ORIGINAL ARTICLE

Comparison of Anti Thyroid Drugs, Radioactive Iodine and Surgery for Graves' Disease: a Systematic Review and Meta-Analysis

Dian Daniella[1], Ida Bagus Aditya Nugraha[2*], Wira Gotera[2]

1 Internal Medicine Resident, Faculty of Medicine, Prof. Dr. I.G.N.G. Ngoerah General Hospital/Universitas Udayana
2 Division of Endocrinology and Metabolism, Department of Internal Medicine, Prof. Dr. I.G.N.G. Ngoerah General Hospital/Universitas Udayana

**Corresponding author:*
Ida Bagus Aditya Nugraha, MD.
Division of Endocrinology and Metabolism, Department of Internal Medicine, Prof. Dr. I.G.N.G. Ngoerah General Hospital/Universitas Udayana Denpasar, Bali, Indonesia.
Email: ibadityanugraha@gmail.com

ABSTRACT

Selection of therapy for Graves' Disease (GD) has always been a puzzling decision to be taken by both the patient and physician. This is due to the three modalities (Anti Thyroid Drug (ATD), Radioactive Iodine (RAI) and surgery) in with each one being just as established as the other two in being an effective treatment strategy. Therefore, this study was conducted in purpose to compare ATD, RAI and surgery for GD. The author searches from several databases such as PubMed, Directory of Open Access Journals (DOAJ), and Science Direct as well as registers, such as Cochrane Central Register of Controlled Trials (CENTRAL). The systematic review was incorporated to all of seven studies and six studies has been selected to be included in the analysis. ATD has higher risk of relapse compared to RAI (RR 2.77, 95% CI 0.99-7.75); p=0.05) and surgery (RR 6.60, 95% CI 3.76-11.58); p<0.00001). In comparison to surgery, RAI has higher risk of relapse (RR 2.52, 95% CI 0.66-9.67); p 0.18). ATD has lower success rate compared to RAI (RR 0.47, 95% CI 0.35-0.63); p<0.00001) and surgery (RR 0.44, 95% CI 0.34-0.58); p<0.00001). ATD has lower risk of hypothyroid compared to RAI (RR 0.08, 95% CI 0.02-0.27); p<0.0001) and surgery (RR 0.09, 95% CI 0.02-0.40); p=0.001). ATD has the highest risk of relapse compared to RAI and surgery. RAI and surgery did not differ significantly in risk of relapse and hypothyroid.

Keywords: *Thyroid hormone, hyperthyroid, methimazole, iodine*

INTRODUCTION

Hyperthyroid happens to 1.2% population. The three top leading causes of hyperthyroidism are Graves' Disease (GD), toxic multinodular goitre, and toxic adenoma.[1] Graves' disease, also known as toxic diffuse goiter, is an autoimmune condition where the circulation of the Thyroid-Stimulating Hormone (TSH) caused an unregulated stimulation to the thyroid that leads to overproduction of thyroid hormones.[2] It was first described in 1835 as exophthalmic goiter due to its pathognomonic feature of ophthalmopathy. Untreated GD has a negative impact towards the quality of life and puts one at crucial risk of psychosis, tachyarrhythmia and cardiac failure.[3] cardiovascular disease is the most prominent factor causing the death of patients with hyperthyroidism, and an effective control of hyperthyroidism is known to lower cardiovascular mortality.[4] Therefore, one must select with care but still decide quickly on which effective treatment to take.

According to American Thyroid Association Guidelines 2016, patients with overt Graves' hyperthyroidism should be treated with any of the following modalities, such as Anti Thyroid Drug (ATD), Radioactive Iodine (RAI) and surgery.[5] Selection of therapy has always been a challenge for both patient and physician because these three modalities have been established as an effective treatment strategy. These three modalities have not shown any differences in quality of life.[6] Multiple countries showed different preferences in therapy. In the United States of America (USA), RAI is the preferred therapy, but in Europe, Latin America and Japan, ATD is the preferred therapy.[7,8] Each of the modalities has its own risks and benefits. Graves' disease is known as a remitting and relapsing disease. ATD was associated with high relapse rate compared to other modalities and hypothyroid was more common in patients undergone RAI and surgery. Effectiveness and side effect of therapy should be taken into consideration in managing patients as periods of hyperthyroidism and hypothyroidism are detrimental and lead to higher mortality risk.[9]

Due to high prevalence of GD and prompt and effective treatment is needed, studies regarding the most effective modality in managing GD is important. The aim of this study, without prejudice, was to compare ATD, RAI and surgery for adult GD patients.

