The effect of lithium on radioiodine thyroid tissue ablation

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► ***Short report***

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ABSTRACT

Background: Pretreatment with lithium in thyroid cancer patients before radioiodine therapy (RIT) has been suggested to improve the results of therapy in terms of higher radiation to thyroid tissue and limiting extra-thyroid irradiation. ***Materials and Methods:*** The beta and gamma radiation to the thyroid gland and lungs in 8 female New Zealand rabbits weighing 2.7 to 3.6 kg were simulated employing GATE Monte Carlo code. The study design was before-after and crossover; rabbits were orally treated with 165 to 288 µCi ^{131}I with or without pretreatment with 60 mg per day lithium. SPECT/CT imaging was done 20 to 24 hours after RIT providing the distribution and attenuation maps for simulation. The S-values were calculated and compared between the rabbits prepared with and without lithium before RIT by analysis of covariance. ***Results:*** For beta radiation, the thyroid to lung S-value ratios (TLR) was 10.5 ± 1.6 with lithium pretreatment and 15.9 ± 12.5 without it. For gamma rays, TLR was 4.8 ± 1.8 vs. 6.7 ± 3.1 in rabbits with and without lithium pretreatment. The values of TLR were higher without lithium pretreatment but statistically insignificant. ***Conclusion:*** Lithium demonstrated no improvement in radioiodine uptake in thyroid tissue. Pretreatment of differentiated thyroid cancer patients with lithium before RIT, which is backed by old literature, should be reconsidered.

Keywords: *Monte Carlo simulation, lithium, ^{131}I, specific dosimetry.*

INTRODUCTION

RIT reduces the risk of future tumor recurrence and validates the thyroglobulin measurements for follow-up with a few side effects including xerostomia, xerophthalmia, and infertility (1-3). To minimize side effects, thyroid iodine uptake should be optimized. Administration of lithium has been suggested for this purpose. Lithium restrains thyroid hormone release (4) and increases iodine trapping within the thyroid follicular and differentiated thyroid cancer cells (5). Consequently, the effect of RIT could be enhanced and the possibility of side effects would be reduced. Could the RIT be improved by lithium, the radioiodine dose for RIT may be lowered. In contrast to remarkable research (6-9) and recommendations provided by American Thyroid Association (10), very few centers employ this medication. To verify the effect of Lithium on RIT, we performed dosimetry of radioiodine in rabbit with and without lithium administration. This is the first dosimetry study to assess the effect of lithium on RIT.

MATERIALS AND METHODS

The study was conducted on 8 New Zealand female rabbits aged about 1 year and weighed between 2.7 to 3.6 kg. The rabbits were provided by Razi Vaccine and Serum Research Instituteand were kept for the study period in the animal lab of faculty of pharmacy (Tehran University of Medical Sciences, Tehran, Iran). Rabbits were allocated into group A (n= 3) and group B (n=5). The treatment flowchart is presented in figure 1.

The rabbits were imaged by a dual-head SPECT/CT (Symbia T1, Siemens, Germany) 20 to 24 hours after radioiodine administration. The following specifications were used: 30-second projections were collected at 4° in the step-and-shoot mode and the matrix sizes were 256*256. The distribution map and the attenuation map were extracted from the DICOM images of SPECT and CT, respectively. Interested organs were segmented using ITK-SNAP (version 3.2.0). For internal dosimetry, simulation with GATE Monte Carlo (6.0.0) was employed generating dose maps. Using MIRD [11] formalism S-values were allocated to each organ in MATLAB (2009).

The S-values were calculated for beta particle (mean energy of 202 Kev) and gamma rays, and the TLR was compared between rabbits pretreated with or without lithium. Study protocol was approved by Tehran University of Medical Sciences' ethics committee (IR.TUMS.SPH.REC.1395.761- 10 Oct 2016). For analyses, IBM SPSS (version 25) was employed; paired t-test and general linear models (both repeated measurement and univariate) were employed.

Figure 1. Visual depiction of the method of the study. The rabbits were allocated into 2 groups and totally 8 comparisons were done. Radioiodine treatment dose was 165- 288 µCi ^{131}I. lithium dose was 60 mg per day (2×30mg) 2 weeks prior to radioiodine treatment. The lithium and the iodine were administrated by gavage using oral feeding needles.

RESULTS

TLR for the S-value of beta and gamma radiations are presented in table 1. The TLR with and without lithium are 10.5 ± 1.6 vs. 15.9 ± 12.5 for beta; and 4.8 ± 1.8 vs 6.7 ± 3.1 for gamma rays (figure 2). The difference is not statistically significant (p=0.3 for beta and 0.1 for gamma). The dosimetry parameters of groups are tabulated in table 2. There is no interaction effect for the order of lithium administration and RIT; TLR was insignificantly higher in the rabbits without lithium pretreatment compared to those received lithium pretreatment (figure 2).

