

**RANDOMIZED CONTROL STUDY USING VITAMIN D
(CALCITRIOL) IN PREVENTING POST TOTAL
THYROIDECTOMY TRANSIENT HYPOCALCEMIA**

By

**DR LAI CHUNG KET
MD USM, MMED SURGERY**

**Dissertation Submitted In Partial Fulfilment Of The Requirements For
The Degree Of Master Of Medicine (GENERAL SURGERY)**



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2011

Disclaimer

I hereby certify that the work in this dissertation is my own except for the quotation and summaries which have been duly acknowledged.

Date:

Dr Lai Chung Ket

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First of all, I would like to thank my wife. She provided me constant support throughout this study. She gave me a lot of good idea and opinion. She always sits beside me and accompanies me to carry out this study. Without her, I think I might not be able to complete this study.

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Abstrak

Objektif:

Tujuan kajian ini adalah untuk mengenalpasti peratusan kejadian hypokalsemia sementara di kalangan pesakit yang menjalankan pembedahan kelenjar tiroid di Malaysia dan mengenalpasti sama ada pemberian ubat vitamin D kepada pesakit sebelum pembedahan dapat mengurangkan kejadian hypokalsemia.

Tatacara:

Kajian ini adalah kajian Randomized Control Trial yang melibatkan jumlah 74 orang pesakit dari Hospital Universiti Sains Malaysia dan Hospital Raja Perempuan Zainab II. Kajian ini bermula dari 5 Mei 2008 sehingga 30 April 2010. Kajian ini telah mendapat kelulusan dari Jawatankuasa Etika (Bahagian Manusia), Universiti Sains Malaysia dan Jawatankuasa Etika Institusi Penyelidikan Negara, Kementerian Kesihatan Malaysia. Tujuh puluh empat pesakit yang menjalani pembedahan kelenjar tiroid telah dipilih ke dalam dua kumpulan secara rambang. Pesakit dari kumpulan kajian akan menerima ubat vitamin D (calcitriol) 1.5ug sehari selama dua hari sebelum pembedahan diikuti oleh 1.0ug sehari dan ubat kalsium laktat 1.8g sehari selama 7 hari sementara pesakit dari kumpulan kawalan tidak diberikan ubat vitamin D. Semua pesakit akan dinilai berdasarkan tanda-tanda klinikal dan biokimia.

Keputusan

Tiada perbezaan yang ketara di antara kumpulan kajian dan kumpulan kawalan bagi faktor umur, jantina, penyakit, masa pembedahan, penanaman semula kelenjar paratirod, paras asal kalsium, fosfat dan paras hormon PTH. Kejadian hypokalsemia sementara di kalangan kumpulan kajian adalah 16.7% berbanding dengan kajian kawalan adalah 75%. Dikalangan kes-kes ini, 50% daripada kumpulan kajian dan 64.3% daripada kumpulan kawalan adalah kes simptomatik. Kejadian kes hypoparatiroid kekal adalah 2.7%. Perbezaan yang ketara dikesan dalam kejadian hypokalsemia yang tidak simptomatik dan simptomatik di kalangan kumpulan kajian dan kumpulan kawalan. Perkara yang sama dikesan dalam kejadian perubahan aras kalsium mengikut masa di antara dua kumpulan ini. Tiada perbezaan yang ketara dalam kejadian hypoparatiroid kekal di kalangan dua kumpulan ini. Kumpulan kawalan menjalani tempoh rawatan hospital selepas pembedahan yang lebih panjang iaitu 4.59 hari berbanding dengan kumpulan kajian iaitu 3.92 hari.

Kesimpulan

Pemberian ubat vitamin D mempunyai kesan yang ketara untuk mengurangkan kejadian hypokalsemia sementara dalam kes pembedahan kelenjar tiroid.

Abstract

Objective:

The aim of our open label randomized control study was to determine the incidence of transient hypocalcemia developing post total thyroidectomy in Kelantan (Malaysia) and the benefit of pre-operative treatment using oral vitamin D for post total thyroidectomy.

Methodology:

This is a randomized control study which recruits a total of 74 patients from Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II. The study was carried out over one year duration since 5th May 2009 until 30th April 2010. The ethical approval was obtained from The Research Ethical Committee (Human), Universiti Sains Malaysia and Ethical Board Clinical Research Center (CRC), Ministry of Health. Seventy four patients that underwent total thyroidectomy were randomized into two groups. Study group: 37 patients treated with oral vitamin D (calcitriol) 1.5ug/day for 2 days duration before operation followed by 1.0ug/day plus oral calcium lactate 1800mg/day for 7 days after operation. Control group: 37 patients did not receive oral Vitamin D or calcium lactate. All the patient were assessed clinically and biochemically for hypocalcemia.

Result:

There was no significant difference between the study and control group in terms of demographic distribution of age, sex, diagnosis, surgeon, operating duration, parathyroid gland autotransplant, and baseline level of serum calcium, phosphate and intact PTH. The incidence of post total thyroidectomy transient hypocalcemia in the study group is about 16.7% compared with control group of 75%. Among the cases, 50.0% in the study group and 64.3% in control group are symptomatic. The incidence of permanent hypoparathyroidism is 2.7%. There was significant difference in term of incidence of asymptomatic hypocalcemia and symptomatic hypocalcemia between these two groups since p value is <0.001. There was also significant difference between control and study group with regards to the trend of post-operative serum calcium changes since p value <0.001. However, there was no significant difference in the risk of developing permanent hypoparathyroidism. The post operative stay is significantly longer in control group, 4.59 days compared with study group, 3.92 days (p value : 0.001).

