STUDY ON COMPLICATIONS AND THEIR ASSOCIATED FACTORS OF TOTAL THYROIDECTOMY FOR MANAGEMENT OF BENIGN THYROID DISEASE IN KELANTAN.

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LIST OF ABBREVIATIONS

HUSM	Hospital Universiti Sains Malaysia
HKB	Hospital Kota Bharu
MNG	Multinodular goiter
RLN	Recurrent laryngeal nerve
HypoPTH	Hypoparathyroidism
TSH	Thyroid stimulating hormone
TFT	Thyroid function test
FNAC	Fine needle aspiration cytology
FNNAB	Fine needle non-aspiration biopsy
USFNA	Ultrasound-guided FNA
PTU	Propylthiouracil
SLN	Superior laryngeal nerve
HPE	Histopathological examination
KKM	Kementerian Kesihatan Malaysia
ENT	Ear, nose and throat

ABSTRAK

STUDY ON COMPLICATIONS AND THEIR ASSOCIATED FACTORS OF TOTAL THYROIDECTOMY FOR MANAGEMENT OF BENIGN THYROID DISEASE.

Latarbelakang: Tiroidektomi total ialah operasi yang kebiasaannya dilakukan sebagai sebahagian rawatan untuk tumor tiroid. Namun, kebelakangan ini penggunaannya telah meningkat untuk rawatan goiter multinodular lebih-lebih lagi dalam rawatan goiter multinodular menyeluruh dimana kesemua kelenjar tiroid terlibat, kerana dengan menjalani tiroidektomi total, keseluruhan penyakit dapat dibuang secukupnya, mengelakkan pembedahan semula untuk penyakit yang berulang, yang boleh membawa risiko komplikasi yang lebih besar. Penjagaan terhadap saraf laring berulang dan kelenjar-kelenjar paratiroid masih menjadi aspek penting semasa operasi ini.

Objektif kajian: Untuk mengkaji tahap keselamatan tiroidektomi total untuk rawatan penyakit tiroid benign yang dilakukan di Hospital Universiti Sains Malaysia (HUSM) dan Hospital Kota Bharu (HKB) disamping mengkaji prevalens malignan tersembunyi dalam penyakit tiroid benign.

Jenis kajian: Analisis retrospektif dengan menggunakan rekod pesakit-pesakit yang menghidapi penyakit tiroid benign yang menjalani operasi tiroidektomi total di HUSM dan HKB dari 1 Januari 2000 hingga 31 Disember 2005 (jangkamasa 6 than)

Keputusan: Seramai 156 pesakit telah dimasukkan ke dalam kajian ini, meliputi 143 (91.7%) perempuan dan 13 (8.3%) lelaki dengan umur mean pada 42.36 ± 13.58 tahun. Majoriti adalah melayu (87.2%). 98(62.8%) dari pesakit menghidapi goiter multinodular, 38 (24.4%) adalah goiter menyeluruh dan 20 (12.8%) adalah benjolan solitari. Sitologi secara sedutan jarum halus menunjukkan 67(42.9%) adalah goiter multinodular, 66 (42.3%) adalah goiter koloid. 88.5% (138) daripada pesakit tergolong dalam kumpulan eutiroid, 10.9% (17) pula mengalami tirotoksikosis sementara itu 0.6%(1) mengalami hipotiroidisme. Tiada mortaliti dalam kajian ini. Pendarahan selepas operasi berlaku dalam 5.1% (8) kes sementara itu, infeksi luka pembedahan berlaku dalam 1.9% (3) kes. Kecederaan sementara pada saraf laring berulang ialah 17.8% (27) sementara untuk kecederaan saraf laring berulang kekal sebanyak 6.6% (10). 24.7% (38) pesakit mengalami hipokalsemia sementara dan 17.5% (27) mengalami hipokalsemia kekal. Didapati kelelahan (nilai p = 0.022) dan kekasaran suara sebelum tiroidektomi (nilai p = 0.038) merupakan faktor berkaitan signifikan untuk kecederaan saraf laring berulang, sementara itu diagnosa pre-operasi sebagai goiter multinodular (nilai p = 0.006) menjadi faktor berkaitan yang signifikan bagi hipokalsemia selepas tiroidektomi. Prevalens untuk kejadian malignan nyata hasil kajian histopatologi ialah 8.3% (13) sementara untuk malignan tersembunyi ialah 7.1% (11).

