Original article

The minimum amount of fluids needed to achieve the fastest time to reach permissible level for release in well-differentiated thyroid patients undergoing high-dose I-131 therapy

ABSTRACT

Radioiodine (131I) therapy is the mainstay of treatment for patients who had undergone total thyroidectomy for well differentiated thyroid carcinoma. Increased fluid intake has always been encouraged to minimize the risk of non-target organ exposure to I-131radiation. This study aimed to determine the minimum amount of fluids needed for patients to have the fastest time to achieve permissible level for release after high dose I-131therapy. Methodology: All the patients who were treated with high dose I-131from 18th January 2016 till 31st December 2016 in Hospital Pulau Pinang, Malaysia were recruited. The data from 126 patients on thyroxine hormone withdrawal (THW) group and 18 patients on recombinant human thyroid stimulating hormone (rhTSH) group were analysed. There is no change in patient management in terms of preparation, dose or post therapy whole-body scan. Fluid intake of patients were monitored strictly and whole-body retention of I-131are measured using ionizing chamber meter immediately after ingestion of I-131then at 1 hour, 24 hours, 48 hours, 72 hours and 96 hours. Results: The median time to achieve permissible release limit (50 μSV/hr at 1 meter) was 21.6 hours and 22.1 hours post-ingestion of I-131in the THW and rhTSH group respectively. The minimum amount of fluid needed to reach permissible release limit in the fastest time was 2,103 ml and 2,148ml for the THW and TSH respectively. Conclusion: Clinicians would be able to evidently advise their patient on the amount of fluid to consume and utilize their isolation wards faster to treat more patients.

Keywords: Differentiated thyroid cancer, fluid, I-131, whole body retention

INTRODUCTION

Radioiodine (I-131) therapy for well-differentiated thyroid carcinoma has been used since 1940's, and the therapy has shown tremendous success in curing patients. Most patients who had undergone total thyroidectomy would undergo I-131 remnant ablation therapy depending on their risk stratification. Some patients would need further I-131 therapies to eliminate any functioning residual disease. Studies have shown that thyroid cancer patients treated with I-131 have increased the risk of second primary malignancy compared to thyroid cancer patients not treated I-131.[1,2] Secondary malignancies such as myeloid neoplasm, salivary gland cancers, and kidney cancers have been found to be more prevalent in this group of patients.[3,4] Nevertheless, the complications of therapeutic I-131 are rare and is limited by observing the 2 Gy (200 rad) limit of I-131 in the blood as a measure of toxicity to the bone marrow as well as ensuring the whole body retention is <4.4GBq (<120 mCi).[5] To

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minimize the radiation exposure to the nontarget organs, increased fluid intake has always been encouraged in patients undergoing I-131 therapy. There is, without doubt, increased fluid intake promotes urinary excretion of I-131 despite various confounding factors that influence the whole-body retention of I-131 in patients' bodies such as the activity administered, the thyroid-stimulating hormone (TSH)-stimulating protocol used and patient's renal function. Increased fluid intake has always been advocated to promote urinary excretion of I-131, but there has not been any study in our knowledge that evidently quantified the amount of fluid that is actually needed to facilitate faster washout of I-131 from the body. This study was proposed to address this conundrum and thus enable clinicians to evidently advise patients on the amount of fluid to consume when undergoing I-131 therapy.

METHODOLOGY

Design of study and sampling

This demographic universal sampling study was conducted in the Department of Nuclear Medicine, Hospital Pulau Pinang from January 18, 2016, to December 31, 2016. There were 181 differentiated thyroid cancer patients admitted to the isolation rooms for I-131 therapy during this period. The number of patients admitted to the isolation rooms per week is limited as there are only 5 isolation rooms available. The inclusion criteria for the study were the patients with differentiated thyroid cancer regardless of age, gender, stage of disease, number of previous treatments and renal function. Only 144 patients were recruited into the study whereas the remaining 37 patients with incomplete data are excluded from the study. This study was approved by the Malaysian Medical Research and Ethical Committee (NMRR-15-2175-28659). There is no change in patient management in terms of preparation, dose or posttherapy whole-body scan in this study. Informed consent was taken from the patients before the recruitment.

