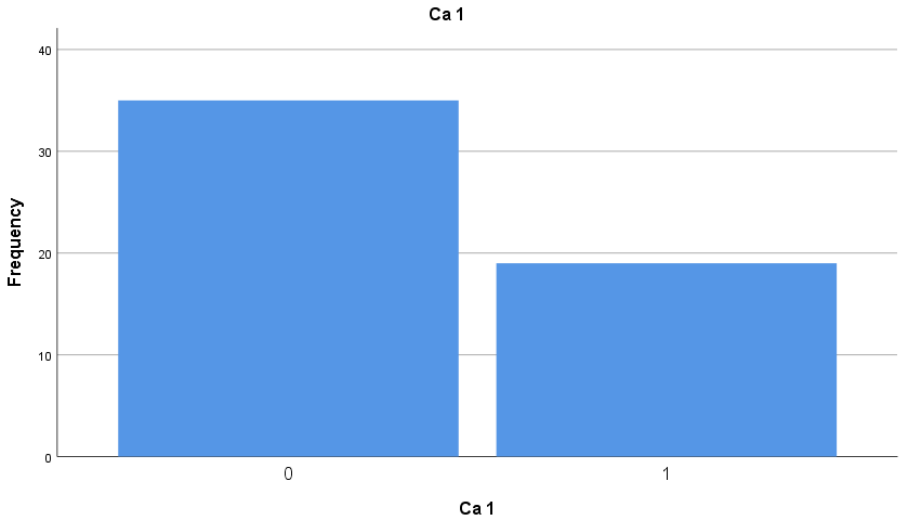
Figure 3.6 Pie diagram showing Seasonal distribution

Ca 1-Preoperative Calcium

Preoperative serum calcium was sent for all the patients and 19 of them (35.2%) had low serum calcium values without any clinical signs and symptoms of hypocalcemia

Table 2.8 Preoperative Calcium

Preoperative Calcium	Number of patients	Percentage
0-Normal	35	64.8
1-Low	19	35.2
Total	54	100.0



Frequency- Number of patients

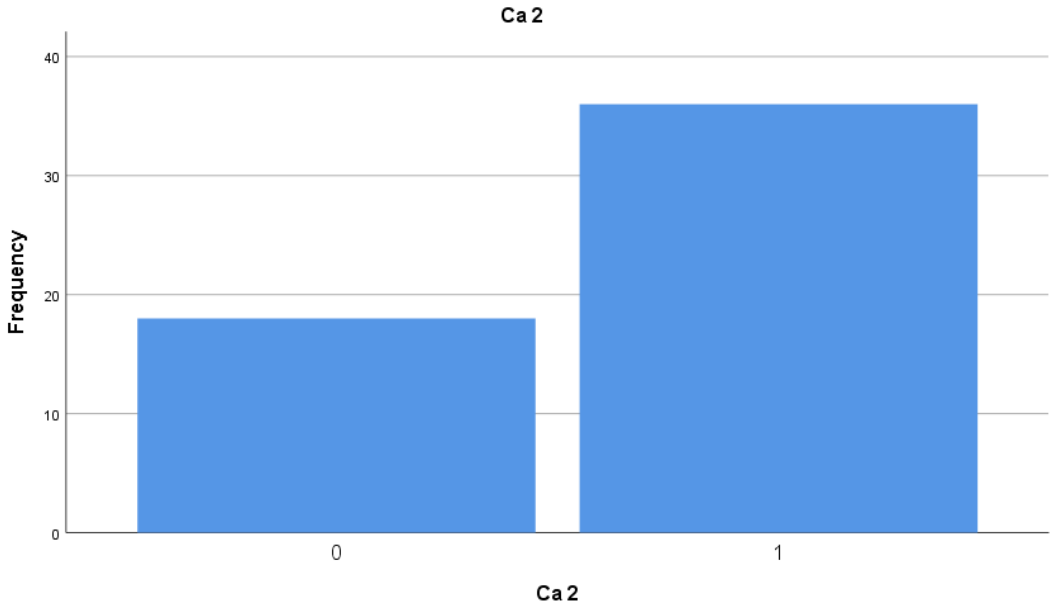
Figure 3.7 Bar diagram of Preoperative Calcium levels

Ca 2- Post operative Calcium (2 Hours)

Serum calcium was repeated in the immediate post op period and 66.7% patients had low biochemical values

Table 2.9 Post operative Calcium levels

Post op Calcium	Number of patients	Percentage
0-Normal	18	33.3
1-Low	36	66.7
Total	54	100.0



Frequency- Number of patients

Figure 3.8 Bar diagram of Post operative calcium levels

Ca 3- Post operative Calcium (24 Hours)

24 hours post op serum calcium was found to be low in 72.2% of the patients

Table 2.10 24-hour calcium values

24-hour Ca	Number of patients	Percentage
0-Normal	15	27.8
1-Low	39	72.2
Total	54	100.0

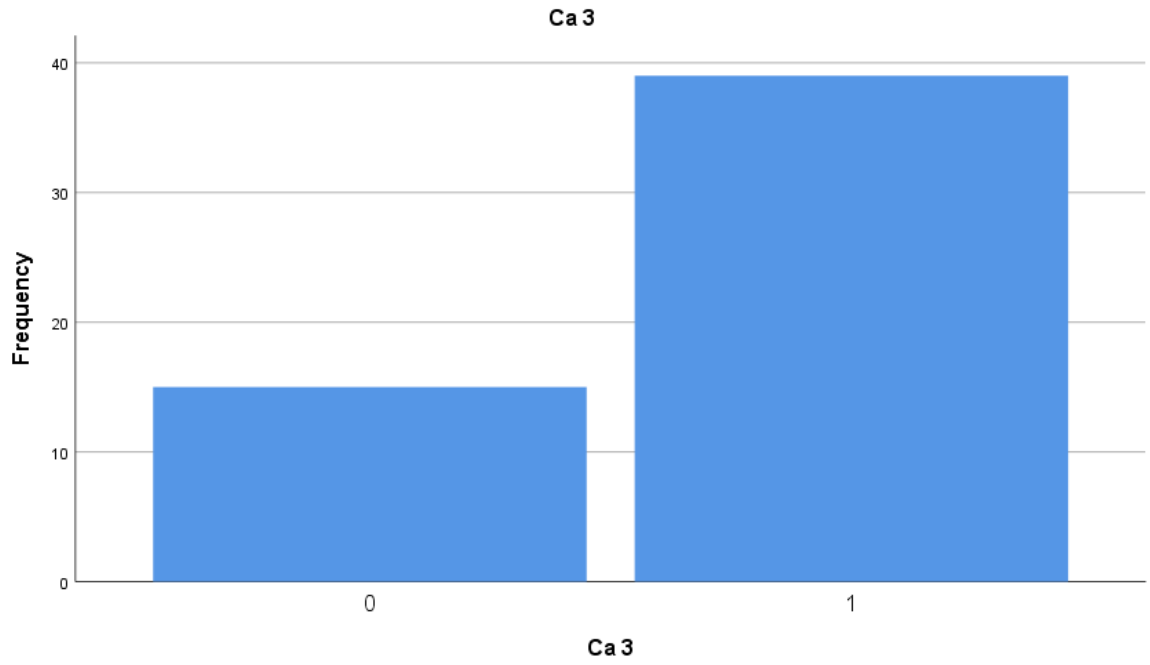


Figure 3.9 Bar diagram of 24-hour calcium

Frequency- Number of patients

Vitamin D

Preoperative serum Vitamin D was measured for all the patients and 19 patients (35.2%) had deficiency, 30 patients (55.6%) had insufficiency and only 5 patients (9.3%) had sufficient vitamin D

Table 2.11 Vitamin D level

Vitamin D	Number of patients	Percentage
0-Deficient	19	35.2
1-Insufficient	30	55.6
2-Sufficient	5	9.3
Total	54	100.0