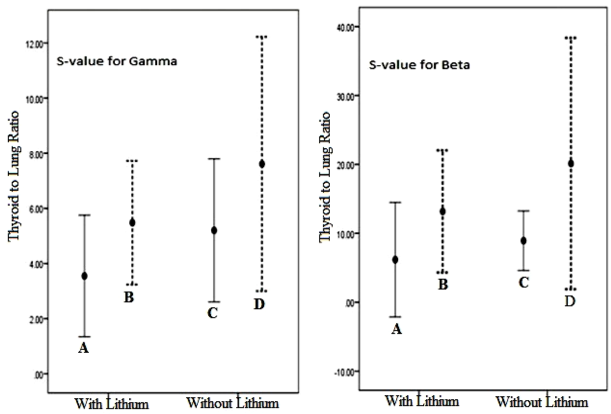

Figure 2. The thyroid to lung ratio (TLR) for beta and gamma S-values. A and B represent TLR values of rabbits receiving lithium in their first and second imaging episode, respectively. C and D represent values of rabbits which did not receive lithium and were in their second or first imaging episode, respectively.

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Table 1. Thyroid to lung S-value ratios for beta and gamma radiation. Paired t-test and repeated measures general linear model analyses were employed. No statistical difference was detected.

Subject	Sequence	Lithium treatment	S-value (thyroid/lung ratios for gamma)	S-value (thyroid/lung ratios for beta)
1	Lithium-first	With	3.44136	5.21103
1	Lithium-first	Without	6.32118	10.72026
2	Lithium-second	Without	5.45588	13.51816
2	Lithium-second	With	4.25204	7.24471
3	Lithium-first	With	4.48447	9.90529
3	Lithium-first	Without	5.03064	8.81029
4	Lithium-second	Without	4.00905	7.23919
4	Lithium-second	With	5.70649	13.6657
5	Lithium-first	With	2.7208	3.4259
5	Lithium-first	Without	4.25204	7.24471
6	Lithium-second	Without	12.00332	36.16323
6	Lithium-second	With	3.08659	4.87959
7	Lithium-second	Without	5.3509	7.89921
7	Lithium-second	With	7.2413	18.49555
8	Lithium-second	Without	11.24277	35.79913
8	Lithium-second	With	7.12014	21.60000

Table 2. Quantitative specification for each subgroup; analysis of covariance with general linear model design indicated no statistically significant deference.

Lithium phase		S-value of thyroid to lung ratio (With lithium, gamma radiation)	S-value of thyroid to lung ratio (Without lithium, gamma radiation)	S-value of thyroid to lung ratio (With lithium, beta particle)	S-value of thyroid to lung ratio (Without lithium, beta particle)
First lithium intake (A group)	Number of rabbits	3	3	3	3
	Mean ± SD	3.5489 ± .88674	5.2013 ± 1.04507	6.1807 ± 3.34678	8.9251 ± 1.74062
Second lithium intake (B group)	Number of rabbits	5	5	5	5
	Mean ± SD	5.4813 ± 1.80830	7.6124 ± 3.71513	13.1771 ± 7.13290	20.1238 ± 14.68049

DISCUSSION

Lithium may increase the iodine trapping within the thyroid gland [12]. The more the iodine in the thyroid tissue is accumulated, the better the outcome would be in term of higher radiation to the target organ (i.e. thyroid gland) and low radiation elsewhere. Conversely, it has been documented that lithium reduces thyroid hormone production by reducing follicular cell colloid pinocytosis [13] which consequently affect iodine internalization and organification [14]. This concept is against the main theory to pretreat patients with lithium before RIT. The results of the current study indicated that thyroid iodine absorbed dose was higher when the radioiodine was administered without pretreatment with lithium, albeit insignificantly.

Our study is limited because we performed the dosimetry once between 20 to 24 hours after RIT; however, the iodine is absorbed mostly in the first 24 hours after administration. Furthermore, the power of the study was not reasonably acceptable secondary to low sample size. We conducted our study in animal models because the pretreatment with lithium in thyroid cancer patients had ethical concerns for confronting patients with side effects without remarkable privilege. The thyroid function in rabbit and human are essentially similar.

The internal dosimetry for rabbits was done similar to our previous studies in human and

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phantom [15-18]. GATE code is a dedicated code for simulation of the events after administration of nuclear medicine diagnostic and therapeutic radiopharmaceuticals [19]. The beta and gamma irradiation to the thyroid and the lung, an organ where radiation is unwanted and should be limited, were simulated.

To sum up the current before-after crossover study does not support pretreatment of the thyroid cancer patients with lithium before RIT.

Compliance with Ethical Standards

All applicable institutional and/or national guidelines for the care and use of animals were followed.

Funding

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Authorship

Shima Yavari: prepared the animals for the study, performed the simulation, imaged the animals, administrated drugs (lithium, radioiodine, anesthetic).

Parham Geramifar: supervised the protocol of acquisitions (imaging), and simulation.

Maryam Fallahpoor: co-conceived verification and validation of the simulation.

Alipasha Meysamie: performed the data analysis

Vahid Changizi: co-conceived the performing of the study and participated in data interpretation

Mahdi Gholami: care-giving the animals during the research.

Saeed Farzanehfar: co-conceived the clinical phases.

Mehrshad Abbasi: supervised the clinical phases analysis, adjusting dosage, evaluating the protocol accuracy, imaging analysis and interpretation, and drafted the paper.

Conflicts of interest*: *Declared none.

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