Patient preparation, protocols for thyroid-stimulating hormone stimulation and I-131 administration

Every patient had been instructed to follow a low-iodine diet for at least 2 weeks before the therapy and on thyroxine hormone withdrawal (THW) for at least a month unless they are for recombinant human TSH (rhTSH) stimulation. The five isolation rooms used are fully-air-conditioned and fitted with lead-proofed walls, individualized toilets and bathrooms with commissioned sewage-decay tanks system. For safety purposes, patients are discouraged from performing vigorous exercises in the wards. In our center, all patients are warded on Mondays and occasionally on Tuesdays. For the THW group, the patients are administered I-131 on the same day that they are warded. On the contrary, patients on rhTSH protocol are administered the first dose of rhTSH on day-1 they are warded (Monday) and the second dose the following day. I-131 is only administered on day-3 (Wednesday). Patients due for I-131 therapy are required to fast at least 2 h before therapy and followed by 1 h fast after therapy. I-131 therapy is given in liquid form based on the attending doctors' prescription ranging from 3.0GBq to 7.4GBq (80 mCi-200 mCi). Posttherapy scans are done routinely at 72 h post-I-131 therapy in our center. All patients are allowed home once their whole body retention of I-131 reaches the permissible level for release.

Study tools

All patients are given cups with measurable volumes, and they are required to document the amount of fluid (regardless if it is water, juices milk, etc.), they drink each time on a given form. The ward nurses were also instructed to keep a strict input (fluids only) chart for each patient, and they were tasked to calculate the total daily amount each patient consumes. No specific advice on the amount of fluid is given to patient other than the general advice for them to consume lots of fluids. The physicist would be required to monitor the radiation emitted (using digital ionizing chamber [IC]-Victoreen 452 P Ion Chamber Survey Meter) by patient 1 h after ingestion of I-131 (90% uptake is considered to have occurred 1 h after ingestion) then daily (at 24, 48, 72, 96 h postingestion) until the patients is discharged from ward or achieve permissible limit for release (<50 μSv/h at 1 meter). The measurement using digital IC is performed by directing the probe in the direction of the patient at a fixed distance of 1 meter. Only two patients in the rhTSH group were monitored up more than 72 h as they failed to reach permissible level by the day-3 (Friday) post-I-131 ingestion. All the demographic data including the age, gender, race, weight, height, thyroid cancer histology, thyroglobulin and antithyroglobulin levels, blood tests (including renal profile and thyroid function test) are documented. All thyroglobulin (Tg) samples were analyzed at Institute of Medical Research IMR in Kuala Lumpur, a government-gazetted institution using enzyme-linked immunosorbent assay (Microwell Method). Only a single institution was used for the analysis to standardize the results. The Tg levels are then categorized to those <10 ng/mL and those ≥ 10 ng/mL.[6] The test analyses are compliant to the CRM-457 international standard but are limited by the inherent functional sensitivity between 1 ng/mL (minimum) and 300 ng/mL (maximum).

Length of hospitalization and hospitalization time required

The hospitalization time required (HTR) in our center is shorter than the length of hospitalization (LoH). The HTR is defined as the time necessary to quarantine patients

until their whole body retention of radioactivity reaches permissible threshold for release.[7] In our center, patients are admitted individually to the 5 quarantine rooms at 12.00 pm on Monday and are given I-131 therapies based on their protocols. For those on THW protocol, I-131 is given on the same day at 2.00 pm whereas patients on rhTSH protocol are given intramuscular rhTSH (Thyrogen®) 0.9 mg daily for first 2 days (Monday and Tuesday) at 2.00 pm. I-131 is only given on day 3 at 2.00 pm. The whole body retention of I-131 is measured from time I-131 is administered till permissible limit for release is achieved. Posttherapy whole body scans are performed on day 3 or day 4 postingestion of I-131 but the outcome of the scans were not included in the study.

Statistical analysis

The data analysis was performed using IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA. Nonparametric tests such as Mann–Whitney test (comparison of two independent groups) and comparison of proportions for categorical variables were performed using Chi-square test and Fisher' Exact test. $p < 0.05$ was taken as the level of statistical significance.