Conclusion:

The administration of oral vitamin D pre-operatively had significantly reduced the incidence of transient hypocalcemia post total thyroidectomy.

CHAPTER 1: INTRODUCTION

Thyroid operation was introduced in year 1800s. During that time, the operation carries high risk and its mortality and morbidity was up to 40%. With the discovery and advancement in the knowledge of physiology and anatomy of thyroid gland, the improving surgical skills, techniques and new technology, the thyroid operation became a very safe operation. The general mortality and morbidity of this operation is now 0.5-1.0% (Sharma, 2007).

The common complications of thyroid operation are bleeding, injury to the superior and recurrent laryngeal nerve, thyroid storm, hypothyroidism, transient hypocalcemia and infection (Burge 1998; Sharma 2007). Sterile techniques and standard operating theater procedure has reduced the rate of infection. The current infection rate is less than 1% (Dionigi, Rovera et al. 2008). Johnson and Wagner (1998) had conducted a retrospective study regarding use of prophylactic antibiotic in thyroid operation. They concluded thyroid operation is a clean operation and antibiotic is unnecessary.

Thyroid gland is a very vascular gland. Previously, it was a very bloody operation. However, current surgical skill has grossly reduced the perioperative bleeding rate. Moreover, multiple trials and studies has been conducted to compare effectiveness of harmonic scarpel, ligasure, bipolar diathermy toward simple suture ligation method in terms of bleeding and surgery time (Cordón, Fajardo et al. 2005). Schoretzanitis et al (1998) has conducted a randomized control study regarding the use of post-op drain in hemithyroidectomy and concluded that there is no difference between post-op with or without drain. There are also ongoing studies for post-op drain in total thyroidectomy.

Surgeon and patients alike are in constant fear of laryngeal nerve injury. A unilateral nerve injury causes hoarseness of the voice while complete bilateral nerve injury cause respiratory obstruction with loss of voice which may necessitates tracheostomy. Current knowledge of thyroid gland has improved the risk of laryngeal nerve injury to 0.2-1.0%. The risk for reoperation is relatively high and estimated about 2-12%. Recently, the use of Electromyography (EMG) to identify the recurrent laryngeal nerve in difficult cases is claimed to reduce the rate of nerve injury as well (Sharma, 2007).

Hypoparathyroidism is another main thyroidectomy complication especially in the case of total thyroidectomy. The inferior parathyroid gland receives blood supply from inferior thyroid artery and superior parathyroid gland may receive blood supply from either superior or inferior thyroid artery. During mobilization of the thyroid gland, surgeon will indirectly injure or disturb the blood supply to the parathyroid gland. The parathyroid glands become ischemic and this will affect its function. If the ischemia is temporary then it only causes temporary hypoparathyroidism otherwise it can result in rarely occurring permanent hypoparathyroidism (Kihara, 2000; Sharma, 2007).

The improvement in surgical technique has reduced the risk of parathyroid injury. Recently, many surgeons practice autotransplantation of parathyroid gland. However, preserving the original parathyroid gland is still the gold standard of thyroid operation. The technique of autotransplantation of parathyroid gland might help to reduce the risk of permanent hypoparathyroidism but it increases the risk of temporary hypoparathyroidism (Lo & Lam, 1998).

The issue we are interested in is transient hypocalcemia. Despite advancement of surgical skill and new technique, rate of transient hypocalcemia did not change much. Currently, the risk of asymptomatic hypocalcemia is about 40-60% and symptomatic hypocalcemia is about 15-25% (Sharma, 2007). This problem causes discomfort to the patient and might even threaten patient's life and prolong hospital stay. There are many studies emphasizing on calcitriol and calcium supplement in post-op care given either during period of hypocalcemia or as a routine management (Tartaglia, Giuliani et al. 2005; Roh and Park, 2006). However, we are interested in the prevention of transient hypocalcemia rather than its treatment because prevention is definitely better than treating the complications. Testal et al had given oral vitamin D pre-operatively and achieve superior result in terms of preventing transient post total thyroidectomy hypocalcemia. However, oral calcium and hydrochlorothiazide were also given together with oral vitamin D in his study which causes side effects such as vomiting and giddiness due to hypercalcemia and hypotension. His hypothesis is not based on using vitamin D to compensate for hypoparathyroidism instead to induce hypercalcemia before surgery (Testa et al,2006).

The pathogenesis of transient hypocalcemia is (1) impairment of blood supplies to parathyroid gland and causes the gland ischemic and affects its function. (2) the release of calcitonin from the parafollicular cell during removal of parathyroid gland. (3) 'hunger bone syndrome' secondary to sudden drop of high thyroid hormone after total thyroidectomy. Long period of hyperthyroidism causes bone hungry for calcium and sudden removal of the stimulus will cause bone aggressively absorb the calcium from the blood. It occurs in the case of pre-operative hyperthyroidism. Among these 3 hypotheses, parathyroid gland ischemia is the main factor for transient hypocalcemia (Sortino, Puccini et al. 1994; Sturniolo, Lo Schiavo et al. 2000; Sharma, 2007)

As we know calcium metabolism is based on 3 main hormones interaction: (1) parathyroid hormone, (2) calcitonin and (3)1,25-dihydrocholecalcitriol (vitamin D). Parathyroid hormone and vitamin D increases the blood calcium level meanwhile calcitonin reduces the blood calcium level. Parathyroid hormone inhibits bone osteoblastic activity and increase osteoclastic activity to release calcium from bone to the blood. It increases the vitamin D production and increase calcium absorption and phosphate secretion in the kidney. Vitamin D increases calcium absorption in the intestine and reduces calcium secretion in the kidney. It maintains the balance of bone metabolism. The calcitonin inhibits the osteoclastic activity in the bone (Linda S. Costanzo, 1998; mazzafferri, 2005; Moreno, 2006; Ganong, 1995).