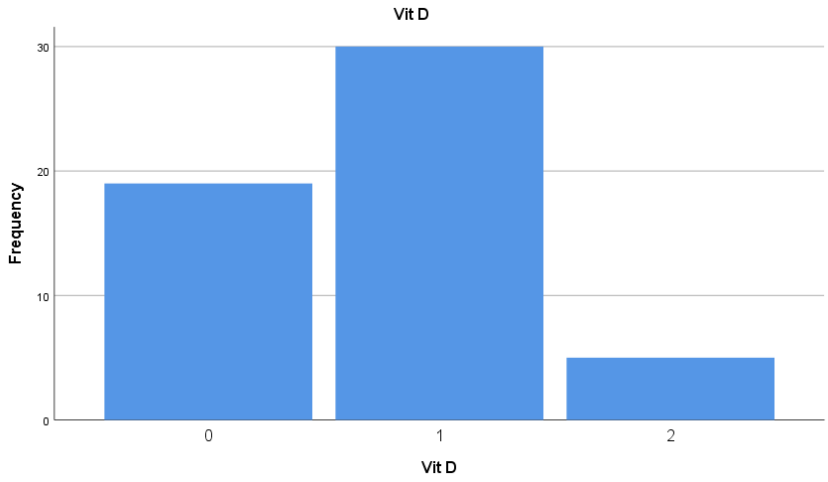


Figure 3.10 Bar diagram of Vitamin D level

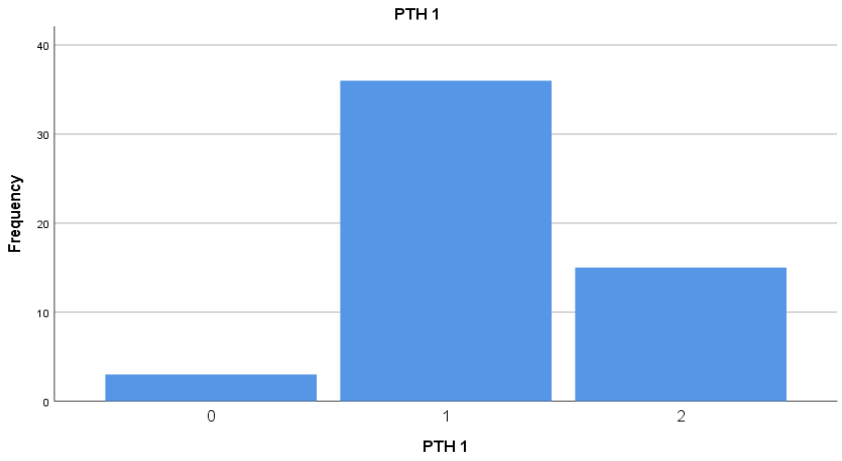
Frequency- Number of patients

PTH 1- Preoperative PTH

Only 3 patients had low serum PTH values preoperatively. 66.7% of the patients had normal serum PTH values and 27.8% patient had PTH values more than normal.

Table 2.12 Preoperative PTH levels

Preoperative PTH	Number of patients	Percentage
0-Low	3	5.6
1-Normal	36	66.7
2-High	15	27.8
Total	54	100.0



Frequency- Number of patients

Figure 3.11 Bar diagram of Preoperative PTH

PTH 2- Post operative PTH

24 hours post op serum PTH was measured and 6 patients had low values. 79.6% of the patients were having normal post op PTH values.

Table 2.13 Post operative PTH levels

Post operative PTH	Number of patients	Percent
0-Low	6	11.1
1-Normal	43	79.6
2-High	5	9.3
Total	54	100.0

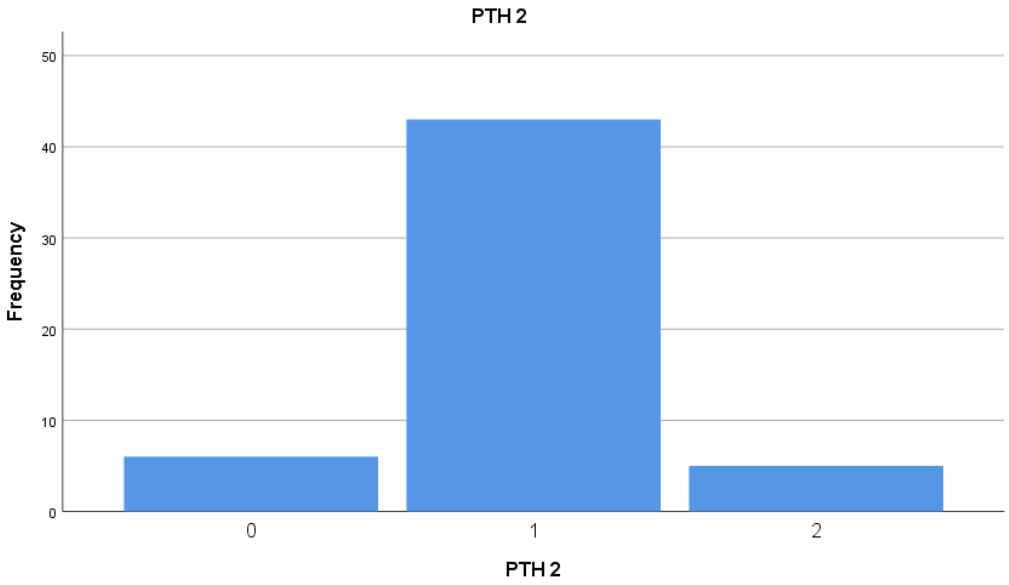


Figure 3.12 Bar diagram of Post operative PTH

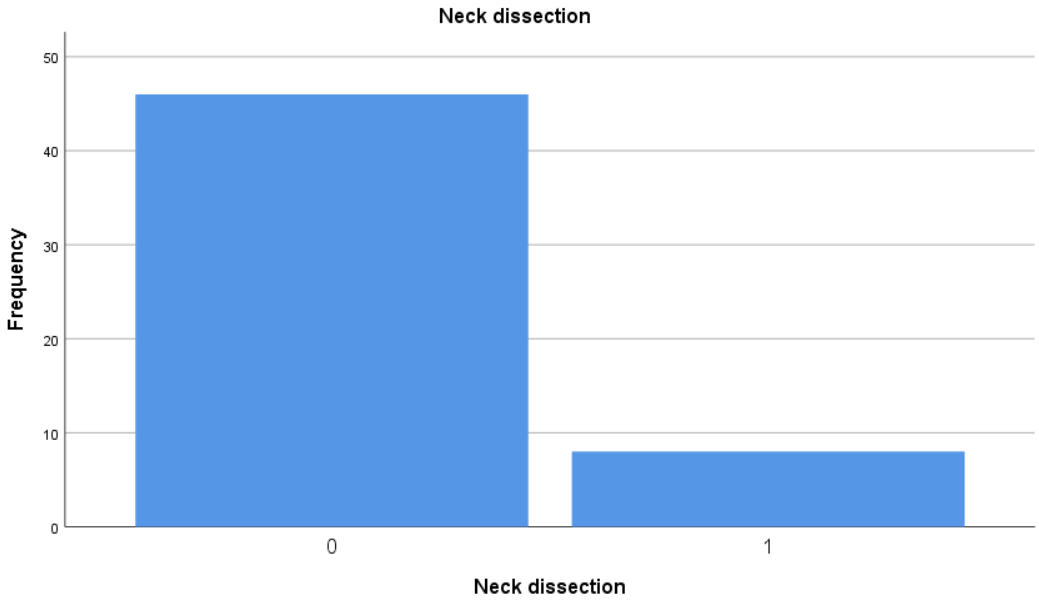
Frequency- Number of patients

Neck dissection

Neck dissection was done in only 8 patients (14.8%)

Table 2.14 Neck dissection

Neck dissection	Number of patients	Percent
0-Not done	46	85.2
1-Done	8	14.8
Total	54	100.0