RESULTS

The data from 144 patients warded in the Department of Nuclear Medicine were collected and analyzed [Table 1]. These patients were categorized into two main groups for the analysis – the THW group and the rhTSH group. There were 111 women and 33 men with median age of 52 years old. Majority (n = 89, 86.1%) of the study patients were younger than 45 years old. Due to the skewed distribution of the collected data, median whole-body retention of I-131 as well as the median cumulative fluid intake was used in the

Table 1: Characteristics of study patients in relation to whole-body retention of I-131

Characteristic	rhTSH group (n=18)	THW group (n=126)	Total (%)	Median	Range	p
Gender						
Male	13	28	33 (22.9)			0.562**
Female	5	98	111 (77.1)			
Age (years)						
<45	2	53	55 (38.2)	52	19-81	
≥45	16	73	89 (61.8)			
TSH						
Stimulated (≥30 miU/L)	18	119	137 (95.1)			0.596**
Not stimulated (<30 miU/L)	0	7	7 (4.9)			
TG levels (ng/mL) regardless of anti-TG status						
<10	0	42	42 (29.2)		<1->300	0.004**
≥10	18	84	102 (70.8)			
Histopathological type						
Papillary thyroid cancer	6	95	103 (71.5)			
Follicular thyroid cancer	10	26	32 (22.9)			
Poorly differentiated thyroid cancer	3	0	4 (2.8)			
Mixed papillary and anaplastic thyroid cancer	1	0	1 (0.7)			
Mixed papillary and follicular thyroid cancer	1	2	3 (2.1)			
CKD stage						
Normal	3	12	15 (10.4)			0.156**
I (>90 mL/min)	1	29	30 (20.8)			
II (>60 mL/min)	9	55	64 (44.4)			
III (>30 mL/min)	4	29	33 (22.9)			
IV (>15 mL/min)	1	1	2 (1.4)			
V (ESRF)	0	0	0			
BMI						
Underweight (<18.5)	0	6	6 (4.2)	25.8	16.4-43.1	0.093**
Normal (18.8-24.9)	9	52	61 (42.4)			
Preobesity (25-29.9)	9	42	51 (35.4)			
Obesity (≥30)	0	26	26 (18.1)			
Dose (GBq)						
<5.6	1	71	72 (50)	140.3	80-200	0.001*
≥5.6	17	55	72 (50)			

*Chi-square test; **Fisher's exact test. rhTSH: Recombinant human thyroid stimulating hormone; THW: Thyroxine hormone withdrawal; TG: Thyroglobulin; CKD: Chronic kidney disease; ESRF: End stage renal failure; BMI: Body mass index

analysis. There was no significant association between the protocol groups (THW/rhTSH) and the median whole-body retention of I-131 ($p = 0.341$).

Fifty-six patients (38.9%) were received I-131 therapy for the first time whereas 88 patients (61.1%) had I-131 therapy more than once. The majority of the patients ($n = 102$, 70.8%) received I-131 dose >3.7 GBq (4.4 GBq, 5.6 GBq or 7.4 GBq). The remaining 42 patients (29.2%) received dose ≤3.7 GBqmCi.

When the renal function for all the patients was reclassified into those with estimated glomerular filtration rate (based Cockcroft-Gault equation) of <60 ml/min (CKD III) and those with ≥60 ml/min, no statistical association was noted (Fisher exact test, $p = 0.775$).

There were 20 patients (15.9%) in the THW group with positive anti-Tg and 4 patients (22.2%) in the rhTSH group with positive anti-Tg. As we consider the Tg levels for patients with positive anti-Tg as unreliable, we omit these patients from the tumor burden analysis based on Tg calculations. The results are as shown in Table 2. For the Tg levels analyzed in this study, the lowest measurable limit was 1 ng/mL, and the highest measureable limit was 300 ng/mL.