The question here is can vitamin D compensate for the sudden drop in parathyroid hormone to maintain the calcium level? Parathyroid hormone has a very short half life about 2-3 minutes (Linda S. Costanzo, 1998; Ganong, 1995). Most of the transient hypocalcemia is due to the temporary hypoparathyroidism which mostly recover within 1 week (Sturniolo, Lo Schiavo et al. 2000; Sianesi, Del Rio et al. 2006). Most of the thyroid operation is performed in an euthyroid patient. The issue of hunger bone syndrome may be uncommon. The hypothesis of calcitonin release during operation might be less important as calcitonin has a short half about 1 hour only (Wolfe HJ, 1975; Ganong, 1995).

We have conducted a study in which we have given 0.5ug vitamin D 8 hourly to our patients for 2 days before he or she goes for total thyroidectomy operation followed by one week duration of 1.0ug vitamin D daily and 1800mg per day calcium lactate. Vitamin D has a half life of 8 hour and it takes about 5 half lives to achieve a stable vitamin D level (Kartzung, 1995; Boger and Perrier, 2004; Glorieux, 2004). Our intention was to evaluate the effect of

vitamin D to compensate for the temporarily low parathyroid hormone by looking into the result of laboratory hypocalcemia and symptomatic hypocalcemia. A positive result from the study can then be incorporated into our clinical practice in total thyroidectomy management.

1.1 LITERATURE REVIEW OF POST TOTAL THYROIDECTOMY TRANSIENT HYPOCALCEMIA

Thyroid operation has progressed tremendously since the past few decades. Currently, it is a safe operation and some centres have been performing this operation as a day care surgery with the general morbidity and mortality of 0.5-1.0%. However, the burdensome incidences of hypocalcemia is still taxing the surgeon despite many studies being conducted to look into this problem (Sharma, 2007).

The incidence of transient hypocalcemia post total thyroidectomy case is 42% for asymptomatic hypocalcemia and 14 % for symptomatic hypocalcemia (Gac, Cabane et al. 2007). The independent risk factors for transient hypocalcemia are female gender, elevated free thyroxine, total thyroidectomy and autotransplant parathyroid gland (Abboud, 2002). Grave's disease and thyroid cancer has relatively higher risk of post-op hypocalcemia (Tonioto, 2008). The incidence of transient hypocalcemia in autotransplanted parathyroid gland is higher (21.4%) compared to control group (8.1%) but the permanent hypocalcemia is lower in autotransplant group(0%) compared to control group (26%) (Lo and Lam, 1998).

Bellantone et al in 2002 had conducted a study to compare the incidence of transient hypocalcemia post total thyroidectomy among (1) control group (2) patient given oral calcium 3g per day after surgery and (3) patient given oral calcium 3g per day and vitamin D 1ug per day after surgery. The findings shows group (3) had superior result with less incidence of hypocalcemia compared to group (1) and (2). No significant difference was noted between group (1) and group (2). Post operatively routine oral calcium did not reduce the incidence of hypocalcemia. (Rocco Bellantone, 2002).

A study was conducted by Roh and Park et al (2006) to compare routine administration of oral calcium 3g/d and calcitriol 1ug/d with control group prescribed with placebo in total thyroidectomy patient. The study group had lower laboratory hypocalcemia 13% versus 36% and lower symptomatic hypocalcemia 7% versus 24% (Roh and Park, 2006).

F.Tartaglia et al (2005) had done a comparison between (1) patient given oral calcium 1.5g/day only, (2) patient given oral calcium 1.5g/d + oral vitamin D 1ug/day and (3) patient given oral calcium 1.5g/d + oral vitamin D 2ug/d. The result shows incidence of severe hypocalcemia (tetany) in group (1) 7.4% , group (2) 2.9% and group (3) 0%. He concluded that Vitamin D 2ug/day in his study had significantly reduced the risk of severe hypocalcemia. Risk of tetany is high if the serum calcium level is less than 7.5mg/dl. He noticed there was no difference of PTH recovery in these 3 groups after cessation of medication (Tartaglia, Giuliani et al. 2005). He also concluded that oral calcitriol did not reduce the incidence of severe hypocalcemia at post-operative Day 1 but it had significant effect at post-operative Day 2.

Sturniolo et al found that post total thyroidectomy hypocalcemia is a transient event with nadir of serum calcium level attained 24 hours after surgery and returned to normal level within seven days. A reduction in post-operative Day 1 PTH more than 75% show significant high risk of hypocalcemia with positive predictive value of 100% (Sturniolo, Lo Schiavo et al. 2000).