Frequency- Number of patients

Figure 3.13 Bar diagram of Neck dissection

Blood Loss

Only 9 patients had blood loss more than 200ml

Table 2.15 Blood loss during surgery

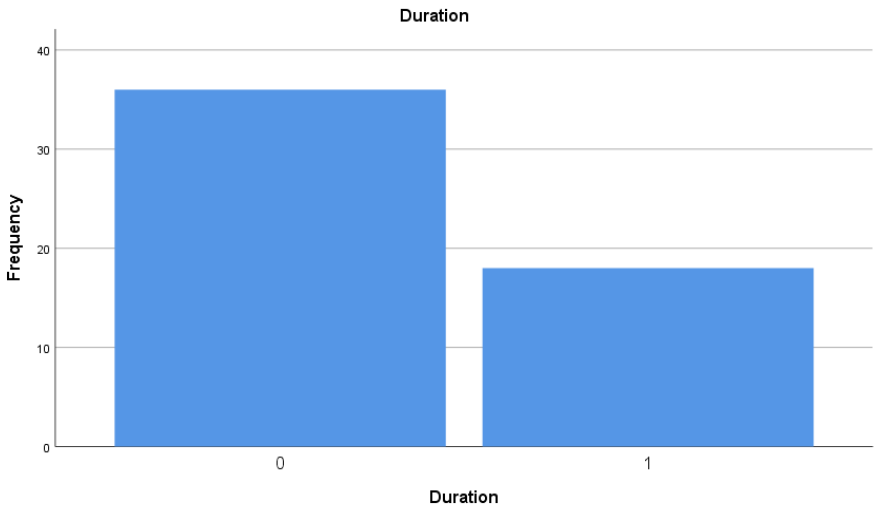
Blood loss	Number of patients	Percent
0-<200ml	45	83.3
1->200ml	9	16.7
Total	54	100.0

Duration Of Surgery

Duration of surgery was more than 3 hours in case of 18 patients (33.3%)

Table 2.16 Duration of surgery

Duration of Surgery	Number of patients	Percent
0 < 3 Hours	36	66.7
1 > 3 Hours	18	33.3
Total	54	100.0



Frequency- Number of patients

Figure 3.14 Bar diagram of Duration of surgery

Fall in PTH > 20 units

More than 20 international unit fall in serum PTH was observed in 46.3% of the patients who underwent thyroidectomy.

Table 2.17 Fall in PTH

Fall in PTH	Number of patients	Percent
0-No	29	53.7
1-Yes	25	46.3
Total	54	100.0

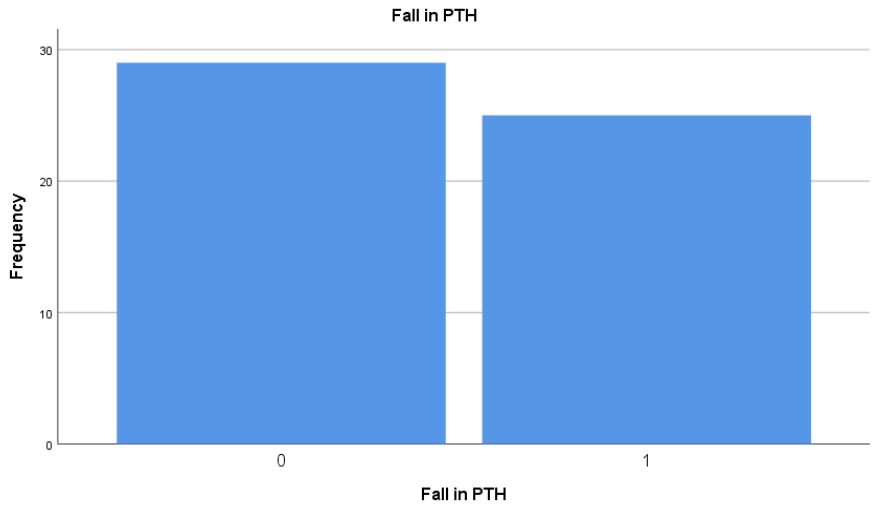


Figure 3.15 Bar diagram of Fall in PTH

Frequency- Number of patients

Out of the 54 patients who got operated, mean value of preoperative calcium was 8.99 mg/dl and mean value of 24 hour post operative calcium was 8.56 mg/dl. The mean value of serum Vitamin D was 16 IU.

Table 2.18 Statistics

Statistics						
	Ca 1	Ca 2	Ca 3	Vit D	PTH 1	PTH 2
N	54	54	54	54	54	54
Mean	8.9913	8.6115	8.5620	16.3791	62.2574	47.3217
Median	9.0000	8.6400	8.5150	14.0000	57.1500	46.4000
Mode	9.10	9.01	7.70	6.09	3.40	26.70
Std. Deviation	.45397	.45399	.72996	10.28620	30.52404	25.07489
Variance	.206	.206	.533	105.806	931.717	628.750
Minimum	8.15	7.76	5.10	4.00	3.40	3.00
Maximum	10.21	10.07	10.06	57.00	145.10	129.50

Ca 1- Preoperative calcium

Ca 2- Post operative calcium (2 hour)

Ca 3- Post operative calcium (24 hour)

Vit D- Pre operative vitamin D

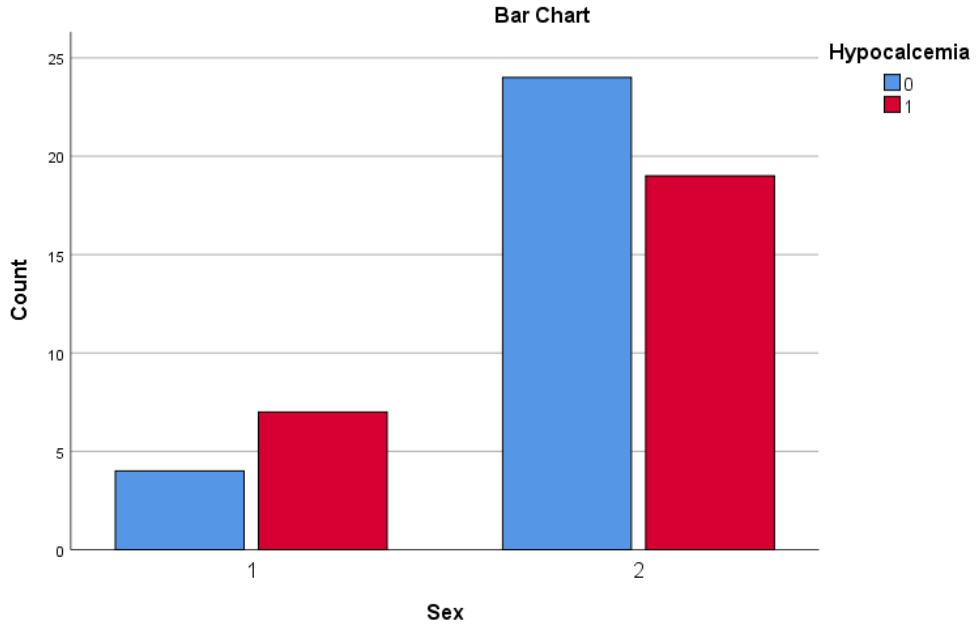
PTH 1- Pre operative PTH

PTH 2- Post operative PTH (24 hour)

Table 2.19 GENDER AND HYPOCALCEMIA

		Hypocalcemia		Total
		0	1	
1-Male	Count➔	4	7	11
	% within Hypocalcemia	14.3%	26.9%	20.4%
2-Female	Count➔	24	19	43
	% within Hypocalcemia	85.7%	73.1%	79.6%
Total	Count➔	28	26	54
	% within Hypocalcemia	100.0%	100.0%	100.0%

Chi-Square Tests for gender and hypocalcemia					
	Value	**df**	**Asymptotic Significance (2-sided)**	**Exact Significance (2-sided)**	**Exact Significance (1-sided)**
Pearson Chi-Square	1.327	1	.249		
Continuity Correction	.663	1	.416		
Likelihood Ratio	1.337	1	.248		
Fisher's Exact Test				.320	.208
Linear-by-Linear Association	1.303	1	.254		
N of Valid Cases	54				



Count- Number of patients

Figure 3.16 Bar diagram of Gender and Hypocalcemia

No correlation was found between gender and development of post operative hypocalcemia even though most of the patients were females.