METHODOLOGY

Eligibility Criteria

The authors compiled all studies analyzing different modalities of therapy in adult GD patients (>18 years). The authors excluded studies that were not in English.

Study Search And Selection Strategy

This meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[10] This study was registered in PROSPERO (CRD42023467907). The author has sourced from several databases such as PubMed, Directory of Open Access Journals (DOAJ), and Science Direct as well as registers, such as Cochrane Central Register of Controlled Trials (CENTRAL) with the search words: ((antithyroid drug) OR (methimazole) OR (carbamazepine) OR (propylthiouracil)) AND (radioactive iodine) AND (thyroidectomy) AND (Graves' disease). This study is still being reviewed in PROSPERO. There were no limitations applied for the year of study in the search. The authors conscientiously reviewed the obtained articles and resolved any disagreements through consensus among themselves.

Data Extraction

The Microsoft Excel program was utilized by the author to carry out data extraction. The data sought were the country, author, year, study design, number of samples, duration of ATD therapy, mean dose of RAI, type of surgery, follow-up duration and research outcomes. The quality of studies was gauged with NOS (Newcastle-Ottawa quality assessment scale), with grading details as such; Poor (score 0-3), Fair (score 4-6) or High (score 7-9).[11]

Analysis using Review Manager 5.4.1 (Copenhagen: The Cochrane Collaboration,

2020). To compare and asses the efficacy of using ATD, RAI and surgery in managing GD, analysis of risk ratio (RR) on relapse and success was performed. The Mantel-Haenszel Formula was employed to compute the dichotomous variables. The risk ratio, along with its 95% confidence interval (CI), indicates statistical significance when $p < 0.05$.

Assessment to deduce heterogeneity was conducted with the I2 test, which examines variation between studies. A result where I2 is greater than 50% suggests significance, urging the usage of a random-effect model. A qualitative assessment for publication bias was conducted through funnel plot analysis, with an asymmetrical shape indicating the presence of publication bias.

RESULTS

Baseline Characteristics

Seven studies were compiled in our conscientious review and six studies was selected to be statisticaly analyzed (Figure 1). Four thousand and five subjects were given ATD, 2,586 subjects were managed with RAI and 513 subjects undergone surgery (Table 1). Most studies were cohort and female dominant. All studies were comparing subjects that were given ATD or RAI or surgery. Most of the surgery were subtotal thyroidectomy, with one study[12] using subtotal thyroidectomy and three studies using total and subtotal thyroidectomy.[13-15] All of the studies compiled were studies of good quality.