Kesimpulan kajian: Kadar kecederaan saraf laring berulang dan hipokalsemia yang tinggi adalah disebabkan operasi tiroidektomi total telah dijalankan di hospital-hospital yang tidak mempunyai pakar-pakar bedah endokrin, tetapi dilakukan oleh pakar bedah am dan juga pelatih-pelatih kepakaran surgeri dibawah pengawasan pakar bedah.

ABSRACT

STUDY ON COMPLICATIONS AND THEIR ASSOCIATED FACTORS OF TOTAL THYROIDECTOMY FOR MANAGEMENT OF BENIGN THYROID DISEASE.

Background: Total thyroidectomy is an operation that has generally been reserved for the management of differentiated thyroid carcinoma. But lately, it become increasingly used for multinodular goiter especially in diffuse multinodular goiter where the entire gland is involved, because it will remove the disease adequately; prevent patients from undergoing re-operation for recurrent disease with associated higher risk of complications. Protection of recurrent laryngeal nerve and parathyroid glands is still being the important aspect in dealing with benign thyroid disease.

Objectives: To study on safety of total thyroidectomy as a management of benign thyroid disease done at Hospital Universiti Sains Malaysia (HUSM) and Hospital Kota Bharu (HKB) and the prevalence of occult malignancy in benign thyroid disease.

Methodology: A retrospective study using previous record of patients with benign thyroid disease who underwent total thyroidectomy, admitted to Hospital Universiti Sains Malaysia (HUSM) and Hospital Kota Bharu (HKB) from 1st January 2000 until 31st December 2005 (6 years duration).

Results: 156 patients involved in this study with 143 (91.7%) female and 13 (8.3%) male with mean age 42.36 ± 13.58 years. Majority 136 (87.2%) were Malays. 98 (62.8%) had multinodular goiter, 38 (24.4%) and 20 (12.8%) had diffuse and solitary goiter respectively. FNAC showed 67 (42.9%) and 66 (42.3%) had multinodular goiter and colloid goiter respectively. 138 (88.5%) were euthyroid whereas 17 (10.9%) had thyrotoxicosis and 1 (0.6%) had hypothyroidism. No mortality was reported in my study. Postoperative bleeding occurred in 8 (5.1%) whereas 3 (1.9%) had postoperative surgical site infection. 27 (17.8%) and 10 (6.6%) of patients had transient and permanent recurrent laryngeal nerve palsy respectively whilst 38 (24.7%) had transient hypocalcaemia and 27 (17.5%) had permanent hypocalcaemia. Shortness of breath (p value = 0.022) and preoperative hoarseness of voice (p value = 0.038) were significantly associated factors for RLN injury whereas preoperative diagnosis of multinodular goiter (p value = 0.006) was significantly associated factor for post-operative hypocalcaemia. The prevalence of frank malignancy from HPE report was 13 (8.3%) whereas that of occult malignancy was 11 (7.1%).

Conclusion: Higher rates of recurrent laryngeal nerve palsy and hypocalcaemia contributed by the facts that the total thyroidectomies were done at non-specialized hospital by general surgeons or surgical trainees with supervision.

1. INTRODUCTION

Benign thyroid disease is the most common endocrine disorder which requires surgical intervention. The World Health Organization (WHO) reported that 5% of world's population is suffering from goiter and majority of them (75%), are those living in iodine deficient areas.(Colak et al., 2004)

Surgical resection, including bilateral subtotal thyroidectomy, near total thyroidectomy and total thyroidectomy has been an option for surgical treatment benign thyroid disease for decades. Currently, the indications for surgery are suspected malignancy, compression-induced symptoms, hyperthyroidism and cosmetic reason. However, the debate about the optimal surgery considering the potential benefits and complications of each procedure has been a never ended story.(Bron and O'Brien, 2004)

Total thyroidectomy has always been an option of surgical treatment, provided that a careful and meticulous surgery is practiced in preserving recurrent laryngeal nerves (RLN) and parathyroid glands.(Hisham et al., 2001) There are few benefits of total thyroidectomy such as total removal of the disease, prevention of recurrence and avoidance of re-operation for recurrent and malignant transformation as well as occult malignancy.