Table 2.20 TYPE OF SURGERY AND HYPOCALCEMIA

PROCEDURE		Hypocalcemia		Total
		0	1	
1- Left Hemithyroidectomy	Count ➔	11	5	16
	% within Hypocalcemia	39.3%	19.2%	29.6%
2- Right Hemithyroidectomy	Count ➔	11	16	27
	% within Hypocalcemia	39.3%	61.5%	50.0%
3- Total Thyroidectomy	Count ➔	6	5	11
	% within Hypocalcemia	21.4%	19.2%	20.4%
Total	Count➔	28	26	54
	% within Hypocalcemia	100.0%	100.0%	100.0%

Chi-Square Tests for type of surgery and hypocalcemia			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	3.197	2	.202
Likelihood Ratio	3.254	2	.197
Linear-by-Linear Association	.859	1	.354
N of Valid Cases	54		

No correlation was found between type of surgery and development of post operative hypocalcemia.

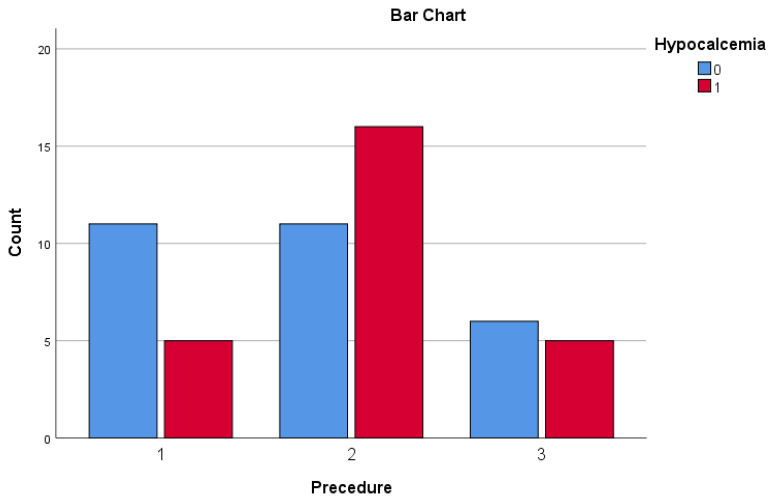


Figure 3.17 Bar diagram of Type of surgery and hypocalcemia

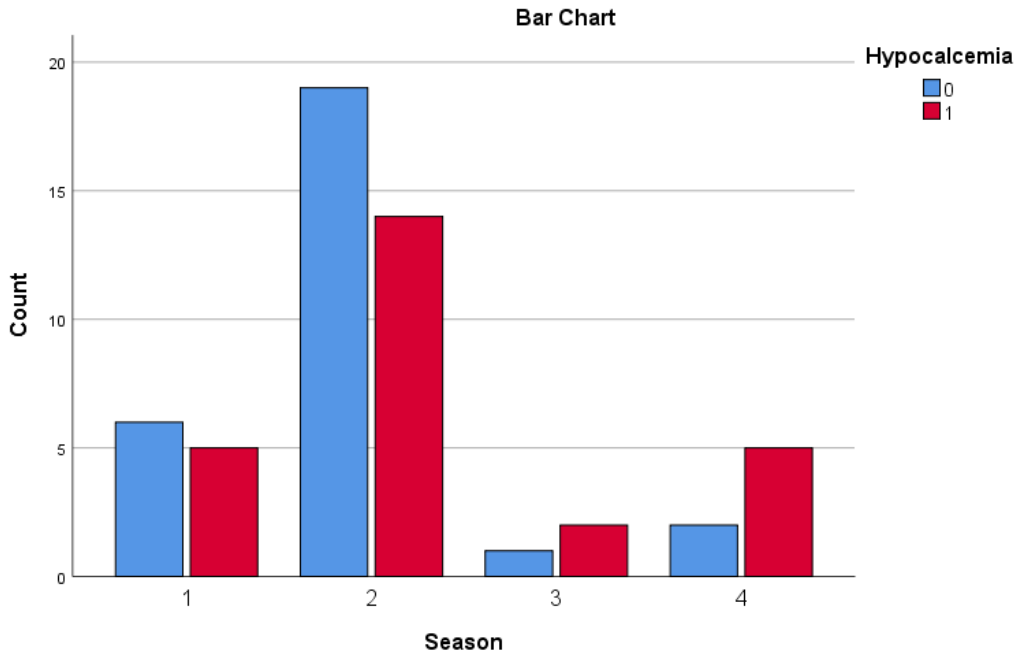
Count- Number of patients

Table 2.21 SEASON AND DEVELOPMENT OF HYPOCALCEMIA

Season		Hypocalcemia		Total
		0-No	1-Yes	
1-Summer	Count➔	6	5	11
	% within Hypocalcemia	21.4%	19.2%	20.4%
2-Winter	Count➔	19	14	33
	% within Hypocalcemia	67.9%	53.8%	61.1%
3-Monsoon	Count➔	1	2	3
	% within Hypocalcemia	3.6%	7.7%	5.6%
4-Post monsoon	Count➔	2	5	7
	% within Hypocalcemia	7.1%	19.2%	13.0%
Total	Count➔	28	26	54
	% within Hypocalcemia	100.0%	100.0%	100.0%

Even though most of the patients were operated in winter season, no significant association was found on analysis between season in which surgery was done and development of post operative hypocalcemia.

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	2.397	3	.494
Likelihood Ratio	2.446	3	.485
Linear-by-Linear Association	1.608	1	.205
N of Valid Cases	54		



Count- Number of patients

Figure 3.18 Bar diagram of Season and Hypocalcemia

1-Summer

2-Winter

3-Monsoon

4-Post monsoon

Table 2.22 PREOPERATIVE VITAMIN D AND HYPOCALCEMIA

			Hypocalcemia		Total
			0	1	
Vit D	0	Count➔	9	10	19
		% within Hypocalcemia	32.1%	38.5%	35.2%
	1	Count➔	15	15	30
		% within Hypocalcemia	53.6%	57.7%	55.6%
	2	Count➔	4	1	5
		% within Hypocalcemia	14.3%	3.8%	9.3%
Total		Count➔	28	26	54
		% within Hypocalcemia	100.0%	100.0%	100.0%

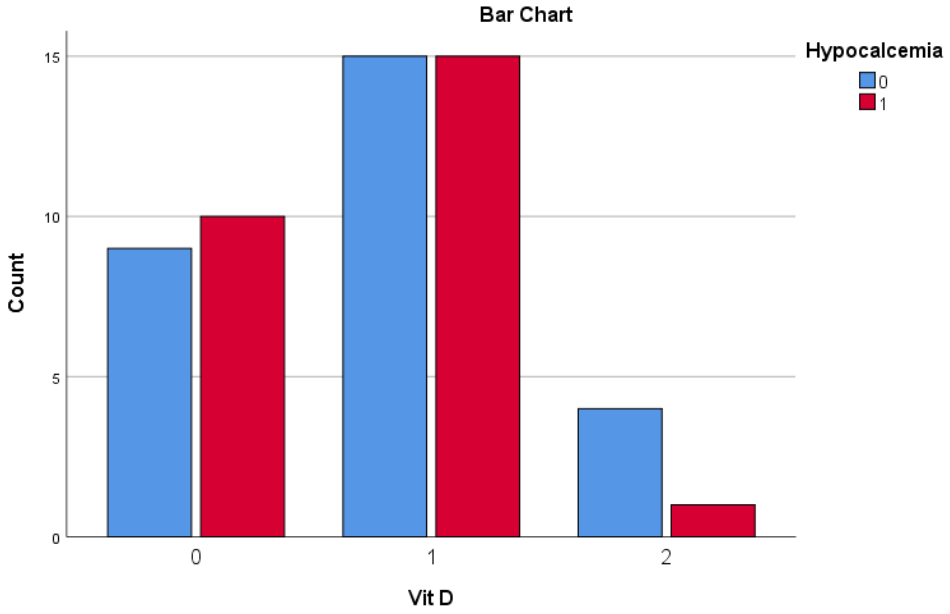
0- Deficient Vitamin D

1- Insufficient Vitamin D

2- Sufficient Vitamin D

No significant correlation was found between preoperative vitamin D values and development of post operative hypocalcemia.