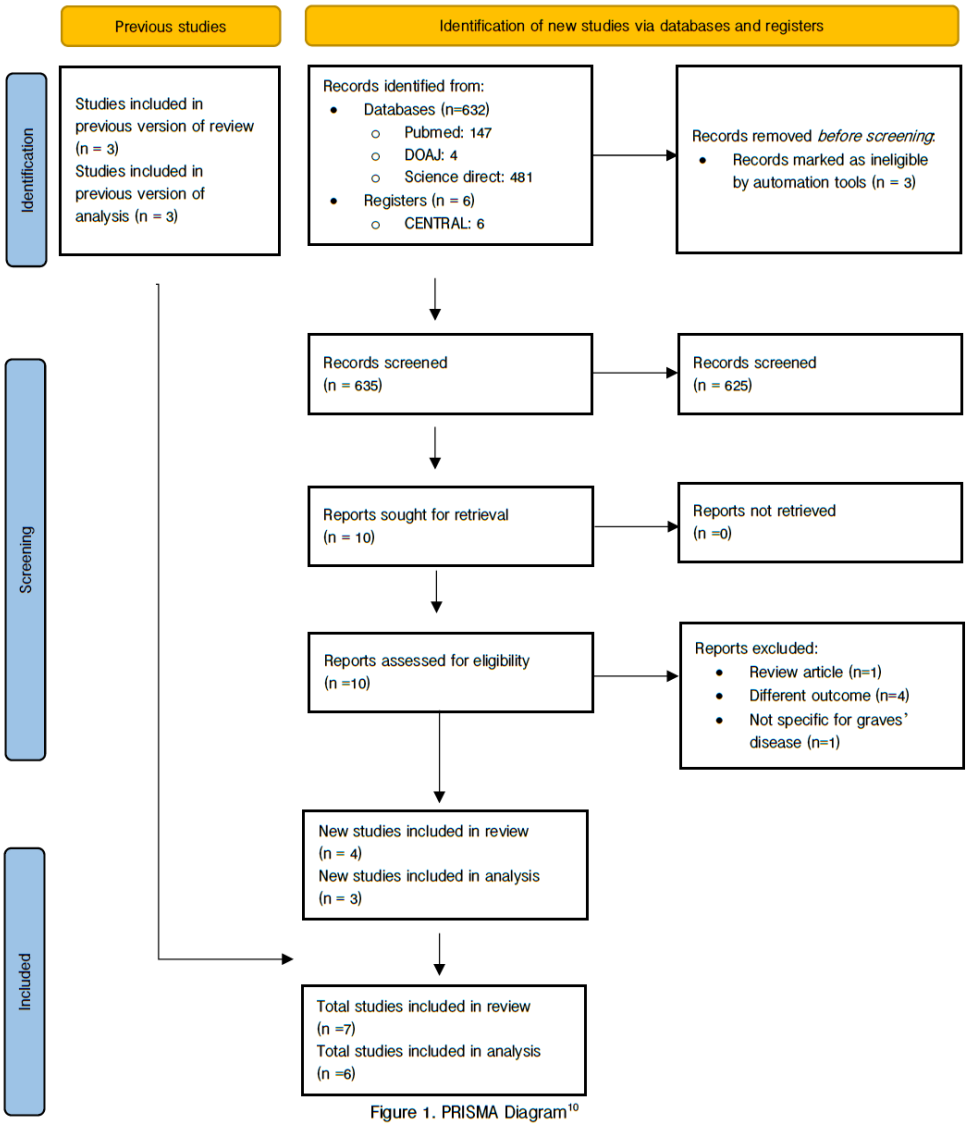

Figure 1. PRISMA Diagram[10]

