Original Article

The effect of retinoic acid in the ability of cold solid thyroid nodule to take up radioactive iodine: A preliminary study

ABSTRACT

One of the treatment options for benign thyroid nodules is radioactive iodine (RAI). However, this treatment is more effective for hot/warm solid thyroid nodules. Cold thyroid solid nodules are characterized by the lack of iodine uptake compared to normal thyroid tissue. Oral retinoic acid (RA) is a synthetic derivative of Vitamin A. The effect of RA on the uptake of RAI is still controversial. The aim of this study was to evaluate the effect of RA in the ability of a cold solid thyroid nodule to take up RAI. Individuals with a cold solid thyroid nodule based on ultrasonography and thyroid scintigraphy were included. Participants with liver dysfunction, smokers, and pregnant patients were excluded from the study. Each participant underwent thyroid uptake scintigraphy twice (pre- and post-RA consumption) using 35–37 MBq NaI-131. Participants consumed RA at a dose of 1 mg/kg body weight (BW) followed with 1.5 mg/kg BW. This study was approved by Dr. Hasan Sadikin General Hospital Ethic Committee. A total of 12 cold thyroid solid nodules were evaluated. The mean percentage of the nodule uptake value pre- and post-intervention was 1.11% and 0.62%, respectively (P = 0.004), while normal thyroid tissue uptake values pre- and post-intervention were 27.57% and 13.40%, respectively (P = 0.002). The percentage alteration of nodules and normal thyroid tissue uptake value were 42.4% and 51.5% lower, respectively (P = 0.354). This study showed that RA reduces the ability of cold solid thyroid nodule, as well as normal thyroid tissue, to take up RAI.

Keywords: Cold solid thyroid nodule, radioactive iodine therapy, retinoic acid

INTRODUCTION

Nodules in the thyroid gland, whether solitary or multiple, are very common in clinical practice. According to several epidemiologic studies, there is approximately 5% prevalence in women and 1% in men who live in iodine-sufficient parts of the world.[1,2] Radioactive iodine (RAI) (NaI-131) has been used for over 50 years to treat clinical or subclinical hyperthyroidism due to Graves' disease or autonomously functioning thyroid nodules (either toxic or nontoxic).[3] The sodium iodide (Na^+/I^-) symporter (NIS), which was identified in 1996, is responsible for active iodine trapping to the thyroid follicular cell.[4] Cold thyroid nodules (CTNs) are characterized as nodules with less iodide uptake than normal thyroid tissue.[5] NIS expression in cold nodules is similar to nonnodular tissue due to TSH. Hot nodules have about 1.5 fold NIS expression compared to CTNs.[6,7]

Oral retinoic acid (RA) is a synthetic derivative of Vitamin A. It is an important regulator of a diverse spectrum of physiological processes, including cell proliferation, differentiation, morphogenesis, angiogenesis, and apoptosis.[8] RA can induce several re-differentiating effects such as induction of 5'-deiodinase (D1)[9,10] and increased

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expression of NIS mRNA.[11] In 2009, Handkiewicz-Junak *et al.* showed that RA increased RAI uptake in thyroid tissue in 17% of the 53 epithelial cell thyroid carcinoma patients studied, whose previous posttherapeutic I-131 scans were negative.[12] However, Schmutzler *et al.* showed that RA suppresses NIS expressions in normal thyroid tissue.[11]

The aim of this study is to evaluate the effect of RA to the uptake value of RAI in cold solid thyroid nodule.

MATERIALS AND METHODS

Subject

Between September 2017 and November 2017, a total of 10 patients were included in this study. Two participants were dropped off due to side effects of RA. Patients' characteristics are summarized in Table 1.

Inclusion criteria

Individuals with solid thyroid nodule based on ultrasonographic examination were evaluated for the thyroid nodule characteristics. Individuals with cold nodule were included in this study.