Subtotal thyroidectomy, a procedure which left about 4 to 6 g of thyroid tissue behind, has higher risk of recurrence as high as 23% which indirectly will lead to increase risk of injury to RLN and hypoparathyroidism (hypoPTH) in re-thyroidectomy.(Ozbas et

al., 2005) Furthermore, the incidence of occult malignancy is around 7 – 10% which usually the tumors are well-differentiated tumors like papillary or follicular type. (Giles et al., 2004, Ozbas et al., 2005) In addition, the incidence of malignant transformation of the thyroid residual following subtotal thyroidectomy is ranging between 4 – 17%.(Ozbas et al., 2005, Hisham et al., 2001) Moreover, leaving behind a small part of thyroid tissue has not shown any benefit of preventing hypothyroidism. (Ozbas et al., 2005)

The aim of this study is to determine the safety of total thyroidectomy in those with benign thyroid disease as well as to look for the prevalence of occult malignancy in benign thyroid disease as discovered by post-operative Histopathological Examination reports.

2. LITERATURE REVIEW

2.1 HISTORICAL REVIEW OF THYROID SURGERY

Goiter has been recognized as a disease entity since the earliest as 2700 BC in China. Abdul Kasan Kelebis Abis of Baghdad in 500 AD performed the first recorded goiter excision which ended with massive postoperative bleeding; however the patient survived.(Randolph, 2003) The early development in thyroid surgery technique was in the twelfth and thirteenth centuries in School of Salerno, Italy. During that period, two setons inserted at right angle into the thyroid mass with the help of a hot iron bar. These setons manipulated to the skin surface twice daily until it pierced the mass. In other way, the goiter's surface was cut and hooked out while the skin dissected away from the goiter. The goiter with its capsule removed with a finger once exposed. Pedunculated goiter was ligated as a whole with a bootlace and removed. The treatment was successfully reduced the goiter size, but they loss the patient as well following sepsis or massive bleeding.(Randolph, 2003)

Leonardo da Vinci, an artists and scientists, drew the anatomy of thyroid as two globular glands which he thought filled up empty spaces in the neck. The gland acquired its name after the work of Batholomaeus Eustachius of Rome in 1700s; "*glandulum thyroideum*" means shield shaped in Latin. In 1791, in Paris, Pierre Joseph Desault performed a successful partial thyroidectomy and his footsteps were followed by Guillaume Dupuytren in 1808 when he performed the first total thyroidectemy. In 1850s, a variety of skin incision introduced – longitudinal, oblique

and Y-shaped – and performed for thyroidectomy. Most surgeons used blunt dissection at that time after skin incision, which leads to massive bleeding that, was not adequately controlled. The wound was left open and neck dead spaces were packed or left to be filled with blood. (Randolph, 2003)

Developments in surgery and medicine in 1800s has helped in the surgical revolution, converting the traditional and bloody surgery to a safe and effective operation. With the introduction of anaesthesia, antisepsis and improved hemostatic forceps, allowing for more successful, safe and nonseptic thyroidectomy with better postoperative outcome.

The father of modern thyroid surgery was Theodor Kocher, a Swiss surgeon who has a meticulous surgical technique and paid careful attention to hemostasis. He was the first to introduce the technique of ligation of inferior thyroid arteries which subsequently reduced the risk of bleeding. Kocher used to preserve a strap muscles and usually used collar incision. His meticulous surgical technique produced a bloodless operative field and removal of most of the thyroid tissue while preserving the surrounding structures like parathyroid glands and recurrent laryngeal nerve. (Randolph, 2003, Falk, 1997)

Besides post-operative hemorrhage and infection, tetany has been recognized as one of the complication of thyroidectomy. This complication was fist described by Anton Wőlfler in 1879. Eugéne Gley in 1891 reported the cause of post-thyroidecomy tetany could be related to removal of parathyroid glands or to interference of their blood

supply. William Halsted, a Kocher's student, advocated the prevention of parathyroid injury during thyroidectomy and experimentally injected intravenous calcium gluconate to treat post-thyroidectomy tetany in animals. In 1926, autotransplantation of human parathyroid glands into the sternocleidomastoid muscle has been described by Lahey. Sam Wells in 1976, while performing a subtotal parathyroidectomy excised all parathyroid glands and autotransplanted into the forearm muscles which can be removed later should hyperparathyroidism occur. (Randolph, 2003, Falk, 1997)

