

EFFECT OF ATORVASTATIN IN LIPID PROFILE CHANGES AND INFLAMMATION MARKER ON DIABETES PATIENT WITH DYSLIPIDEMIA

Syahrudi^{1*}, R Yoga Wijayahadi²

¹Clinical Pharmacy Master Program, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia ² Division of Head and Neck Surgery, Department of Surgery, Faculty of Medicine, Universitas Airlangga, Dr Soetomo Hospital, Surabaya, Indonesia

ABSTRACT

Thyroid cancer is one of the commonest cancer, while the incidence of occult thyroid cancer is only 0.05%. The completion total thyroidectomy as one of treatments choice for thyroid cancer which initially diagnosed preoperatively as benign thyroid mass, has remained controversial. This study aimed to understand the effectiveness of completion total thyroidectomy after partial thyroidectomy by analyzing the proportion of malignant contralateral thyroid tissue, post operative complications, and recurrence of cancer. This retrospective study collected medical record data in 2011 and 2016. The samples were 16 patients consisting of 15 females and 1 male. There was no significant difference on contralateral thyroid tissue malignancy proportion between completion total thyroidectomy and without total thyroidectomy ($P = 0.375$). It was found that 3 surgical complications (50%) of 6 patients with completion total thyroidectomy and 3 complications (30%) of 10 patients without completion total thyroidectomy. The complications were temporary injury of recurrent laryngeal nerve ($P = 0.511$), seroma ($P = 0.375$), and hypoparathyroidism ($P = 0.375$). No recurrence event after 4 years follow up amount both groups. In conclusion, there is no advantage in completion total thyroidectomy analized from proportion of malignant contralateral thyroid tissue, post operative complication, and recurrence in 4 years-follow up.

Keywords: *occult thyroid cancer; partial thyroidectomy; completion total thyroidectomy*

ABSTRAK

Kanker tiroid merupakan keganasan kelenjar endokrin yang paling sering ditemukan, tetapi insiden kanker tiroid tersembunyi (occult) yang tampak secara klinis hanya sekitar 0,05%. Tiroidektomi total completion sebagai terapi standart masih kontroversial, dan belum ada konsensus untuk pasien yang dioperasi dengan tumor jinak tiroid dan didiagnosis kanker setelah operasi. Tujuan penelitian ini adalah untuk mengetahui efektifitas tiroidektomi total completion dengan riwayat tiroidektomi parsial dilihat dari proporsi keganasan jaringan tiroid kontralateral, komplikasi post operasi, dan proporsi rekurensi kanker. Penelitian ini adalah penelitian retrospektif menggunakan rekam medis pada periode 2011-2016. Total terdapat 16 kasus yang terdiri atas 15 pasien perempuan dan 1 laki-laki. Penelitian ini menghasilkan bahwa tidak didapatkan perbedaan pada proporsi keganasan jaringan tiroid kontralateral antara tiroidektomi total completion maupun tanpa total completion ($P = 0,375$). Komplikasi post operasi tiroidektomi total completion dijumpai pada 3 kasus (50%) dari 6 pasien, sedangkan pasien tanpa tiroidektomi total completion 3 kasus (30%) dari 10 pasien. Jenis komplikasi adalah cedera nervus laringeus rekuren sementara ($P = 0,511$), seroma ($P = 0,375$) dan hipoparatiroid ($P = 0,375$). Tidak didapatkan rekurensi kanker kontralateral dalam follow up selama 4 tahun pada kedua grup. Sebagai kesimpulan, tidak didapatkan manfaat tindakan tiroidektomi total completion dalam hal proporsi keganasan jaringan tiroid kontralateral, komplikasi post operasi, maupun rekurensi kanker tiroid tersembunyi selama follow up 4 tahun.

Kata kunci: *kanker tiroid tersembunyi; tiroidektomi parsial; tiroidektomi total completion*

Correspondence: Syahrudi, Surgery Program, Department of Surgery, Faculty of Medicine, Universitas Airlangga, Dr Soetomo Academic Hospital, Jalan Prof dr Moestopo 6-8, Surabaya 60286, Indonesia. E-mail: syahrudi84@gmail.com

INTRODUCTION

Thyroid cancer is the most common malignancy of endocrine gland and the incidence is increasing in some areas. Based on pathology data in Indonesia, thyroid cancer is ranked as the 9th most common cancer. However, the incidence of clinically apparent occult thyroid cancer is only about 0.05%. The incidence in Europe is about 1.75 per 100,000 population (0.00175%) in males and 6.38 (0.00638%) in females. Only about 1-2% of occult thyroid cancers alter clinically during life. Incidents around the world ranged from 3 to 4 per 100,000 population with the most incidents in Iceland and Hawaii (15 per 100,000). The small number of occult thyroid cancers incidence has led to prolonged debate on the management of the patients' therapy (Ganly et al 2009, Manuaba 2010).