Chi-Square Tests for vitamin D and hypocalcemia			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	1.781	2	.410
Likelihood Ratio	1.906	2	.386
Linear-by-Linear Association	.985	1	.321
N of Valid Cases	54		



Count- Number of patients

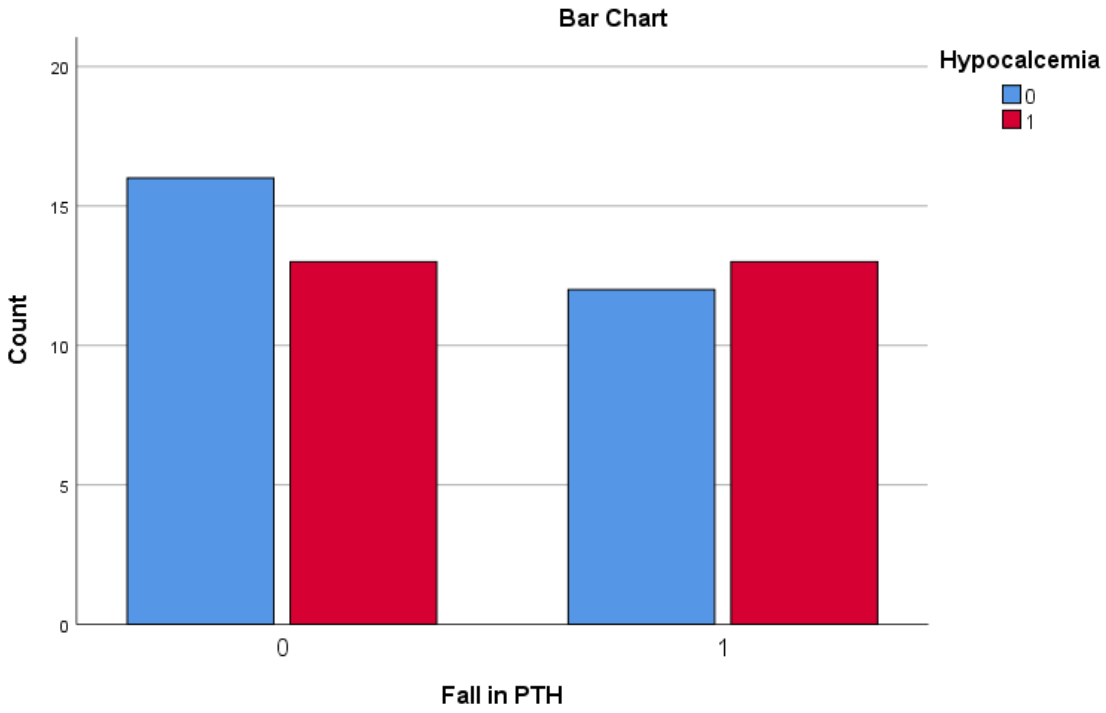
Figure 3.19 Bar diagram of Vitamin D and Hypocalcemia

Table 2.23 FALL IN PTH AND HYPOCALCEMIA

			Hypocalcemia		**Total**
			0 (No Fall)	**1 (Fall)**	
Fall in PTH >20 IU	0-No	Count➔	16	13	29
		% within Hypocalcemia	57.1%	50.0%	53.7%
	1-Yes	Count➔	12	13	25
		% within Hypocalcemia	42.9%	50.0%	46.3%
Total		Count➔	28	26	54
		% within Hypocalcemia	100.0%	100.0%	100.0%

Chi-Square Tests for fall in PTH and hypocalcemia					
	Value	**df**	**Asymptotic Significance (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	.277	1	.599		
Continuity Correction	.064	1	.800		
Likelihood Ratio	.277	1	.599		
Fisher's Exact Test				.785	.400
Linear-by-Linear Association	.272	1	.602		
N of Valid Cases	54				

No significant correlation was found between fall in serum PTH value more than 20 units and development of post operative hypocalcemia.



Count- Number of patients

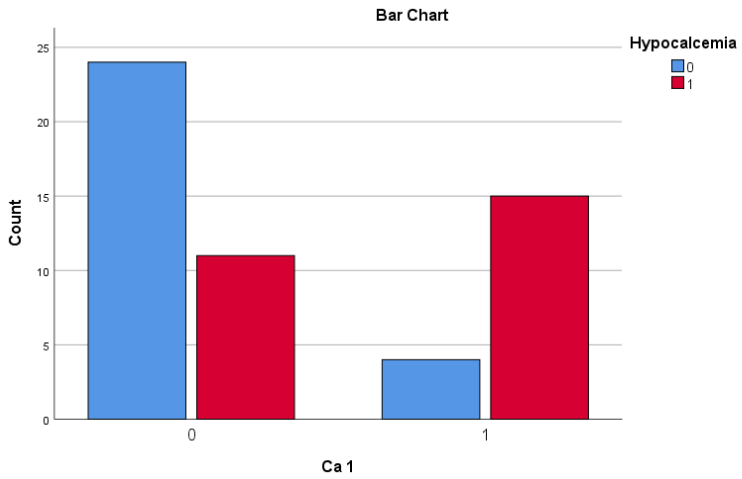
Figure 3.20 Bar diagram of Fall in PTH and Hypocalcemia

Table 2.24 PREOPERATIVE CALCIUM AND HYPOCALCEMIA

Preoperative Calcium			Hypocalcemia		Total
			0	1	
Ca 1	0-Normal	Count➔	24	11	35
		% within Hypocalcemia	85.7%	42.3%	64.8%
	1-Low	Count➔	4	15	19
		% within Hypocalcemia	14.3%	57.7%	35.2%
Total		Count➔	28	26	54
		% within Hypocalcemia	100.0%	100.0%	100.0%

Chi-Square Tests for preoperative calcium and hypocalcemia					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	11.138	1	.001		
Continuity Correction	9.316	1	.002		
Likelihood Ratio	11.655	1	.001		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	10.932	1	.001		
N of Valid Cases	54				

Significant association was found between low preoperative serum calcium value and development of post operative symptomatic hypocalcemia.