Table 1. Baseline Characteristics

Author (year)	Country	Design	Age (years)	F (%)	ATD			RAI			Thyroidectomy			Outcome
					Total	Duration of therapy (mo)	Follow-up duration	Total	Mean dose of RAI	Follow-up duration	Total	Follow-up duration	Type of surgery	
Berglund et al. [16] (1991)	Sweden	Cohort	Mean 52 (14 -88)	170 (80.2)	83	Median 20 (7-54)	108 (2-192) mo	106	6.7 mCi (1.75-43.8)	108 (2-192) mo	23	108 (2-192) mo	Subtotal thyroidectomy	Relapse: ATD (43%) vs RAI (9%) vs surgery (5%)
Torring et al. (old cohort) (1996)[6]	Sweden	Cohort	ATD 45 ± 6; RAI 45 ± 5; surgery 45 ± 6	100 (84.0)	35	18	30	39	6.8 mCi	48	37	42	Subtotal thyroidectomy	Relapse: ATD (42%), vs RAI (21%) vs surgery (3%)
Torring et al. (young cohort)[6] (1996)	Sweden	Cohort	ATD 29 ± 4; Surgery 29 ± 4	49 (81.7)	25	18	30	N/A	N/A	N/A	28	48	Subtotal thyroidectomy	Relapse: ATD (34%) vs surgery (8%).
Leary et al.[17] (1999)	Ireland	Cohort	Mean 37 (9-76)	107 (84)	74	Median 24	10.5 (2.3-18) y	72	7.5 mCi (5-10)	10.5 y (2.3-18 y)	26	10.5 y (2.3-18 y)	Subtotal thyroidectomy	Relapse: ATD (68%) vs surgery (19%).
Sundaresh et al. (2017)[13]	USA	Cohort	Mean 49.3 (14.9)	552 (76.7)	118	>12	1.5 (2.2) y	543	16.5 mCi; 200 µCi/g	3.8 (3)	19	4.3 (3.1)	Subtotal and total thyroidectomy	ATD had an overall failure rate of 48.3% compared with 8% for RAI and 100% for surgery.
Conaglen et al. [12] (2018)	Australia	Cross-sectional	Median 50 ± 16	101 (82)	79	>12	N/A	13	N/A	> 6	31	> 6	Total thyoroidectomy	Patient satisfaction with therapy and quality of life does not differ between treatment
Brito et al. [15] (2019)	USA	Cohort	Mean 48 (14)	3,709 (79.6)	2817	Median 213.94 (148) days	4.5 (2.1) y	1549	N/A	4.7 (2.3) y	295	4.5 (2.1) y	Subtotal and total thyroidectomy	Surgery was most effective (99%), followed by RAI (93%), and ATD (50%).
Sjolin et al.[14] (2019)	Sweden	Cohort	Mean 46.9 (14.4)	973 (82)	774	12-18	8 ± 0.9 y	264	N/A	8 ± 0.9 y	54	8 ± 0.9 y	Subtotal and total thyroidectomy	Remission rate for ATD (43%) is lower than RAI (81.5%)and surgery (96.3%).

ATD, antithyroid drug; RAI, radioactive iodine; USA, United States of America; N/A, not available.

Relapse rate

ATD has higher risk of relapse compared to RAI (RR 2.77, 95% CI 0.99 - 7.75); *p = 0.05*) and surgery (RR 6.60, 95% CI 3.76 - 11.58); *p < 0.00001*). In comparison to surgery, RAI has higher risk of relapse (RR 2.52, 95% CI 0.66 - 9.67); p 0.18), but it is not statistically significant (Figure 2).