Total completion thyroidectomy is an important step in the treatment of thyroid cancer patients, because not all patients receive total thyroidectomy as a standard operation in thyroid cancer. Difficult perioperative procedure in diagnosing cancer leads to the implementation of completion procedure that should have been avoided (Makay et al 2006).

The management of occult thyroid cancer therapy is still in debate. Several studies have demonstrated the advantages of total completion thyroidectomy, such as increasing clinical response to radioactive iodine, ability to accurately monitor thyroglobulin, and removing synchronous tumors in the contralateral lobe. However, this procedure is also at risk for complications, because the number of post completion complication is higher. In terms of cancer recurrence, there is no difference between partial thyroidectomy compared to total thyroidectomy in occult thyroid cancer (Kupferman et al 2002). Currently, there are no data on occult thyroid cancer and the results of the therapy in Indonesia. This study was expected to provide information about profile, complication, proportion of malignancy of contralateral thyroid tissue and occult thyroid cancer recurrence.

MATERIALS AND METHODS

This study was a retrospective study by evaluating medical records of occult thyroid cancer patients who underwent total completion thyroidectomy surgery or no total completion thyroidectomy in terms of postoperative complication, proportion of malignancy of the contralateral thyroid tissue, and proportion of contralateral tumor recurrences. The samples were taken from all patients with history of benign clinical thyroid tumor/occult thyroid cancer post partial thyroidectomy surgery with malignancy from 2011 to September 2016 at Dr. Soetomo Academic Hospital, Surabaya.

RESULTS

A total of 16 patients underwent strumal surgery with anatomical pathology results of thyroid cancer with a cancer size less than or equal to 1 cm called occult thyroid cancer. The most sexes in this study were females as many as 15 patients (93.75%), while male was 1 patient (6.25%). The patients' ages in this study were from 19 years to 64 years. The largest group was in the age range of 41-50 year and the average age of 45 years. Based on AMES for prognostic factors by using age < 50 years as benchmark, there were 11 patients (68.75%) less than or the same as 50 years old and 5 patients (31.25%) were over 50 years. Based on strumal type, the most common struma was multinodosa type in 9 patients (56.25%), uninodosa in 6 patients (37.5%) and diffuse in 1 patient (6.25%). Based on toxicity, the most was non-toxic struma type in 14 patients (87.5%) and toxic in 2 patients (12.5%). The sizes of the struma were between 3 cm to 11 cm with an average size of 6.7 cm.

The types of surgery were subtotal lobectomy in 3 patients (18.75%), total lobectomy in 2 patients (12.5%), isthmulobectomy 4 patients (25%) and subtotal thyroidectomy in 7 patients (43%). Post-operative pathology outcome of occult thyroid cancer showed that the most common type of cancer was papillary cancer in 15 patients (93.75%) and follicular in 1 patient (6.25%), whereas medullary and anaplastic thyroid cancers were not found. In the papillary type, there is no subtype of sclerosing and 1 follicular type with minimally invasive form.

Table 1. Distribution of preoperative diagnosis, type of surgery and pathology results of occult thyroid cancer

Variables	total completion thyroidectomy	without total completion	Total (%)
Strumal type			
Multinodosa	2	7	9 (56.25%)
Uninodosa	3	3	6 (37.5%)
Diffuse	1	0	1 (6.25%)
Size (average (cm))	3.9	6.8	6.7
Toxicity			
Toxic	2	0	2 (12.5%)
Non-toxic	4	10	14 (87.5%)
Type of operation			
Subtotal lobectomy	0	3	3 (18.75%)
Total lobectomy	1	1	2 (12.5%)
Isthmuloectomy	3	1	4 (25%)
Subtotal thyroidectomy	2	5	7 (43.75%)
Type of pathology			
Papillary	5	10	15 (93.75%)
Follicular	1	0	1 (6.25%)
Medullar	0	0	0
Anaplastic	0	0	0
Size (average (cm))	0.8	0.7	0.73
Total cancer			
1	5	9	14 (87.5%)
>1	1	1	2(12.5%)
Extrathyroidal extension			
Yes	4	1	5(31.25%)
No	2	9	11(68.75%)
AMES			
High risk	5	4	9(56.25%)
Low risk	1	6	7 (43.75%)

The size of occult thyroid cancer was averagely of 7mm. The unifocal type were 14 cases and multifocal 2 cases. In 9 cases of struma multinodosa, there were 7 unifocal cases and 2 multifocal cases. Based on AMES score, the scores that affected the risk of cancer recurrence were age and extension of cancer. A total of 9 patients had a high risk consisting of 4 patients without total completion thyroidectomy and 5 patients with total completion thyroidectomy. Based on the size of cancer and metastasis, all patients were at low risk.