Leonides, in the first century recognized the important of avoiding injury to the vocal cord nerves during head and neck operations. He believed, if the nerves were cut, the voice would be lost. Anton Wőlfler also emphasized the importance of protecting the recurrent laryngeal nerve (RLN) during thyroid surgery as he was the first to publish the anatomical detail of the RLN and the operative injury potential. The common practice of preserving the RLN at that time was to identify, isolate and ligate the inferior thyroid artery laterally away from the RLN. Kocher preferred to leave a small posterior part of the thyroid to avoid injury to the nerve. Frank Lahey in 1932 suggested strap muscles division and routine blunt and sharp dissection can demonstrate better the RLN and he reported a significant 0.3% rate of injury using his technique. However, the importance of external branch of superior laryngeal nerve was not emphasized until 1935. (Randolph, 2003, Falk, 1997)

2.2 EMBRYOLOGY AND ANATOMY OF THE THYROID GLAND

The thyroid gland is the first endocrine gland to develop in fetus, as early as 24 days after fertilization.(Moore and Persaud, 1993) Embryologically, the thyroid has originated from the primitive pharynx and the neural crest. The main central part of thyroid tissue originated from the primitive pharynx which started to develop during the second and third gestation weeks. This medial thyroid part develops as a median diverticulum of the endoderm of the floor of the primitive pharynx. The diverticulum descends caudally as it follows the primitive heart, which then forms a solid cord of cells that will form the follicular elements. The diverticulum breaks into 2 parts, the proximal part retracts and disappears leaving a foramen of caecum whereas the distal part forms a bilobe encapsulated structure that descends in the midline of the neck. This structure remains connected to the oral cavity by the thyroglossal duct.(Randolph, 2003) (Fig.1)

The thyroid diverticulum is divided into right and left lobes after solidification of the initially hollow diverticulum. The right and left lobes are connected by an isthmus. The thyroid gland reached anteroinferior part of neck and assumed its definitive shield shape by seven weeks of gestation. A pyramidal lobe which represents a persistent part of the inferior end of the thyroglossal duct extends superiorly from the isthmus in 50% of people. (Moore and Persaud, 1993)

The second part is the neural crest which forms the parafollicular cells or C cells, that secrete calcitonin. These C cells originated from ultimobranchial bodies which form

by fusion of the fourth and fifth branchial pouches. Fusion of fourth and fifth branchial pouches leads to the formation of the caudal pharyngeal complex which consists of ultimobranchial bodies and the parathyroid glands that arising from the endoderm of the fourth pharyngeal pouches. (Randolph, 2003)

The descended main part of the thyroid gland comes in contact with the ultimobranchial bodies in the neck and fuses with them. The fusion between these two structures causes the C cells can be only found in a deep zone of middle to upper thirds of lateral lobes and not scattered throughout of the gland (Fig. 2). This explains why the medullary carcinomas arise initially in the middle and upper third of the lateral thyroid lobes.(Randolph, 2003)

The thyroid primordium is consists of a solid mass of endodermal cells which then broken up into a network of epithelial cords by invasion of surrounding vascular mesenchyma. The cords have divided into small cellular groups by the tenth week. Following that, a lumen forms in each of the small cellular groups and colloid begins to appear in the lumen by the eleventh week. It is called thyroid follicles. Later, iodine concentration and the synthesis of thyroxine start. Epidermal growth factor, insulin-like growth factors and other related factors are involved in the development of thyroid follicular cells. (Moore and Persaud, 1993)