Oral calcitriol with oral calcium is the most recommended treatment to prevent post total thyroidectomy transient hypocalcemia after surgery (Rocco Bellantone 2002; Tartaglia, Giuliani et al. 2005; Roh and Park 2006). Recently, a study conducted in Italy by Testa et al

shows that pre-operative treatment with oral calcitriol had the additional benefit in reducing the incidence of transient hypocalcemia post total thyroidectomy. In this randomized control study, a group of patients prescribed with 1.5ug/day calcitriol plus hydrochlorothiazide for 1 week before total thyroidectomy was compared with a group of patient given placebo. He noticed 1 out of 22 study patient (4.6%) developed asymptomatic hypocalcemia compared with 10 out of 20 patients (50%) in placebo group. None of the study patient (0%) developed symptomatic hypocalcemia compared to 20% of the placebo group (Testa, Fant et al. 2006).

Here, we conducted a study which is similar to the study done by Testa et al but we omitted using hydrochlorothiazide in view that this medication has the effect of lowering the blood pressure and sodium in the blood. No doubt this medication can reduce the incidence of hypercalciuria but it is more recommended for patients on long term treatment of oral calcitriol and calcium especially in the case of chronic renal failure. Hydrochlorothiazide can also cause hypercalcemia (Katzung, 1995).

In our study, we had prescribed pre-operative treatment of oral calcitriol 0.5ug 8 hourly for 2 days followed by another one week duration of oral calcitriol 1.0ug per day and oral calcium lactate 1.8g per day after the surgery. Our hypothesis is based on concept of utilizing vitamin D to compensate for the transient low PTH and most of the parathyroid gland function should recover in one week time. This study was conducted to assess the benefit of giving oral vitamin D to patient before he or she goes for total thyroidectomy. We believe pre-operative treatment of oral vitamin D can give extra benefit compared to routine administration of vitamin D and calcium after surgery. Erbil et al had shown that low pre-operative vitamin D will increase risk up to 28 folds to develop hypocalcemia. Tartaglia et al claimed vitamin D did not reduce the risk of hypocalcemia on post operative day one due to its delayed effect.

However, Vitamin D significantly reduces the risk of hypocalcemia at post operative day two and day three. The medication, Rocalcetriol was chosen because it is an active form of vitamin D (1, 25-dihydroxyvitamin D). This medication does not require to be activated either in the liver or kidney (ROCHE 2004). Thus, parathyroid hormone would not affect the vitamin D level because intact parathyroid hormone plays a major role in activation of vitamin D in the kidney. Our intention was to utilize oral vitamin D to compensate for the transient hypoparathyroidism post total thyroidectomy. This medication was given for 2 days prior to surgery. The half lives of vitamin D was about 6- 8 hours (ROCHE, 2004). According to the principle of pharmacodynamic, five half lives are needed to achieve a plateau drug level (Kartzung, 1995). Oral rocalcetriol given with frequency three times a day for two days is considered adequate to achieve a plateau drug level. The dosage of 1.5 ug oral rocalcetriol was chosen because this dosage is within the safe limit. The normal dosage for treating hypocalcemia in hypoparathyroidism patient ranges from 0.5- 2.0ug (Calcitriol, 2010).

Furthermore, most of the studies which used Vitamin D had demonstrated that it was safe to use vitamin D within the range of 1.0ug to 2.0ug. Testa et al used vitamin D 1.5 ug/day while Roh and Park et al and Bellantone et al used oral vitamin D 1.0ug /day. F. Targalia et al employed vitamin D 2.0ug/day and he claimed the effect of vitamin D 2.0ug/day is superior to the dosage of vitamin D 1.0ug/day. The medication is served three times per day based on its half lives of 6-8 hours. Dosage of 0.5 ug per dose is the dosage deemed as suitable for this study.

Sinensi et al (2006) claimed most of the post total thyroidectomy patients achieves normocalcemia within one week (Sinensi et al, 2006). Sturniolo et al (2000) claimed low

calcium level in post total thyroidectomy patient lasted about 3 days and went back to normal level within 5 days (Sturniolo et al, 2000). All these studies indicate that transient hypoparathyroidism can recover in one week duration. Tartaglia et al (2005) claimed there is no difference of parathyroid recovery if patient is treated with vitamin D, oral calcium or placebo (Tartaglia et al ,2005). Loh and Park et al (2006) claimed administration of vitamin D does decrease the function of parathyroid hormone but did not prevent its recovery. In this study, oral vitamin D of one week duration with oral calcium supplement was utilised to compensate for the hypoparathyroidism while waiting for the parathyroid gland recovery (Loh and Park et al , 2006).

Oral calcium lactate was chosen because it was more easily absorbed by the body. It can be absorbed at various pH and does not need to be taken with food to facilitate absorption. Furthermore, it causes less gastric upset (Straub, 2007). However, the elemental calcium content in calcium lactate which constitute about 13% of its content is actually lower compared to other forms of calcium salts (Kartzung, 1995). In this dosage, it was given basically as supplement rather than treatment dose. A 600mg calcium tablet is given three times a day to meet the daily dosage of 1800mg and the total elemental calcium per day of 234mg. The daily requirement of calcium in adult is about 1000mg (Health, 1994). Hence, prevention of hypocalcemia mainly depends on vitamin D rather than on calcium lactate. Bellantone et al (2002) also claimed there was no significant difference in terms of hypocalcemia between post total thyroidectomy patient treated with either oral calcium 3g/day or placebo (Bellantone et al, 2002).

Serial serum calcium measurement was taken at 6 hours, 24 hours and 48 hours in this study. We believe most of the incidence of hypocalcemia will occur within 24 hour post operation.