The median whole body retention for patients on THW and rhTSH protocols 24 h postingestion of I-131 was the similar at 45 μSv/hr at 1 meter. Based on the current permissible dose level for release of 50 μSv/hr at 1 meter, majority of our patients (88.2%, $n = 127$) in the study would be able to be discharged by 24 h postingestion of I-131 and by 48 h, almost all (99.3%, $n = 143$) can be discharged. Figures 1 and 2 show above were extrapolated exponentially using the data collected. The THW group were shown to have lower whole body retention of I-131 (21.6 h; the value derived from the extrapolated exponential graph [$y = 13.532e^{-0.046x}$]) versus the rhTSH group (22.2 h; the value derived from the extrapolated exponential graph [$y = 19.338e^{-0.061x}$]) [Figure 1]. However, the results were not statistically significant based on Mann–Whitney test ($p = 0.341$). The median fluid intake to achieve permissible limit for release in the fastest time in the THW group was much lower compared to that of the rhTSH group (2,103 mL/day vs. 2,148 mL/day) [Figure 2]. The amount of fluid calculated were extrapolated from the exponential graphs in Figure 2 ($y = 9.3955e^{-3E-04x}$ for THW group and $y = 14.958e^{-3E-04x}$ for rhTSH group).

Table 2: Tumor burden suggested by thyroglobulin levels according to the protocol groups

Protocol group	Number of patients	TG		*P**
		<10 ng/mL	≥10 ng/mL	
THW	106	23 (22.5)	79 (77.5)	0.022
rhTSH	14	0	18 (100.0)	

*Chi-square test. rhTSH: Recombinant human thyroid stimulating hormone; THW: Thyroxine hormone withdrawal; TG: Thyroglobulin

DISCUSSION

Based on our literature search through the PubMed and to our knowledge, the quantification of fluids to facilitate the clearance of I-131 has not been studied. The American Thyroid Association recommended that sufficient fluid (3–4 L/day) should be consumed to encourage frequent urination and thus washout of I-131.[8] There is no doubt that consuming lots of fluids aids urinary excretion of I-131, but the conundrum is the amount of fluid to be consumed. Either ways, excessive or insufficient fluid consumption may lead to various problems. Although rare, excessive fluid intake may lead to electrolyte imbalances especially hyponatremia and also worsen the generalized edema which some patients on THW protocol may already be experiencing. On the other hand, insufficient fluid intake leads to longer retention of I-131 in the body and exposes various organs to higher radiation. Delayed clearance of I-131 would also mean longer period to achieve a permissible level for release; increasing HTR and LoH.

In patients undergoing chemotherapy, adequate hydration is essential to prevent therapy-related complications such as renal impairment. Similarly, patients undergoing I-131 therapy would need an adequate fluid intake to dilute and clear the retained I-131. Being a unique targeted radioactive therapy, I-131 is mainly excreted through the urinary route (>90%) and the rest through bowel, salivary, and sweat.[9] Nevertheless, body retention of I-131 doses varies according to the amount of functioning thyroid tissue present, and also the rate of renal and bowel excretion which is affected by the patients' behavior.[10] In patients

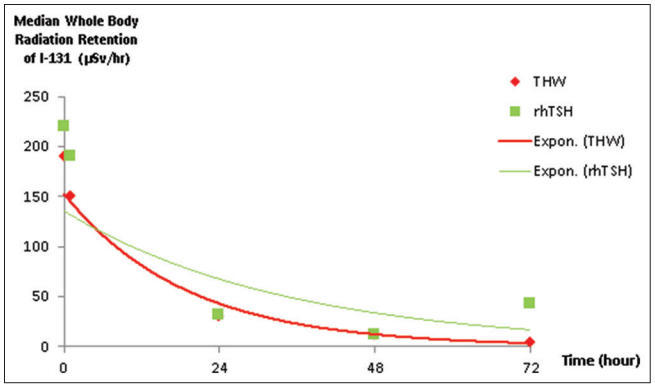

Figure 1: The median whole body retention of I-131 over time according to protocol