Postoperative complications were found in 3 (30%) of 10 patients undergoing partial thyroidectomy with temporary recurrent laryngeal nerve injury. In 6 patients performed total completion thyroidectomy surgery postoperative complication was found in 3 patients (50%), such as seroma, hypoparatiroid and temporary recurrent laryngeal nerve injury. There were no differences in complications in patients either with completion or without completion, either on recurrent laryngeal nerve injury ($p = 0.511$), hypoparathyroid ($p = 0.375$) and seroma ($p = 0.375$).

Table 2. Postoperative complications

Types of complication	Partial thyroidectomy (n=16)	Total completion thyroidectomy (n=6)
Recurrent n. laringeus injury	3	1
Hypoparathyroid	0	1
Seroma	0	1

The proportion of malignancy was obtained from pathologic surgery after total completion thyroidectomy and evaluation 6-12 months after thyroid surgery. One patient had positive residual tumor after total completion thyroidectomy and no new cancers were

found in patients not undergoing total completion thyroidectomy. The results showed no significant difference between the proportion of malignancy of contralateral thyroid tissue, either in total completion thyroidectomy or without total completion ($p = 0.375$).

Table 3. Pathology of contralateral thyroid

Types of operation		With Cancer	Without cancer
Completion Thyroidectomy (n=6)	Total	1	5
Without Completion Thyroidectomy (n=10)	Total	0	10

Evaluation of cancer recurrence could be performed in 10 patients, consisting of 3 patients with total completion thyroidectomy and 7 patients without total completion thyroidectomy. From 4 years evaluation, there was no recurrence of cancer, either in total completion thyroidectomy or not. Six of 16 patients could not be evaluated because the surgery was performed less than 4 years before and not routinely visited the doctor's office.

DISCUSSION

In this study, most occult thyroid cancers were found in women (93.75%, n: 15) with an age range of 19-64 years, and are often found between 41-50 years. The findings were consistent with the literature that thyroid cancer in women occurred 2-4 times more often than in men, often found in the age of the fourth or fifth decade, and rarely found in children to adults (Schlumberger 2004). The study of Roti et al also found that the percentage in women was about 85% and men 15%. The average age at diagnosis was between 41-55 years (Roti et al 2008).

The occult thyroid cancers were often found in well-differentiated cancers. The histologic type of partial thyroidectomy results was papillary type (93.75%, n: 15) and only 1 patient (6.25%) with follicular type. This result was almost identical to the histologic distribution of well differentiated thyroid cancers in general, where papillary strains were often found to be about 80% and follicular about 5-10% (Figge 2006). From the results of Roti et al's study, the percentage of papillary thyroid microcarcinomas ranged from 65 to 99% of cases. Of the follicular thyroid cancers found, about 0.3-23.6%, 11% of the follicular type was diameter < 1 cm (Roti et al 2008).

Postoperative complications were obtained in 3 (18.75%) of 16 patients who performed partial thyroidectomy with temporary recurrent laryngeal nerve injury. Complications were obtained on subtotal thyroidectomy, isthmobectomy of more than 5 cm in size and TOETVA (Trans Oral Endoscopic Thyroidectomy Vestibular Approach) subtotal lobectomy, which was a new endoscopic technique in

Dr. Soetomo. Laryngeal nerve injury temporarily recovered within 6-9 months after surgery. In 6 patients performed thyroidectomy total completion, postoperative complications were obtained as many as 3 patients (50%), such as hypoparathyroid, sera and temporary recurrent laryngeal nerve injury.

Hypoparathyroid complication was treated with calcium supplementation. In seroma, we performed sterile aspiration of the fluid and recovered within 16 days after surgery. Recurrent laryngeal nerve injury was temporary and resolved within 2 months after surgery. Fujimoto (2005) revealed that in patients with low-risk papillary thyroid cancer, hemiroidectomy has advantage to reduce the risk of hypoparathyroid complications and recurrent laryngeal nerve injuries was primarily performed by surgeons with low operating experience. Post-operative euthyroid conditions did not require hormone replacement therapy for life.

In the case of contralateral pathologic malignancy, 1 patient showed cancer pathology after total completion thyroidectomy. The distance between the first operation with the second was less than 1 month. The type of pathology was similar to that of the previous partial and multifocal thyroidectomy, but there was no difference in the proportion of malignancy of the contralateral thyroid tissue ($P = 0.375$). Residual malignancy of tumor tissue should be noted during surgery especially in multifocal type. Turanli et al's study of 97 cases of occult thyroid cancer was after total completion thyroidectomy showed that in multifocal tumors malignancy most likely occurred in the residual thyroid ($P = 0.02$; relative risk 4.9; 95% confidence interval). However, malignant detection of residual thyroid tissue had no effect on disease free survival ($P = 0.39$) (Turanli et al 2011).