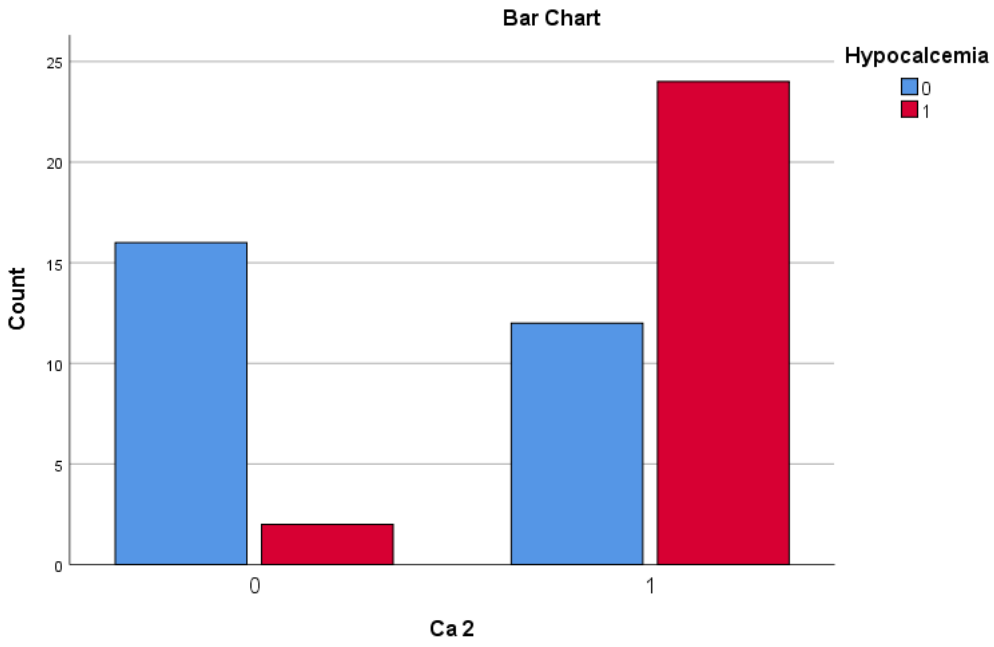
Count- Number of patients

Figure 3.21 Bar diagram of Preoperative calcium and Hypocalcemia

Table 2.25 POST OPERATIVE CALCIUM AND HYPOCALCEMIA

			Hypocalcemia		Total
			0	1	
Ca 2	0	Count➔	16	2	18
		% within Hypocalcemia	57.1%	7.7%	33.3%
	1	Count➔	12	24	36
		% within Hypocalcemia	42.9%	92.3%	66.7%
Total		Count➔	28	26	54
		% within Hypocalcemia	100.0%	100.0%	100.0%

Chi-Square Tests for post operative calcium and hypocalcemia					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	14.835	1	.000		
Continuity Correction	12.693	1	.000		
Likelihood Ratio	16.399	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	14.560	1	.000		
N of Valid Cases	54				



Count- Number of patients

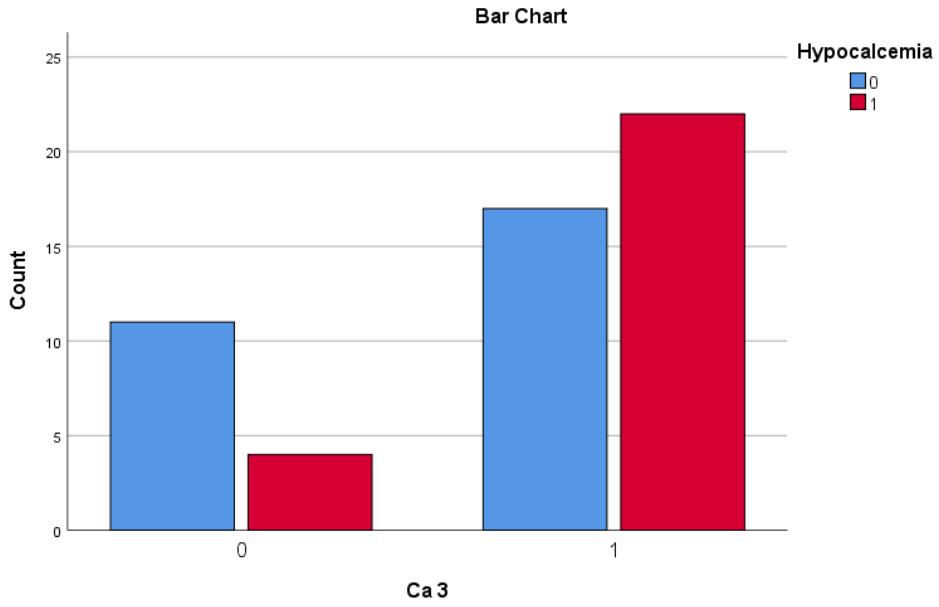
Figure 3.22 Bar diagram of Post op calcium and Hypocalcemia

92.3% of the patients with low serum calcium values post operatively (immediate post operative value) developed symptomatic hypocalcemia and a significant association was found between immediate post operative low calcium value and development of symptomatic hypocalcemia.

Table 2.26 24 Hour Calcium and Hypocalcemia

Ca 3- 24 hours calcium		**Hypocalcemia**		**Total**
		0	**1**	
0- Normal	Count➔	11	4	15
	% within Hypocalcemia	39.3%	15.4%	27.8%
1- Low	Count➔	17	22	39
	% within Hypocalcemia	60.7%	84.6%	72.2%
Total	Count➔	28	26	54
	% within Hypocalcemia	100.0%	100.0%	100.0%

Chi-Square Tests for 24 hour Calcium and Hypocalcemia					
	Value	**df**	**Asymptotic Significance (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**
Pearson Chi-Square	3.839	1	.050		
Continuity Correction	2.740	1	.098		
Likelihood Ratio	3.966	1	.046		
Fisher's Exact Test				.070	.048
Linear-by-Linear Association	3.768	1	.052		
N of Valid Cases	54				



Count- Number of patients

Figure 3.23 Bar diagram of 24-hour calcium and Hypocalcemia

84.6% of the patients with low 24 hours post operative serum calcium developed postoperative symptomatic hypocalcemia but no significant correlation was found on analysis.

DISCUSSION

As India enters the third year of combating SARS COVID-19 outbreak, there were significant reduction in the number of elective surgeries in our hospitals including thyroidectomies, especially when it's done for benign thyroid lesions. Thyroidectomy is considered as the most widely used management modality of thyroid nodules. As reported by epidemiological studies, the incidence of thyroid cancer is showing an increasing trend in previous decades (16,17). So, prevention and management of complications of thyroidectomy including the most frequent postoperative hypocalcaemia is very important(73).

The present study is a prospective observational cohort study conducted in 54 patients who underwent thyroidectomy procedure in Department of Otorhinolaryngology, AIIMS Jodhpur. This study aimed at identifying predictors of post operative hypocalcaemia in patients undergoing thyroidectomy. In this study, patients of all age were included, the youngest one was an 18-year-old girl and oldest was a 61-year-old lady. Similar protocol has been followed for each patient. All patients undergoing thyroidectomy for primary thyroid pathology were included in this study. Patients with concomitant hyperparathyroidism were excluded from the study. Patients were recruited into study after getting an informed consent. All patients were assessed clinically. Preoperative testing for serum calcium, PTH and Vitamin D were done on the day of surgery. These patients were subjected to surgery as per preoperative clinical discussion. Postoperative testing for PTH was done 24 hours after surgery and serum calcium on day 0 and 1. All patients were assessed clinically for signs and symptoms of hypocalcemia till 48 hours post operatively and this was correlated with the biochemical parameters and the season in which surgery was performed.

Marco A Mascarella et al (15) studied the seasonal difference in post-thyroidectomy hypocalcemia in McGill university health center Montreal, Canada in 2015 and it was found that patients operated in winter were 5.6 times more likely to develop hypocalcemia as compared to those in summer. Patients who are having Grave's disease are more prone to develop low serum calcium and vitamin D values in winter compared to summer and thereby more susceptible for development of post operative symptomatic hypocalcemia(74).

Seasonal variation was also monitored in our study and **Kordel et al** (63) In his cohort, Comparing total thyroidectomies done in February to those done in April, total thyroidectomies done in August to October had a reduced post-operative calcium therapy

rate. This would suggest that if surgery was performed after the drier season, there would be a lower incidence of post-operative hypocalcemia.

In our study no correlation was found between season and development of postoperative hypocalcemia. This is probably because of no drastic change in temperatures and seasons in India.

Arer IM et al (57) states that, prophylactic oral calcium supplementation therapy can prevent early post thyroidectomy hypocalcemia with the advantages of being cost-effective and safe. Serum PTH levels at postoperative 12 and 24 hours can predict early post thyroidectomy hypocalcemia. In this study the incidence of hypocalcemia was 33.9% where as in our study the incidence was 48%. **Del Rio et al** (40) states that, the only variables (among all those analyzed) that affect the development of early hypocalcemia are perioperative changes in serum calcium, surgical procedure and sex (female gender is a high risk factor) and 37.7% patients in this study developed hypocalcemia.