Sturniolo et al (2000) found that post total thyroidectomy hypocalcemia is a transient event with nadir of serum calcium level being achieved 24 hours after surgery (Sturniolo et al, 2000). De Pasquale et al (2000) claimed 85% of hypocalcemia incidence occurs on post operative day one (De Pasquale et al ,2000). Nahas et al (2006) noted similar result (Nahas et al, 2006). He found that if the serum calcium level is more than 2.00mmol/L at post operative 12 hours, it is unlikely for the patient to develop significant hypocalcemia. Considering previous findings by other researchers, we believe it is safe to discharge the patients if they had been normocalcemic at post operative 48 hours.

The measurement of serum phosphate together with serum calcium is an extra objective in this study. As was widely known, serum phosphate level is highly correlated with serum iPTH and Vitamin D. Intact PTH function is to decrease serum phosphate meanwhile vitamin D is to increase serum phosphate. We were also interested to know the trend of serum phosphate after thyroidectomy. No study that was done before had actually looked into this aspect.

In this study, we had intact parathyroid hormone (iPTH) level measured after 24 hours post operatively. We believe it is easier to handle, cost effective and more accurate to predict hypocalcemia. Kara et al (2009) claimed a single measurement of iPTH taken any time from post operation 10 min will be able to predict post thyroidectomy hypocalcemia. Toniato et al (2008) claimed iPTH measurement at post operative day one is less expensive than intra-operative quick iPTH (Toniato et al, 2008). In our setting, iPTH quick test is more costly compared to conventional iPTH test. Conventional iPTH measurement is also more reliable. Assessment of serum calcium, phosphate and intact PTH at post operative day fourteen were also undertaken to evaluate the recovery of parathyroid hormone. Participants both from the

control group and study group were compared to assess the effect of vitamin D toward the recovery process of parathyroid hormone.

Vitamin D and oral calcium are safe medication which had been used for the treatment of hypocalcemia in the case of renal impairment, vitamin D deficiency and hypoparathyroidism (Roche 2004). Most of the recommended dose range from 0.5-2.0ug/d vitamin D. The daily requirement of calcium in normal adult is 800mg -1200mg (Drug.com-calcitriol). A high dose of vitamin D 38ug/d with Paclitaxel in treatment of cancer did not show dose limiting toxicity (2002) Clinical pharmacotherapy). The maximum dosage of calcium lactate that can be given is 9 g per day (Food and Nutrition Board,Washington 1997). Thus, oral calcitriol 1.5 ug/day and oral calcium lactate 1500mg/day are within a very safe dosage, furthermore it is given for a period of less than 10 days (short duration).

Oral calcium supplement is well known to have multiple benefits to our health. It is not only used for the treatment of osteoporosis but it is believed to have an effect in lowering the risk of hypertension, reducing cholesterol level and the risk of colorectal cancer (Allender PS, 1996; Slattery M, 1999). However, intravenous calcium might be able to increase the risk of cardiac arrhythmias in patient taking digoxin and antagonise the effect of calcium channel blocker (Bar-Or D 1981). Hence, these groups of patients were excluded from our study.

1.2 ANATOMY OF THYROID GLAND AND PARATHYROID GLAND

1.2.1 Thyroid gland

1.2.1.1 Embryology

The thyroid medial precursor is derived from the ventral diverticulum of the endoderm from the first and second pharyngeal pouches at the foramen cecum (Hayes B 1985; Sessions 1999). The diverticulum descends from the base of the tongue to its adult pretracheal position through a midline anterior path with the primitive heart and great vessels during weeks 4 to 7 of gestation. The proximal portion of this structure retracts and degenerates into a solid, fibrous stalk; persistence of this tract can lead to the development of a thyroglossal duct cyst with variable amounts of associated thyroid tissue. The lateral thyroid primordia arise from the fourth and fifth pharyngeal pouches and descend to join the central component. Parafollicular C cells arise from the neural crest of the fourth pharyngeal pouch as ultimobranchial bodies and infiltrate the upper portion of the thyroid lobes (Copp DH, 1967). Because of the predictable fusion of the ultimobranchial bodies to the medial thyroid anlage, C cells are restricted to a zone deep within the middle to upper third of the lateral lobes (Wolfe HJ, 1975).

1.2.1.2 Anatomy

The thyroid gland is composed of two lateral lobes connected by a central isthmus, weighing 15 to 25g in adults. A thyroid lobe usually measures about 4 cm in height, 1.5 cm in width, and 2 cm in depth. The superior pole lies posterior to the sternothyroid muscle and lateral to the inferior constrictor muscle and the posterior thyroid lamina. The inferior pole can extend to the level of the sixth tracheal ring. Approximately 40% of patients have a pyramidal lobe

that arises from either lobes or the midline isthmus and extends superiorly (Hollingshead 1958).

The thyroid is enclosed between layers of the deep cervical fascia in the anterior neck. The true thyroid capsule is tightly adherent to the thyroid gland, and continues into the parenchyma to form fibrous septa separating the parenchyma into lobules. The surgical capsule is a thin, film like layer of tissue lying on the true thyroid capsule. Posteriorly, the middle layer of the deep cervical fascia condenses to form the posterior suspensory ligament, or Berry's ligament, connecting the lobes of the thyroid to the cricoid cartilage and the first two tracheal rings (Hollingshead W, 1958).