Of 10 cases that could not be followed up for 4 years, there was no cancer recurrence. This result was probable, because there were no presence of sclerosing papillar types and minimally invasive follicular type. Schroder et al's study (1984) showed that 32 cases of papillary thyroid malformations had a good prognosis in a mean follow-up of 7 years and only 2 cases with metastases to lymph nodes were obtained with occult sclerosing carcinoma (Schroder et al 1984).

Papillary occult thyroid cancer in small size, less than 1 cm, not showing local invasion of the thyroid capsule, had no association with lymph node metastases commonly found at a young age, especially unifocal and of 5 mm in size. Treatment was sufficient with lobectomy without the need for total completion by providing additional hormone suppression therapy and regular monitoring (Kaplan et al 2012). Delbridge et al's study (2002) showed minimally invasive follicular thyroid cancer less than 5% so total completion thyroidectomy and iodine ablation that were not required.

Routine follow up is necessary for the evaluation of cancer recurrence. Patients with high recurrence risk need to be closely monitored. The management of total thyroidectomy surgery is aimed at reducing the risk of recurrence of cancer, because thyroid cancer tends to be multifocal and bilateral. Whereas, in patients with low risk, ie tumor size less than 1 cm, unifocal and intralobar, lobectomy is allowed to be performed (Schlumberger 2004). ATA recommends total completion thyroidectomy in all patients with thyroid cancer except for small one (< 1cm), intrathyroid, without enlarged lymph nodes, and low risk (recommendation B) (Cooper et al 2006).

CONCLUSION

There is no advantage in completion total thyroidectomy analyzed from proportion of malignant contralateral thyroid tissue, post-operative complication and recurrence occult thyroid cancer in 4 years-follow up.

REFERENCES

- American Diabetes Association (2017). Standards of medical care in diabetes. *Diabetes Care: The Journal of Clinical and Applied Research and Education* 40, supplement 1
- American Society of Health System Pharmacist (2011). AHFS Drug Information. Unites States of America
- Bellia A, Rizza S, Galli A, Fabiano R, Donadel G, Lombardo MF, Cardillo C, Sbraccia P, Tesaro M, Lauro D (2010). Early vascular and metabolic effects of rosuvastatin compared with simvastatin in patients with type 2 diabetes . *Atherosclerosis* 210, 199-201
- Chehade JM, Gladysz M, Mooradian AD (2013). Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. *Drugs* 73, 327-339
- Davignon J (2004). Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 109, III39-43
- Deerochanawong C, Buranakitjaroen P, Nitiyanant W, Suwantamee J, Piamsomboon C, Vongthavaravat V, Suwanwela C, Kosachunhanun N, Sukonthasarn A (2007). The atorvastatin goal achievement across risk levels: (ATGOAL) study in Thailand . *J Med Assoc Thai* 90, 72-81
- Grossman A, Grossman E (2017). Blood pressure control in type 2 diabetic patients. *Cardiovascular Diabetology* 16, 1-15
- Lexicomp (2016). Drug Information Handbook. In: Lacy C, Armstrong L, Goldman M, Lance L (eds). Ohio, Lexi-Comp Inc, p 174-177
- Ministry of Health (2013). Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan Republik Indonesia. Jakarta
- Paneni F, Beckman JA, Creager MA, Cosentino F (2013). Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J* 34, 2436-2446
- PERKENI (2015). Konsensus pengelolaan dan pencegahan diabetes melitus tipe 2 di Indonesia. Jakarta, PB PERKENI, p 1-79
- Schachter M (2005). Chemical, pharmacokinetic and pharmacodynamic properties of statin : an update. *Fundam Clin Pharmacol* 19, 117-125
- Shaw JE, Sicree RA, Zimmet PZ (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 87, 4-14
- Stancu C, Sima A (2001). Statins: mechanism of action and effects. *J Cell Mol Med* 5, 378-387
- Triplitt C, Reasner C (2011). Diabetes mellitus. In: DiPiro J, Talbert RL, Yee G, Matzkee G, Wells B, Posey LM. *Pharmacotherapy: a pathophysiologic approach* 8th ed, New York, McGraw-Hill
- Tousoulis D, Oikonomou E, Economou EK, Crea F, Kaski JC (2016). Inflammatory cytokines in atherosclerosis: current therapeutic approaches. *Eur Heart J* 37, 1723-1732
- Wu L, Parhofer KG (2014). Diabetic dyslipidemia. *Metabolism* 63, 1469-1479
- Zhou Q, Liao JK (2010). Pleiotropic effects of statins: basic research and clinical perspectives. *Circ J* 74, 818-826