In our study, it was found that preoperative low calcium is a clear predictor of post thyroidectomy hypocalcemia.

Dionigi G et al (14) states that, pre-operative low calcium, parathormone (PTH), 25-hydroxyvitamin D increases the risk of hypocalcemia. The calcium drop rate also matters, a decrease of 1 mg/dL calcium over 12 hours after surgery is independently correlated with the risk of symptomatic hypocalcemia. **Wang Y H et al**(58) states that, The extent of thyroidectomy, gender, lateral lymph node dissection, operating time, and usage of carbon nanoparticles were all substantially associated with postoperative hypocalcemia and hypoparathyroidism occurrence. These findings were crucial for guiding surgeons to prevent the occurrence of hypocalcemia and hypoparathyroidism. **Edafe O et al** (59) states that, PTH during surgery, vitamin D before surgery, and calcium fluctuations after surgery are biochemical indicators of post-thyroidectomy hypocalcemia. Clinical predictors include female sex, Graves' disease, need for parathyroid auto transplantation and inadvertent excision of parathyroid glands.(75)**Celesteno pio et al** states that, a single intact PTH value can identify which patients are likely to experience clinically obvious or symptomatic post-operative hypocalcemia and which patients may be allowed to go home earlier. No such correlation was found between serum PTH value and development of post operative hypocalcemia in our study.

Jong-lyel et al(76) states that, rapid intraoperative PTH assay can also identify thyroidectomy patients who are prone to development of post operative hypocalcemia. When used as a clinical guide for discharge following total thyroidectomy, intraoperative PTH has no significant disadvantage compared to early postoperative PTH, but a PTH value of >15 pg/mL and 70% decline in intact PTH after total thyroidectomy can easily identify normocalcemic patients or those who need postoperative calcium(77).

On statistical evaluation the mode (The value that appears most often in a set of data values) of parathyroid hormone levels in our study was 26.7pg/mL. In a study by **Vanderlei et al**, it was found that a fall in serum PTH by 73.5% can predict symptomatic hypocalcemia after thyroidectomy(78). So, in our study the fall in PTH cut off was taken as 20 pg/mL (73.5% of mode value 26.7 pg/mL) and no correlation was found between fall in PTH and development of hypocalcemia**.**

Roderick M et al(79) states that, when the incision is closed, a single parathormone level of less than 10 pg/mL is a strong indicator of postoperative hypoparathyroidism, and these patients should get vitamin D supplements to prevent symptomatic hypocalcemia. Type of surgery can also affect the outcome of thyroid surgery. Compared to conventional total thyroidectomy, intracapsular total thyroid enucleation has less side effects, such as postoperative hypocalcemia (80–82).

Stanley H et al states that preoperative 1,25-dihydroxyvitamin D levels are not predictive of postoperative calcium levels, same finding was observed in our study. There is very little chance of calcium replacement therapy in patients who have parathyroid adenoma removal or complete lobectomy(83). Low risk of postoperative hypocalcemia exists in patients undergoing complete thyroidectomy or partial parathyroidectomy with 8-hour postoperative PTH levels greater than or equal to 15 pg/mL (1.6 pmol/L), but high risk exists in patients with PTH levels less than 15 pg/mL (1.6 pmol/L), whereas no such correlation was observed in our study.

Bove et al(84) states that low preoperative blood 25-OHD levels are significantly correlated with postoperative hypocalcemia. Their studies demonstrated that vitamin D deficiency (<25 ng/mL) is an independent predictive factor of postoperative hypocalcemia. We had patients with vitamin D deficiency, insufficiency and sufficiency in our study and no correlation was

observed with development of postoperative hypocalcemia. **Erbil Y et al** (85) states that, impact of incidental parathyroidectomy was also studied and there was no relationship found.

Haluk et al(86)states that, In patients with benign multinodular goiter, near complete thyroidectomy may provide an advantage over total thyroidectomy in terms of postoperative hypocalcemia, whereas in our study only hemithyroidectomy and total thyroidectomy procedures were done.

(63)The volume of operations a surgeon performs annually, or the number of surgeries, can potentially have an impact on the emergence of postoperative problems (36) which was not a criteria in our study.

Sands et al(87) states that, The likelihood of transitory post-thyroidectomy hypocalcemia is probably higher in women. Despite the statistical significance of this link, its magnitude and clinical importance are unknown and may not be meaningful. (88) A prophylactic calcium and magnesium dietary supplement, which might be easily adopted in the preoperative environment, may assist to avoid, prevent, or lessen the symptoms associated with hypocalcemia and enhance quality of life. If successful, this preoperative technique could be an ideal approach to get patients ready for thyroidectomies and could perhaps lower the costs associated with the disease by lowering the incidence of postoperative complications.

Colleen Donahue et al states that, after a complete thyroidectomy, commencing calcium and calcitriol supplementation before surgery did not lessen postoperative hypocalcemia compared to postoperative supplementation alone. These results contradict the widespread recommendation to regularly supplement with calcium and calcitriol before total thyroidectomy(89).

In this single center study, the smaller sample size is probably what has led to no evidence of seasonal variation and we therefore suggest multicenter study with larger sample size for better understanding and evaluation of risk factors for post thyroidectomy hypocalcemia.

STRENGTHS AND LIMITATION

STRENGTHS:

1. All the patients were enrolled after complete evaluation.
2. It was a prospective cohort study
3. Patients of all age group were included

LIMITATIONS:

1. No long term follow up was done
2. Single centre study
3. Sample size was less
4. Cases were operated by multiple surgeons having different surgical technique

RECOMMENDATIONS

Since the incidence of thyroid neoplasms has been increasing worldwide and in India in the last three decades, prevention and management of complications of thyroidectomy including the most frequent postoperative hypocalcaemia is very important. As a part of prevention, we need to identify the risk factors for the development of post operative hypocalcaemia. As per results of this study we recommend that to screen every patient preoperatively for low calcium values as it is a risk factor for development of post operative symptomatic hypocalcaemia. Active intervention can be taken as early as possible since immediate post operative low serum calcium value is a clear predictor of symptomatic hypocalcaemia. We also recommend to add Vitamin D supplementation preoperatively as most of the patients in our study was having insufficient serum Vitamin D values. However, this needs to be further evaluated by a multicentre study with larger sample size.

CONCLUSION

As per this study, we conclude that there is relationship between low preoperative serum calcium and development of post thyroidectomy hypocalcaemia and immediate post operative low serum calcium value is a clear predictor of post thyroidectomy symptomatic hypocalcaemia. However, this study is prospective and the sample size is small and the results needs to be further investigated with a multicentre study with a larger sample size to confirm the findings and to establish robust evidence.

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ANNEXURE- A: INFORMED CONSENT FORM (ENGLISH)

Serial no._____

INFORMED CONSENT FORM

All India Institute of Medical Sciences Jodhpur

Subject: - Consent for taking information about my disease in patients of thyroidectomy and to use their information for research purpose.

Participant's registration number: _____.

I declare that on date ..... all the details of this information sheet given to me has been explained to me in my language. I am told that in this process, information about my disease will be taken and will be used for research purpose. This research is being done for studies and treatment. I have been explained that no active intervention will be done by the researcher and my treatment will continue as same decided by my doctors. I understand that all information related to me in this research will be kept by the responsible person of AIIMS Jodhpur. I allow them to see all the information related to me. I have been told that all the information related to me will be kept confidential. I have also been told that the results of this research can be published in any book or journal and can be displayed in any conference. I have also been told that my name or any other identity will not be used without my consent. I know that I am participating in this research with my consent and I can refuse to participate in this research at any time without any reason.

I agree to participate in this research.