Blood supply to and venous drainage of the thyroid gland involves two pairs of arteries, three pairs of veins, and a dense system of connecting vessels within the thyroid capsule. The inferior thyroid artery arises as a branch of the thyrocervical trunk. This vessel extends along the anterior scalene muscle, crossing beneath the long axis of the common carotid artery to enter the inferior portion of the thyroid lobe. Although variable in its relationship, the inferior thyroid artery lies anterior to the recurrent laryngeal nerve (RLN) in approximately 70% of patients. The inferior thyroid artery is also the primary blood supply for the parathyroid glands (Hollingshead W, 1958).

The superior thyroid artery is a branch of the external carotid artery and courses along the inferior constrictor muscle with the superior thyroid vein to supply the superior pole of the thyroid. This vessel lies posterolateral to the external branch of the superior laryngeal nerve (SLN) as the nerve courses through the fascia overlying the cricothyroid muscle. Care should be taken to ligate this vessel without damaging the SLN. Occasionally, arteria thyroidea ima may arise from the innominate artery, carotid artery, or aortic arch, and supply the thyroid gland near the midline. Many veins within the thyroid capsule drain into the superior,

middle, and inferior thyroid veins, leading to the internal jugular or innominate veins. The middle thyroid vein travels without an arterial complement, and division of this vessel permits adequate rotation of the thyroid lobe to identify the recurrent laryngeal nerve (RLN) and parathyroid glands (Sinnatamby, 2006).

The Recurrent Laryngeal Nerve provides motor supply to the larynx and some sensory function to the upper trachea and subglottic area. Careful management of thyroid carcinomas requires a thorough knowledge of the course of the RLN. During development, the RLN is dragged caudally by the lowest persisting aortic arches. On the right side, the nerve recurs around the fourth arch (subclavian artery), and on the left side, the nerve recurs around the sixth arch (ligamentum arteriosum) (Hollingshead, 1958; Sinnatamby, 2006)

The right Recurrent Laryngeal Nerve leaves the vagus nerve at the base of the neck, loops around the right subclavian artery, and returns deep to the innominate artery back into the thyroid bed approximately 2 cm lateral to the trachea. The nerve enters the larynx between the arch of the cricoid cartilage and the inferior cornu of the thyroid cartilage. The left RLN leaves the vagus at the level of the aortic arch, and loops around the arch lateral to the obliterated ductus arteriosus. The nerve returns to the neck posterior to the carotid sheath and travels near the tracheoesophageal groove along a more medial course than the right RLN. The nerve crosses deep to the inferior thyroid artery approximately 70% of the time and often branches above the level of the inferior thyroid artery before entry into the larynx (Rosai, 1992).

The RLN travels underneath the inferior fibers of the inferior constrictor (i.e., the cricopharyngeus muscle) and behind the cricothyroid articulation to enter the larynx. A

“nonrecurrent” laryngeal nerve may rarely occur on the right side and enters from a more lateral course. Occasionally, an aberrant retroesophageal subclavian artery (arteria lusoria) or other congenital malformation of the vascular rings is present (Henry JF, 1988).

The Superior Laryngeal Nerve arises beneath the nodose ganglion of the upper vagus and descends medial to the carotid sheath, dividing into an internal and external branch about 2 cm above the superior pole of the thyroid. The internal branch travels medially and enters through the posterior thyrohyoid membrane to supply sensation to the supraglottis. The external branch extends medially along the inferior constrictor muscle to enter and supply the cricothyroid muscle. Along its course, the nerve travels with the superior thyroid artery and vein. The nerve typically diverges from the superior thyroid vascular pedicle about 1 cm from the thyroid superior pole (Lennquist S, 1987).

1.2.2 Parathyroid gland

1.2.2.1 Embryology

The superior parathyroid gland arises from the fourth pharyngeal pouch. The inferior parathyroid gland developed from the third pouch but displaced caudally by the descent of the thymus from the same pouch (Sinnatamby, 2006).

1.2.2.2 Anatomy

The parathyroid glands are normally located behind the thyroid gland lobes. There are usually four glands in ninety percents of subjects, two glands on each side with each weighing about 5g. The superior parathyroid gland is the most constant in position. It is usually within the thyroids pretracheal fascial capsule at the middle of the back of the thyroid lobe at the same level with the first tracheal ring and above the inferior thyroid artery. The inferior parathyroid gland is less constant in position. It is usually within the pretracheal fascial sheath behind the lower pole but it may be found inside the thyroid gland itself or outside the fascial sheath in variable position in the neck or in the superior or posterior mediastinum. They are brownish yellow in appearance. They are also easily subject to subcapsular haematoma formation on handling. Both glands is usually supplied by the inferior thyroid artery (Sinnatamby, 2006).

1.2.2.3 Histology

These glands consist of chief or principal cells which secrete the parathyroid hormone. It resembles lymphoid tissue but it can be differentiated from the former by the number of blood capillaries and oxyphil cells scattered among the chief cells (Sinnatamby, 2006).