Exclusion criteria

Individuals with liver dysfunction, smokers, and pregnancy patients were excluded from this study.

Thyroid nodule characteristic determination

To determine the characteristic of the thyroid nodule, each participant underwent thyroid scintigraphy. A 1 mCi (37 MBq) of NaI-131 was administered orally, and 24 h later, the thyroid scintigraphy was performed.

Retinoic acid administration

A 1 mg/kg body weight (BW) of RA was taken by the participants for 2 weeks, followed by a 1.5 mg/kg BW for 4 weeks. Liver function test was performed before consuming RA and also 2 and 6 weeks after consuming.

Table 1: Patient characteristics

Characteristics	Total (%)
Patients	
Included	8 (80)
Excluded	2 (20)
Sex	
Male	0
Female	10 (100)
Nodules	
Single	6 (75)
Multi	2 (25)

Thyroid uptake calculation

The baseline uptake imaging values of the thyroid gland and nodule were collected before consuming RA. The imaging was performed at 24 h after administration of 1 mCi (37 MBq) of NaI-131. And 6 weeks after consuming RA, another uptake was repeated.

The uptake was calculated using the following formula:[13]

$$uptake = \frac{P_{\text{thyroid}} - P_{background}}{\text{Precount} - \text{postcount}}$$

where

- P_{thyroid}: decay-corrected total thyroid counts
- $P_{\text{background}}$: decay-corrected background counts
- Precount: decay-corrected counts of the preinjection syringe image
- Postcount: decay-corrected counts of the postinjection syringe image.

Decay correction is calculated by multiplying the image counts by the factor as follows:

$$\exp = (-0.693t)/T_{1/2}$$

where

t: the time that elapses between preparation of the radiopharmaceutical and image acquisition

$T_{1/2}$: half-life time of the tracer

A standard syringe was used to determine the exact t value.

Statistical analysis

A Wilcoxon test was used to analyze sample distribution. Unpaired t-test was used to analyze the significance of the alteration in the uptake value of the nodules and normal thyroid tissues. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 12 cold solid thyroid nodules from eight participants were evaluated. The mean percentage values of the nodule uptake pre- and post-intervention were 1.11% and 0.62% with a median of 0.65% and 0.32%, respectively ($P = 0.004$). The mean percentage uptake value of the normal thyroid tissue was 27.57% in preinterventional evaluation and 13.40% in postinterventional evaluation with a median of 28.42% and 14.45%, respectively ($P = 0.002$) [Figure 1].

The mean alteration percentage uptake of the nodules and the normal thyroid tissues were 42.4% and 51.5% with a median of 35.4% and 50.8%, respectively,

($P = 0.354$). The comparison of the uptake values pre- and post-intervention is shown in Table 2.

DISCUSSION

Thyroid nodules can be detected in <5% of individuals screened by cervical palpation, but autopsy data have shown a 50% prevalence of nodular lesions in clinically normal thyroid glands.[1,2,14] According to a recent study (1999–2002), the use of ultrasonography by endocrinologists in the management of thyroid disease is increasing.[15-18] That trend makes the unexpected detection of nonpalpable thyroid nodules <10–15 mm in diameter more frequent in clinical practice.[19] Most of these nodules are benign, at most only 5% were found to be malignant.[20] The first step in the management of a patient with nodular thyroid disease is to exclude the presence of malignancy. There are several approaches that can be applied to benign thyroid nodules such as surgery, iodine supplementation, levothyroxine, RAI (NaI-131), percutaneous ethanol injection, and percutaneous laser ablation.[21]

RAI has been used for over 50 years to treat clinical or subclinical hyperthyroidism due to Graves' disease or autonomously functioning thyroid nodules (either toxic or nontoxic).[3] The effectiveness of RAI in reducing the size of the thyroid gland is widely recognized.[22,23] Uptake of RAI may be reduced in patients with multinodular goiters, especially the nontoxic forms, so in these cases, higher doses of RAI should be given.[21] The risk of hypothyroidism is approximately 10% after 5 years and unrelated to RAI dose.[24]