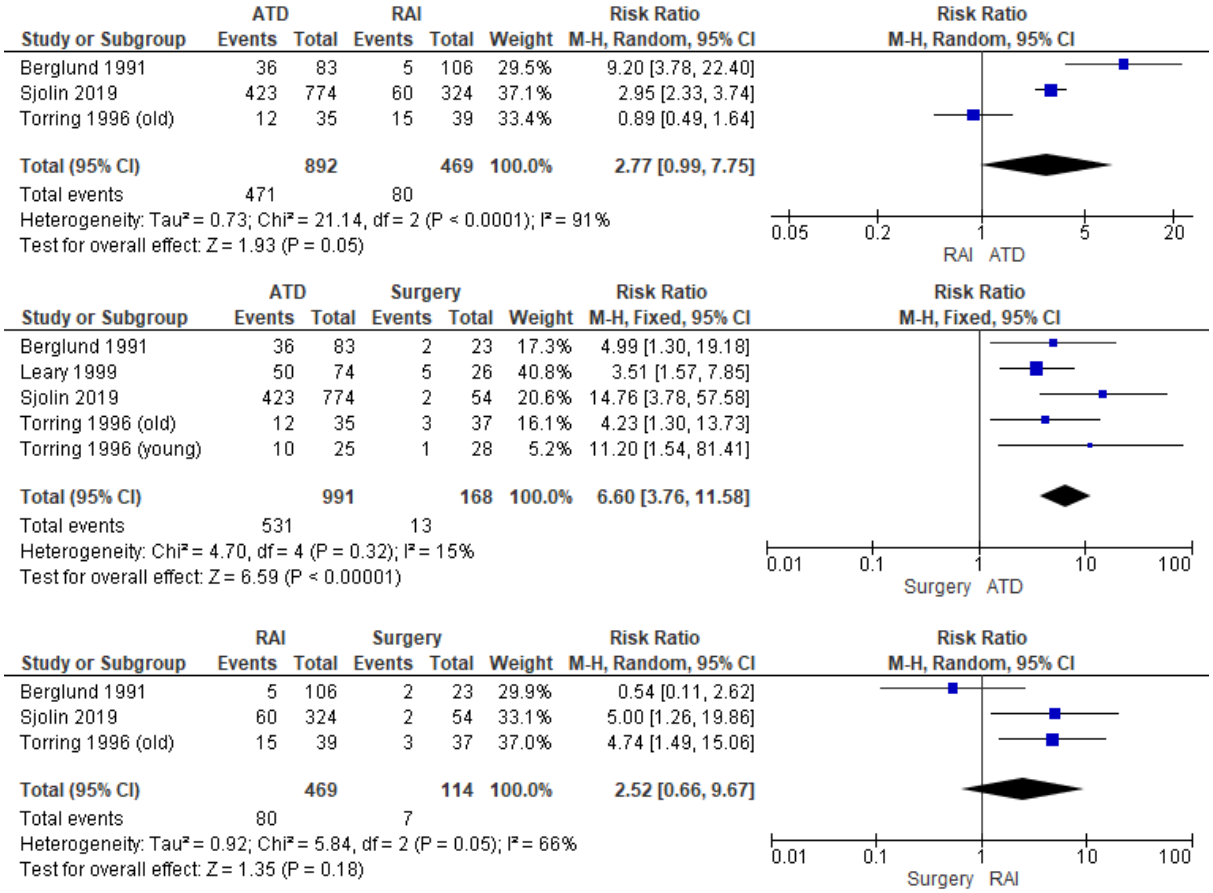

Figure 2. Risk Ratio of Relapse in GD Patients

Success rate

ATD has lower success rate compared to RAI (RR 0.47, 95% CI 0.35-0.63); *p<0.00001*) and surgery (RR 0.44, 95% CI 0.34-0.58); *p<0.00001*). In comparison to surgery, RAI has lower success rate (RR 0.97, 95% CI 0.94-0.99); *p=0.0009*) (Figure 3)