1.3 Thyroid surgery and complication

1.3.1 Thyroid surgery procedure

The procedure is performed with patient lying in supine position. A shoulder roll is used to hyperextend the neck. The neck is cleaned and draped. The neck is infiltrated with 20–30 ml of 1:100,000 epinephrine. A skin crease collar incision is made about 2–3 cm or two finger-breadths above the sternal notch. The incision is made with a number 10 blade with one sweep through the skin, subcutaneous tissue, platysma, and down to the avascular deep investing layer of fascia. Precaution are taken to avoid damage to the anterior jugular veins. Subplatysmal flaps are raised superiorly to the upper border of the thyroid cartilage and inferiorly to the sternal notch. The flaps are retracted using a self-retaining retractor. The sternohyoid muscle is separated along its median raphe and the plane underneath is disclosed using blunt dissection. If the thyroid is large, the straps muscle in the upper third is divided to avoid damage to the ansa cervicalis. The thyroid gland is usually mobilized by initially dissecting the upper pole. The middle thyroid vein may have to be ligated to gain entry into the paracarotid tunnel. Superior thyroid vessel is ligated close to the gland to avoid injuring the external branch of the superior laryngeal nerve. Further dissection on the lateral and inferior parts of the thyroid gland is made to deliver the thyroid through the incision wound.

With the surgeon standing on the same side as the lobe being removed, the assistant rolls the gland medially with a swab to expose the tracheo-oesophageal groove and thyroid bed (Hobbs, 2007). The recurrent laryngeal nerve is always found in the Beahrs triangle. Surgeon has to be aware of non-recurrent nerve if recurrent laryngeal nerve is failed to be identified (Watkinson, 2007). The parathyroid glands are caramel-coloured and are often variable in size and position. The superior parathyroid can be found medial to the upper pole in Joll's

triangle. The inferior parathyroid gland is more inconsistent in its position and mostly found on the lower part of thyroid gland below the inferior thyroid artery. Once parathyroid glands have been identified, the inferior thyroid artery is ligated distal to the branches that supply the inferior parathyroid (G. Akerstrom, 1984). The gland is fully mobilized by cutting through Berry's ligament down onto the trachea. The pyramidal lobe and isthmus were dissected off the trachea. A similar procedure is performed at the contralateral lobe.

After completely removing the thyroid, hemostasis should be secured before closing the skin (Hobbs, 2007). The commonest site for bleeding is in the 'triangle of concern', consist of the trachea medially and the nerve laterally with the thyrothymic ligament and loose fat above the sternum at the base and Berry's ligament at the apex. There are many small branches of the inferior thyroid artery within this triangle. After bleeding is secured, a drain is inserted. Its function is to reduce the seroma but not to substitute the hemostasis (C. Debry). The fascia overlying the strap muscles is closed in the midline using a 3-0 interrupted absorbable suture. The platysma and subcutaneous layer is reapproximated using the same suture after the shoulder roll is removed. Skin can be closed using either glue, stapler or non-absorbable suture (Hobbs, 2007).

1.3.2 Complication of thyroid surgery

In the 1800s when thyroid surgery was first introduced, the mortality rate from thyroid surgery was approximately 40%. With the refinement of thyroid surgery, sterile surgical arenas and general anesthesia, the complication of thyroid surgery was greatly reduced (Sharma, 2007).

In general, complications of thyroid surgery can be divided into minor, rare, or major. The minor complications are post operative seroma and poor scar formation. A small seroma will be reabsorbed naturally but large seroma might need aspiration under sterile method. A small skin incision at the skin crease and avoidance of excessive skin traction can minimise scar formation (Sharma, 2007).

The major complications are bleeding, infection, injury to recurrent laryngeal nerve, injury to superior laryngeal nerve, hypoparathyroidism, hypothyroidism and thyroid storm. The incidence of post surgery bleeding is about 0.3-1.0% which can turn disastrous. A minor bleeding may cause hematoma while major bleeding can result in impending respiratory failure due to upper air obstruction. The immediate management is to re-open the incision site and drain out the hematoma at the bedside (Sharma 2007; Burge 1998). The risk of infection is estimated at about 1-2%. The use of prophylactic antibiotic is unnecessary as thyroidectomy is generally considered as a clean surgery (Dionigi, Rovera et al. 2008).

The most worrying complication feared by surgeons is injury to recurrent laryngeal nerve and superior laryngeal nerve. An in depth knowledge of the anatomical variation of the nerves and meticulous surgical technique is imperative to reduce the risk of injury to these nerves (Chiang, Lee et al. 2004). The left recurrent laryngeal nerve branches from the vagus at the

level of the aortic arch. It then passes below the arch and reverses its course to continue superiorly, posterior to the aortic arch and into the visceral compartment of the neck. It travels near or in the tracheoesophageal groove until it enters the larynx just behind the cricothyroid articulation. The right recurrent laryngeal nerve branches from the vagus more superiorly than does the left, at the level of the subclavian artery. It loops behind the right subclavian artery and ascends superomedially toward the tracheoesophageal groove. It then continues superiorly until entering the larynx behind the cricothyroid articulation. The non-recurrent laryngeal nerve is present in 0.5% of population with the right side being more common than the left side. The nonrecurrent laryngeal nerve branches from the vagus at approximately the level of the cricoid cartilage and directly enters the larynx without looping around the subclavian artery. A left-sided nonrecurrent laryngeal nerve Right Laryngeal Nerve can occur only when a right-sided aortic arch and ligamentum arteriosum are concurrent with a left retroesophageal subclavian artery.

The land mark to identify the recurrent laryngeal nerve is at the inferior thyroid artery. If the surgeon fails to identify the nerve then he must take precaution at the Berry ligament area about 0.5cm below the inferior thyroid corn of thyroid cartilage as it is the entry point to the larynx. The recurrent laryngeal nerve is always found at the tubercle of Zuckerkandl (Hollingshead 1958; Hayes B 1985; Henry JF 1988; Paul G. Gauger and Reeve 2001; Ferwins 2003). Monitoring the Recurrent Laryngeal Nerve during thyroid surgery using electrophysiology device is not done routinely in thyroidectomy yet because there is no randomized study to compare the rate of postoperative Recurrent Laryngeal Nerve palsy in visual versus electrophysiologic Recurrent Laryngeal Nerve detection in thyroid surgery (Ferwins, 2003; Sharma, 2007).