Table 2: Comparison of the uptake values pre- and post-intervention

Uptake value (%)	Nodules ($n=12$)	Normal thyroid tissues ($n=12$)	*P*
Preintervention			
Mean (SD)	1.11 (1.15)	27.57 (6.19)	
Median	0.65 (0.03-4.17)	28.42 (15.79-33.89)	
Postintervention			
Mean (SD)	0.62 (0.80)	13.50 (4.35)	
Median	0.32 (0.03-2.88)	14.45 (3.16-16.99)	
P	0.004*	0.002*	
Percentage alteration of the uptake value			
Mean (SD)	42.4 (29.8)	51.5 (15.0)	0.354**
Median	35.4 (7.7-90.8)	50.8 (23.9-83.7)	

*Wilcoxon test; **Unpaired *t*-test. SD: Standard deviation

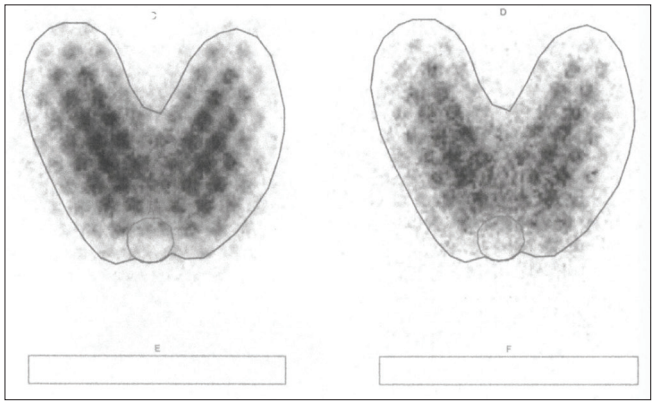

Figure 1: Comparison of the normal thyroid tissue and cold thyroid nodule to take up NaI-131 pre- and post-intervention

The NIS, which was identified in 1996, is responsible for active iodine trapping to the thyroid follicular cell.[4] High level of NIS in benign thyroid nodule may be taken as one of the indicators of the success of RAI therapy in decreasing nodular size. The highest NIS expression is in hot nodules, followed by warm nodules and then cold nodules. In cold nodules, NIS expression is similar to the surrounding nonnodular tissue.[7]

RA is a biologically active metabolite of Vitamin A. It is essential for morphogenesis, differentiation, and homeostasis.[25,26] It is an effective therapeutic and chemopreventive agent for treating several cancers.[27-29] RA regulates thyroid-specific differentiation markers, such as type I D1, thyroperoxidase, and NIS.[30] In 1997, Schmutzler *et al*. showed that RA suppresses the expression of NIS in the normal thyroid cell line FRTL-5.[11]

This study showed a mean of 42.4% decrease in the capability of the nodule to take up RAI after administration of RA and also 51.5% decrease in the normal thyroid tissue.

Nygaard *et al*. found that hypothyroidism occurred in 6%–20% ($P < 0.005$) of 130 multinodular toxic goiter patients after a median of 42 months (range: 3–60 months) and within 5 years of treatment, the hypothyroidism frequency was 14%,[23] while Adamali *et al*. found that in toxic nodular goiter group, hypothyroidism occurred in 22.7% of the patients ($P < 0.001$).[31]

From this study, it was observed that the RAI uptake in the surrounding normal thyroid tissue was decreased more than the uptake in the nodule. It may be postulated that the use of RA will be useful in the RAI therapy for functional nodule in reducing the incidence of hypothyroidism. A further study with larger population with functional nodule is required to confirm the result of this study.

CONCLUSION

This study showed that RA reduces the ability of cold solid thyroid nodule, as well as normal thyroid tissue, to take up RAI.

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Conflicts of interest

There are no conflicts of interest.

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