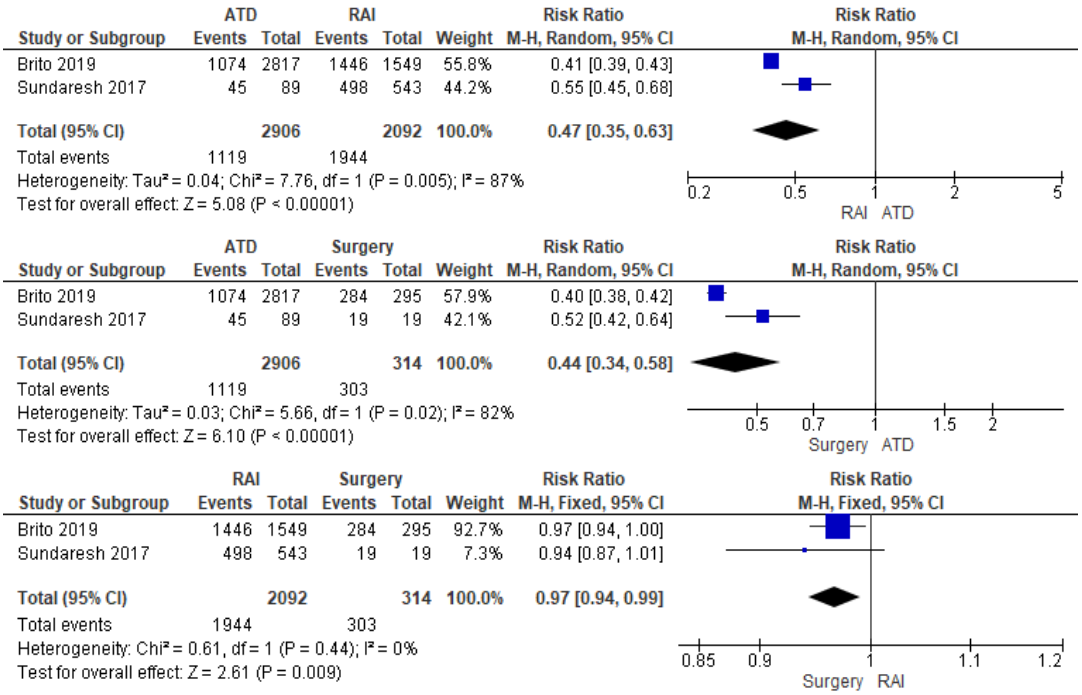

Figure 3. Success Rate in GD Patients

Hypothyroid

ATD has lower risk of hypothyroid compared to RAI (RR 0.08, 95% CI 0.02-0.27); *p<0.0001*) and surgery (RR 0.09, 95% CI 0.02 - 0.40); *p = 0.001*). RAI has higher risk of hypothyroid compared to surgery (RR 1.04, 95% CI 0.66 - 1.62); p = 0.87), but it is not statistically significant (Figure 4).

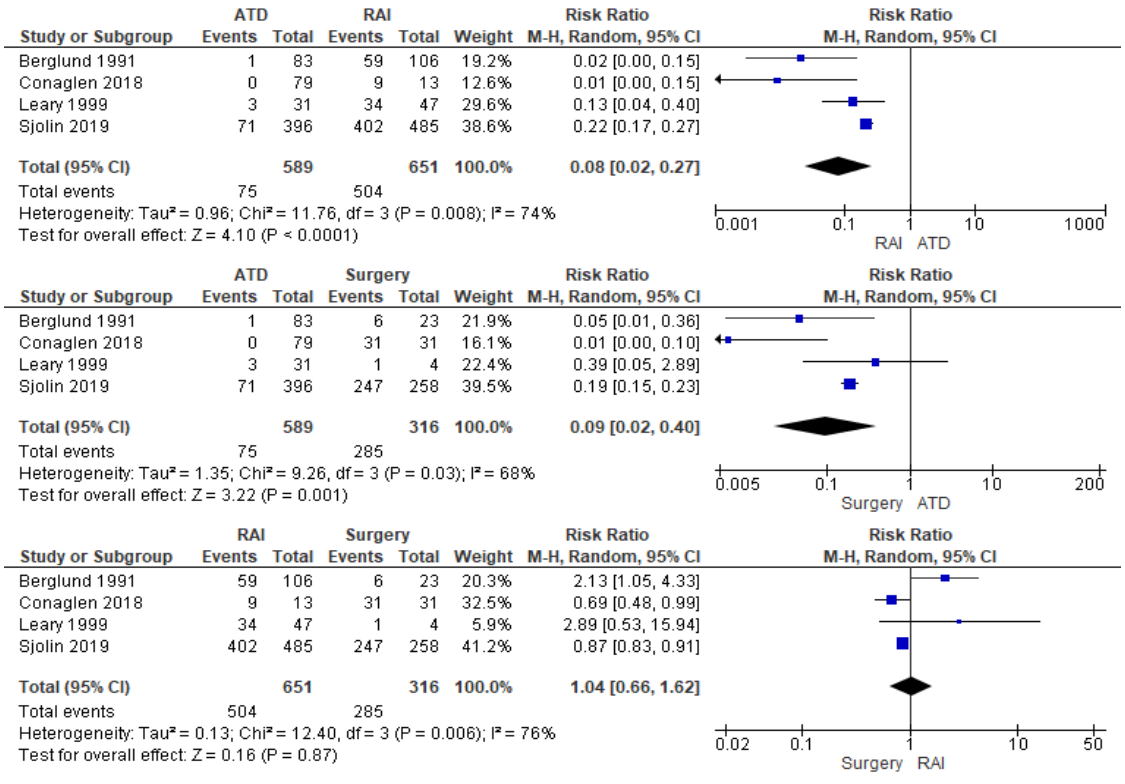

Figure 4. Risk Ratio of Hypothyroid in GD Patients

Publication bias

Due to the limited number of studies that amount to less than 10, there were no qualitative assessment for publication bias performed using the funnel plot analysis.