There are two options of surgical treatment for laryngeal nerve injury either medialization or reinnervation. In medialization, a window in the thyroid cartilage is created at the level of the true vocal fold. An implant is then placed to push the vocal fold medially. Medialization also can be done with an injection of absorbable teflon sponge (Ferwins 2003; Sharma 2007). A number of reinnervation procedures have been described for addressing the permanently injured Recurrent Laryngeal Nerve. These procedures maintain or restore the intrinsic laryngeal musculature tone. Primary neurotomy may be used to immediately repair the transected Recurrent Laryngeal Nerve. Reinnervation procedures have been described by using the phrenic nerve, ansa cervicalis, and preganglionic sympathetic neurons. Improvement in phonation after reinnervation with the ansa cervicalis was found, but no movement is observed. Transfer of neuromuscular pedicles technique have been recently described and reportedly restore movement of the vocal fold (Ferwins, 2003; Sharma, 2007).

Another complication was post thyroidectomy hypoparathyroidism. The rate of transient hypoparathyroidism reported as 2-53% and permanent hypoparathyroidism was 0.4-13.8%. The cause of transient hypocalcemia after surgery is not clearly understood (Kihara 2000; Sharma 2007). It might be due to reversible parathyroid gland ischemia, parathyroid gland hypothermia, calcitonin release or hungry bone syndrome. Hungry-bone syndrome occurs in patients with preoperative hyperthyroidism. These patients have increased bone breakdown in their hyperthyroid state. When a patient's thyroid hormone level drops acutely after surgery, his or her stimulus to break down bone is removed. The bones, now "hungry" for calcium, remove calcium from the plasma and decreasing serum calcium level (Sortino, Puccini et al. 1994; Sturniolo, Lo Schiavo et al. 2000; Sharma 2007).

It is very dangerous to perform thyroidectomy in the hyperthyroid patient. The patient is not only at high risk for hypoparathyroidism but can also result in thyroid storm. Signs of thyrotoxic storm in the anesthetized patient include evidence of increased sympathetic output, such as tachycardia and hyperthermia. Other symptoms and signs in the fully awake patient include nausea, tremor, altered mental status or cardiac arrhythmias. Urgent medical treatment is needed. Intravenous beta-blockers, PTU, sodium iodine, and steroids are administered to control sympathetic activity, the release of thyroid hormone, and hyperthermia. Use cooling blankets and cooled intravenous fluids to reduce the patient's body temperature and monitor the oxygenation because oxygen demands increases during a thyroid storm (Ferwins 2003; Sharma 2007).

Superior laryngeal nerve injury should not be neglected. The rate of injury to this nerve is quite high in thyroidectomy with estimate about 3-25%. The effect of superior laryngeal nerve injury is inability to produce high pitch sound. Caution should be made to prevent this nerve injury by learning its anatomy. This nerve travels across the superior thyroid artery more than 1 cm above the upper pole of the thyroid gland (42%), less than 1 cm above the upper pole (30%), or under the upper pole (14%). Ligation of the terminal branches of the superior thyroid artery is made as close to the thyroid capsule as possible to avoid damaging the nerve. The treatment for superior laryngeal nerve is speech therapy (Paul G. Gauger and Reeve 2001, Ferwins 2003).

Lastly, all patients who have undergone thyroidectomy required lifelong thyroid hormone replacement. Thyroid function test also need to be monitored every 4-6 weeks until appropriate dosage are achieved (Sharma, 2007.)

1.4 Calcium and calcium metabolism

1.4.1 Calcium

Calcium has two important physiologic functions. The first function is to provide the structural foundation on which bones are built to protect internal organs, weight bearing function, and as levers for the muscles to act during movement. Second, soluble calcium ions in the extracellular fluid (ECF) and cytosol are important for an innumerable biochemical reactions, signaling cascades, and electrical systems that are necessary for life.

An adult human contains about 1000 g of calcium, the majority (99%) of which is found in bone. Approximately 1% of total body calcium is contained within the ECF and soft tissues. Therefore, the skeletal bone is utilized as a source of calcium when the ECF concentration falls and at the same time act as a storehouse for excess calcium. The ionized fraction is generally estimated to be approximately 50% of the total circulating calcium, with the remainder of the total serum calcium (40%) bound to serum proteins, primarily albumin. Another 10% of the total serum calcium are complexed with anions, such as citrate or sulfate. The ionized fraction of total serum calcium is physiologically important (biologically active) and is regulated tightly. Although it is possible to measure ionized calcium routinely in large clinical laboratories, proper handling of the specimen is imperative for it to be obtained anaerobically and analyzed promptly. Therefore, total serum calcium is often used as an indirect assessment of the ionized calcium fraction (Wysolmerski, 2007).

Plasma protein concentration, plasma anion concentration and acid-base abnormalities may play an important role in influencing the proportion of ionic calcium and non-ionic calcium. An increase in the plasma protein will increase the total calcium concentration while decreases are associated with decrease in total calcium concentration. However, the changes in plasma protein concentration usually develop slowly over time and do not cause a parallel