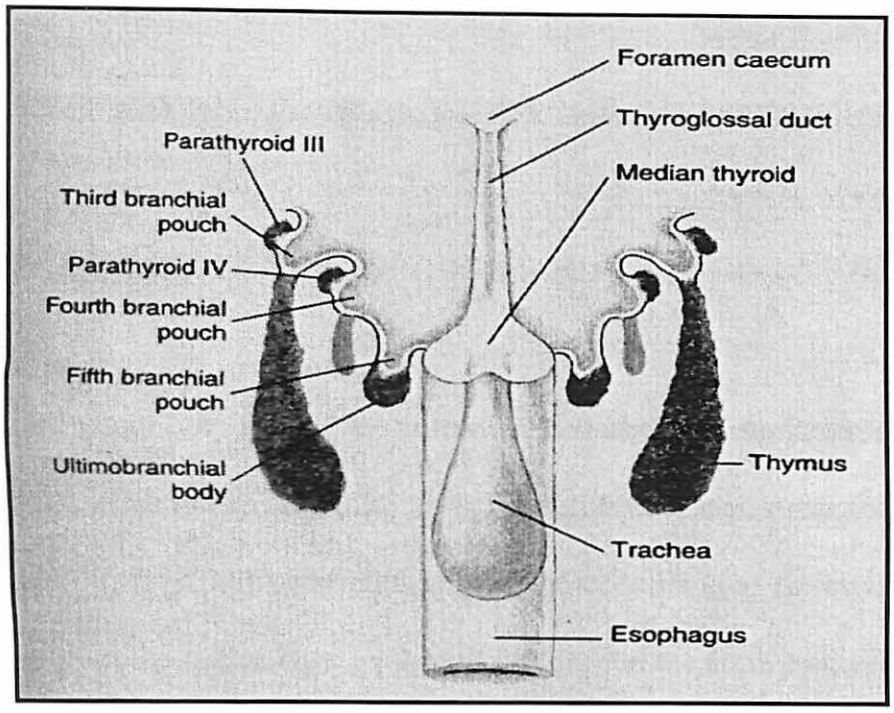

Fig. 2.1: View of the primitive pharynx of an 8- to 10-mm embryo.

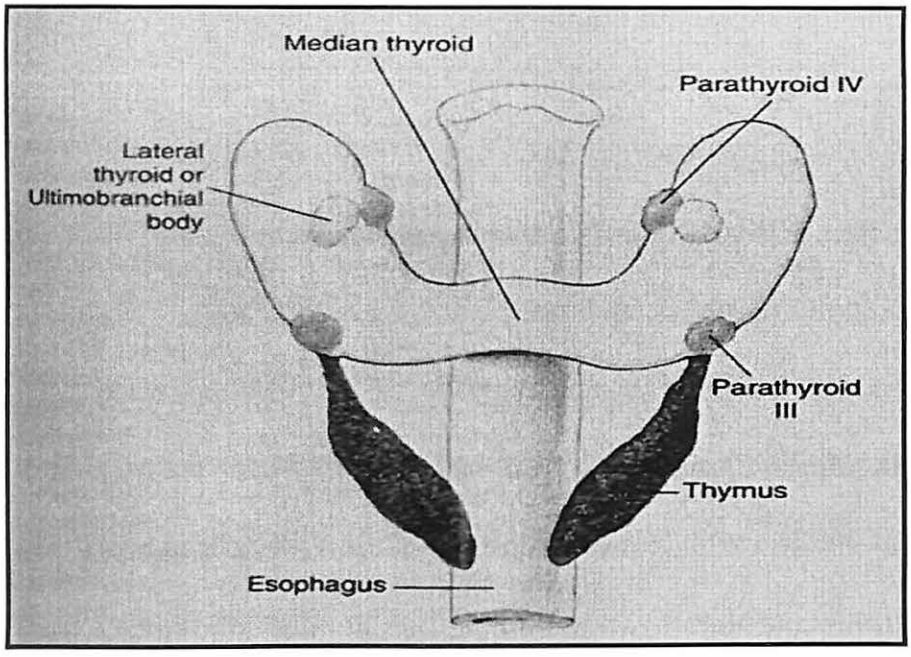

Fig. 2.2: View of the locations of thyroid, parafollicular and parathyroid tissue. The parathyroid III and IV migrate together with the thymus and ultimobranchial bodies, respectively.