DISSCUSION

Total 7,104 participants were included with 56.4 % were given ATD, 36.4 % were given RAI and 7.2 % were done surgery. In our study, we found that ATDs have highest relapse rate compared to RAI and surgery, with the other remaining two modalities having no noticeable difference in relapse rate. This result is like previous meta-analysis.[13] Anti thyroid drugs work by decreasing thyroid hormone synthesis. Radioactive iodine and surgery work by reducing the amount of thyroid tissue.[18] A higher relapse rate is anticipated in the ATD group since the latter two modalities induce hypothyroidism in patients, often requiring lifelong thyroid hormone replacement. Anti-thyroid drugs offer the advantage of enabling the thyroid to return to normal functioning. We also analysed success rate of these three modalities and found that ATD has lower success rate compared to RAI and RAI has lower success rate compared to surgery. The 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism, suggest that patients who are newly diagnosed with GD to be medically treated with methimazole (MMI) as the preferred drug for 12-18 months,[18] but as per the 2019 guidelines from the National Institute for Health and Care Excellence (NICE), RAI stands as the primary treatment choice due to its superior balance of advantages and costs compared to surgery (total thyroidectomy) and its greater cost-effectiveness over ATD.[19]

In patients whereas patients prefer ATDs or in condition where RAI and surgery are contraindicated, long-term ATD treatment is recommended.[20] In order to lower failure rate of ATD, it is advised to be given minimum one year. Longer ATD breaks was also associated to treatment failure (90 days versus 120 days).[15] One study found that when ATD was given for more than 60 months, it has the highest remission rate.[20]

Dosage of RAI in this study range from 6.7 mCi to 16.5 mCi. Dosing was based on thyroid size and iodine uptake. In iodine-deficient countries, participant tend to have higher RAI uptake, resulting in lower doses of RAI. Jeong et al. stated that thyroid volume has significant effect on the outcome of RAI in GD patients, with optimal fixed RAI dose for Korean GD patients with $\geq$ 33 mL thyroid volume should be at least 15mCi.[21] Higher baseline 999m technicium (99m Tc) uptake, male gender, body mass index (BMI) and higher baseline free thyroxine (fT4) level predicted treatment failure following RAI.[22]

Patient and physician should have thorough discussion regarding adverse effect of each modality. Hypothyroid is the most common adverse effect of RAI and surgery. We found ATD has lower risk of hypothyroid compared to RAI and surgery. It should also be taken into consideration, while ATD have lower risk of hypothyroid, ATD have other adverse effects, such as rash in MMI and hepatic involvement in propylthiouracil (PTU).[13] For RAI's adverse effects, new or worsened Graves' ophthalmopathy may arise in 15-33% patients, especially for smokers and radiation thyroiditis in 1% of patients.[23,24] Complications of thyroidectomy is recurrent laryngeal nerve injury.[25]

One study assesses quality of life following treatment of GD. 123 patients with Graves' disease underwent treatment, with 64% receiving only ATD, 11% undergoing RAI, and 25% opting for total thyroidectomy. Additionally, there were 18 untreated patients newly diagnosed with GD. The primary considerations in treatment selection included impacts on daily activities, apprehensions regarding radioiodine usage, potential for depression and anxiety, and recommendations from doctors. Most patients expressed satisfaction with their treatment and its results. Quality of life was higher in treated patients compared to untreated patients.[12] This showed the three modalities for GD did not have different quality of life.

LIMITATIONS

Our study has several limitations, such as 1) our included studies are observational study, therefore it contributes to higher risk of bias. 2) Most of the studies did not include thyroid size

and laboratory results, such as Thyroid Stimulating Hormone (TSHS), thyroxine, and Thyroid-Stimulating Hormone Receptor Antibodies (TRAb), therefore effect of this factors could not be analysed in this meta-analysis.

CONCLUSION

ATD has the highest risk of relapse compared to RAI and surgery. RAI and surgery did not differ significantly in risk of relapse and hypothyroid. This should be taken into consideration in managing GD patients.

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