(Signature) Date:

Place:

Name of the Participant: _____

Son / Daughter / Spouse of: _____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

1) Witness – 1 2) Witness – 2

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Name: Name:

Address: Address:

Signatures of the principal investigator: Dr. Jibin C J

Place: Date:

ANNEXURE- B: INFORMED CONSENT FORM (HINDI)

क्रम संख्या---

सू चत सहमति का दस्तावेज:

अ खल भारतीय आयु र्वज्ञान संस्थान, जोधपुर

वषय- थयरॉइडेक्टमी के मरीजों के बीमारी के बारे में जानकारी लेने और रिसर्च में उस जानकारी का उपयोग करने की सहमति |

मैं यह घोषणा करता/करती हूँ क दिंनाक ..... को मुझे दिए गये इस सूचना पत्र के समस्त ववरण के बारे में मुझे मेरी भाषा में समझा दिया गया है | मुझे यह बताया गया है क इस शोध कार्य में मेरे बीमारी के बारे में जानकारी ली जा रही है और इसका इस्तेमाल इस शोधकार्य के लए कया जायेगा| शोधकर्ता के द्वारा मेरे बीमारी की इलाज़ में कोई परिवर्तन नहीं कया जायेगा| यह कार्य शोध अध्ययन एवं इलाज के लए के लए कया जा रहा है| मैं यह समझता हू क इस शोध में मेरे/मुझसे सम्बं धत समस्त जानकारी एम्स जोधपुर के जिम्मेदार व्यक्ति के द्वारा रखी जायेगी | मैं उन्हें मुझसे सम्बन्धित समस्त जानकारी देखने की अनुमति देता हूँ | मुझे यह बताया गया हें क मुझसे संबं धत समस्त जानकारी को गोपनीय रखा जायेगा | मुझे यह भी बताया गया है क इस शोध के परिणामों को कसी भी पुस्तक या जर्नल में प्रका शत कया जा सकता है एवम् कसी भी कांफ्रेंस में प्रद र्शत कया जा सकता है | मुझे यह भी बताया गया है क मेरा नाम या अन्य कोई भी पहचान मेरी सहमति के बिना काम में नहीं ली जयेगी | मुझे पता है की मैं इस शोध में अपनी सहमति से भाग ले रहा हूँ तथा मैं कसी भी समय बिना कसी कारण बताए इस शोध में भाग लेने से इंकार कर सकता हूँ |

मैं इस शोध में भाग लेने के लए सहमति देता हू |

हस्ताक्षर.. दिनांक..

भागीदार का नाम.. पता/पति/ पत्नी का नाम..

पुरा स्थायी पता..

यह प्रमा णत कआ जाता है क उपरोक्त सहमति मेरी उपस्थति में ली गयी है |

1. गवाह-1 2. गवाह-2

नाम व पता नाम व पता

शोधकर्ता के हस्ताक्षर (डॉ जिबिन सी जे)

ANNEXURE- C: PATIENT INFORMATION SHEET (ENGLISH)

Department of Otorhinolaryngology

All India Institute of Medical Sciences, Jodhpur

PATIENT INFORMATION SHEET

TITLE: Predictors of post-operative hypocalcemia in patients undergoing thyroidectomy

This study requires your detailed information and recall of previous treatment sought elsewhere for the assessment to be done to proceed in this study. You will be subjected to detailed clinical assessment and routine workup and will be followed up till the biochemical values after surgery is known. This study would require the details of preoperative values of serum calcium, PTH and Vit D and postoperative values of serum calcium and PTH. You are expected to attend to all the questions put in front of you in depending on the mutual comfort of you and the investigator. There are no obvious, expected or known adverse effects on the patient due to this study. You have been invited to take part in a study, which will help us in better understanding of the disease. You are free to withdraw from the study at any time and this will not have any negative implication on you/your ward's future treatment in the hospital.

Contact Person for further queries.

Dr. Jibin C J

Mob-+917073092404

ANNEXURE- D: PATIENT INFORMATION SHEET (HINDI)

ऑटोरहिनोलेरिंगोलोजी वभाग

अ खल भारतीय आयु र्वज्ञान संस्थान, जोधपुर

सूचनापत्र

टाइटल: थायरॉयडेक्टॉमी से गुजरने वाले रो गयों में पोस्ट ऑपरेटिव हाइपोकैल्सी मया के पूर्वसूचक

इस अध्ययन में आगे बढ़ने के लए मूल्यांकन के लए इस अध्ययन के लए आपकी वस्तृत जानकारी की आवश्यकता है। आपको वस्तृत नैदानिक मूल्यांकन और रूटीन वर्कअप के अधीन कया जाएगा और सर्जरी के बाद बायोके मस्ट्री रिपोर्ट तक इसका पालन कया जाएगा। । इस अध्ययन के लए प्रीऑपरेटिव सीरम कैल्शियम, पैराथार्मोन और वटा मन दि, पोस्ट ऑपरेटिव सरुम कैल्शियम और पैराथार्मोन ववरण की आवश्यकता होगी। आपको और जांचकर्ता के आपसी आराम के आधार पर आप के सामने रखे गए सभी प्रश्नों में भाग लेने की उम्मीद है। इस अध्ययन के कारण रोगी पर कोई स्पष्ट, अपे क्षत या ज्ञात प्रतिकूल प्रभाव नहीं हैं। आपको एक अध्ययन में भाग लेने के लए आमंत्रित कया गया है, जो हमें आपकी बीमारी को बेहतर समझने में मदद करेगा। आप कसी भी समय अध्ययन से वापस लेने के लए स्वतंत्र हैं और अस्पताल में आपके / आपके वार्ड के भ वष्य के उपचार पर इसका कोई नकारात्मक प्रभाव नहीं होगा।

अ धक प्रश्नों के लए संपर्क करें

डॉ जिबिन सी जे

मोबाइल नंबर-+917073092404

ANNEXURE- E: CASE RECORD FORM

CASE RECORD FORM

A. BIODATA **C.R.NO.:**

1. Name
2. Age/Sex
3. Address
4. Date of Examination

B. HISTORY

Swelling of neck:

- Duration
- Site
- Progression

Compressive features

Any history of dysphagia, hoarseness or dyspnea

Any history suggestive of hyper/hypothyroidism

PAST MEDICAL HISTORY

Any significant history

FAMILY HISTORY

History of thyroid disease in family (first degree relative)

SOCIAL AND PERSONAL HISTORY

Smoking, alcohol consumption

C. CLINICAL EXAMINATION:

I. General Examination

II. Systemic Examination:

III ENT EXAMINATION:

Local Examination

INSPECTION:

PALPATION:

Retrosternal extension:

Carotid Pulsations:

Cervical Lymphadenopathy

AUSCULTATION

Signs of hypo/hyperthyroidism

Vocal cord status

G. RADIOLOGICAL INVESTIGATIONS

1. Ultrasonography neck and thyroid

H. FNAC (Fine Needle Aspiration Cytology)/ USG guided FNAC (Bethesda classification).

I. PRE OPERATIVE

Serum Calcium –

Serum PTH –

Vit D -

J. INTRA OPERATIVE

Date of surgery:- **Duration of surgery**:-

Type of surgery:-

Total blood loss during surgery:-

Lymph node dissection:- Not done

Done

Season in which surgery is done : a) Summer (April-June)

b) Winter (December-March)

c) Monsoon (July-September)

d) Post monsoon (October-November)

K. POST OPERATIVE

Serum calcium –Day 0-

Day 1-

Serum PTH 24HR-

Symptoms of Hypocalcemia- a) Perioral numbness

b) Muscle cramps

c) Others

Signs of Hypocalcemia -a) Chvostek's sign-

-b) Trosseau's sign-

ANNEXURE- F: IEC CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3538 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3373**

Project title: **"Predictors of post operative hypocalcemia in patiens undergoing thyroidectomy"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.S. Dissertation**
Student Name:	**Dr. Jibin C J**
Guide:	**Dr. Kapil Soni**
Co-Guide:	**Dr. Amit Goyal, Dr. Bikram Choudhury, Dr. Mithu Banerjee & Dr. Ravindra Shukla**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

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E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com