2.3 ANATOMY AND PHYSIOLOGY OF THE THYROID GLAND.

2.3.1 ANATOMY OF THE THYROID GLAND

The thyroid gland is located at the inferoanterior aspect of the neck, consists of two symmetrical lobes which united by an isthmus that lies anterior to second, third and fourth tracheal rings. The both lobes situated on either side of the larynx and trachea, extending from the oblique line of thyroid cartilage to the sixth tracheal ring. It has an average weight about 25 g. It is an encapsulated structure which then enclosed by an envelope of pretracheal fascia.(Sinnatamby, 2000, Skandalakis JE, 2000)

The lateral lobe is in pear-shaped with a narrow upper pole and a broader lower pole. Each lateral lobe has lateral, medial and posterior surfaces. The lateral surface is underneath of sternothyroid and sternohyoid muscles. The medial surface lies against the lateral side of larynx and trachea and related to the cricothyroid muscle of the larynx, the inferior constrictor of the pharynx, external and recurrent laryngeal nerve. The posterior surface overlies the medial part of the carotid sheath, and usually in contact with the parathyroid glands.(Sinnatamby, 2000)

The isthmus connects the anterior surfaces of the lobes. The posterior surface of the isthmus is strongly adhered to the second, third and fourth tracheal rings. The whole gland is fixed and invested by pretracheal fascia which responsible for movement of the gland with the larynx during swallowing. The two superior thyroid arteries

anastomoses and run across the upper border of the isthmus while the tributaries of the inferior thyroid veins come out from its lower border.(Sinnatamby, 2000)

The pyramidal lobe is a small part of gland that projects upwards from the isthmus and represents a persistent part of the inferior end of the thyroglossal duct. *Levator glandulae thyroidea* is a muscle that may sometimes present in the pyramidal lobe which innervated by a branch of the external laryngeal nerve.(Sinnatamby, 2000, Skandalakis JE, 2000) (Fig. 2.3)

The superior thyroid artery, the first branch of the anterior aspect of external carotid artery, divides into two branches on the gland. The anterior branch runs down to the isthmus while the posterior branch runs down the back of the lobe which later anastomoses with the ascending branch of inferior thyroid artery. The inferior thyroid artery, a branch of thyrocervical trunk divides outside the pretracheal fascia into branches which pierce the fascia separately to reach the lower pole. It gives small branches to pharynx, oesophagus, larynx and trachea before it reaches the gland. The *thyroidea ima artery*, arises from the brachiocephalic trunk, arch of aorta or right common carotid artery, enters the lower part of the isthmus in 3% of people.(Sinnatamby, 2000) (Fig. 2.4 and Fig. 2.5)

A venous plexus on the surface of the thyroid gland drains into superior thyroid vein which then drains into either the internal jugular vein or facial vein. The middle thyroid vein drains into the internal jugular vein after crossing anteriorly to the

common carotid artery. The multiple inferior thyroid veins drain mainly into the left brachiocephalic vein.

The thyroid gland's lymphatic drain mainly into deep cervical lymph nodes and a small amount goes to prelaryngeal and pretracheal nodes and a few drains directly in the thoracic duct. The thyroid gland is innervated by sympathetic nerve from superior, middle and inferior cervical ganglia which accompany the thyroid arteries.(Sinnatamby, 2000, Skandalakis JE, 2000)

The recurrent laryngeal nerve (RLN) has an important relationship to the thyroid gland in thyroid surgery. The nerve lies in or in front of the traceo-oesophageal groove. The left RLN curves around the arch of aorta, ascends upwards, enters the groove and lies posterior to the inferior thyroid artery. Whilst the right RLN curves around the right subclavian artery, ascends upwards more lateral to the trachea and passes anterior or posterior to inferior thyroid artery or in between their branches. Both nerves are lie behind the pretracheal fascia and run medial or lateral or through the suspensory ligament of Berry, a thickening of the fascia attached to the cricoid cartilage and upper tracheal rings. The nerves divide into two at the level of upper border of the isthmus, anterior branch is the motor branch to laryngeal muscles whilst the posterior branch is for sensation only. The external laryngeal nerve passes closely behind the superior thyroid artery lies on the inferior constrictor to supply cricothyroid.(Sinnatamby, 2000, Skandalakis JE, 2000) (Fig. 2.6)