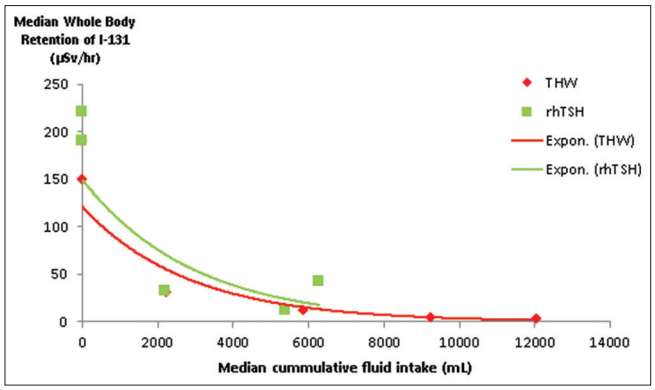

Figure 2: Median cumulative fluid intakes versus median whole body retention of I-131 according to protocol

with poor fluid intake, they will invariably experience slower I-131 washout from the body. Thus, early intervention in the form of advice and encouragement may be beneficial. In Malaysia, loss of I-131 through sweating may play a more significant role than expected. Haghighatafshar *et al*. showed sweating may help promote excretion of 131-I but in our center, the patients are not subjected to similar stress to elicit sweating.[11] The loss of I-131 via sweating due to humidity was not addressed in this study. However, the cool environment (approximately 297 K [24°C]) in the air-conditioned isolation rooms reduces sweating.

The measurement of I-131 retained in the body provides an estimate to the amount of radiation toxicity the patient receives. The assessment of I-131 retention in the body is difficult and variable with multiple confounding factors. Fortunately, Sisson *et al*. reported that the body retention of I-131 is not correlated to any index of health, thyroid hormone, or carcinoma status.[12] In our study, there were no statistical association between the protocol groups and gender, race, renal function as well as body mass index in relation to whole-body retention of I-131. The whole body retention of I-131 would have been best evaluated by using the combination of serial blood tests, evaluation of I-131 in the urine and IC survey meter. The evaluation of I-131 in the blood was not feasible due to the expected repeated I-131 exposure to the phlebotomist and also to the physicist testing the blood samples. Although it was feasible to collect the urine samples, the process would largely dependent on patients' willingness and ability in safely as well as meticulously collecting the urine samples. The possibility of contamination during collection and storage by patients is high and poses unnecessary exposure to the attending staff. The omission of the measurement of the quantity of urine excreted daily was done for similar reasons. The measurement of whole-body retention of radiation in this study was only performed using site-available digital IC survey meter which is a generally accepted tool for this purpose. Due to the limited available gamma cameras and time constraints, measurement of whole body retention based on quantification of I-131 uptake was not performed.

The permissible release dose-limit is variable from country to country. The Malaysian authorities have lowered the maximum dose-rate permissible for release at 1 meter from 66 μSv/hr to 50 μSv/hr in 2016. This regulation would theoretically lengthen the HTR and LoH for each patient, and consequently increases the cost of hospital stay. Nevertheless, this study demonstrated that with adequate fluid intake, most patients (88.2%, $n = 127$) have low levels of radiation ≤50 μSv/hr after 24 h postingestion of I-131 regardless of the protocol they are on. In fact, almost all (99.3%, $n = 143$) can be discharged by 48 h postingestion of I-131 if they had adequate fluid intake. In our center, patients in the THW group are warded approximately 12pm on the day 1 and ingest I-131 by 2pm. This group of patients would be permissible to leave the isolation wards by 2pm on day 2 (approximate HTR and LoH of 24 h and 26 h, respectively). In the past, the whole-body retention was only measured on day 3 (LoH of 50 h) in our center with the assumption most patients would have had achieved permissible release limits at that point in time. Hence if patients were to consume adequate fluids after ingestion of I-131, clinicians would be able to utilize the isolation rooms faster and subsequently able to treat more patients. Furthermore, hospitalization costs will decrease significantly.

It is known that patients on rhTSH protocol have a faster clearance of I-131 in the body leading but have enhanced residence time in the targeted remnant thyroid tissues.[13-15] The mean I-131 effective half-life in euthyroid patients treated with rhTSH is shorter by 31% compared to hypothyroid patients undergoing THW.[16] Logically, it was expected that those on rhTSH protocol in this study would need less time to achieve lower whole-body retention of I-131 and also need less fluid for the washout of I-131. On the contrary, despite statistically insignificant, this study showed that patients on THW protocol achieve lower retention faster with less fluid intake needed to achieve that permissible release limit. This could be attributed to the fact that rhTSH protocol is frequently used in our center for differentiated thyroid cancer patients with metastatic disease unable to tolerate THW protocol and those who previously had low levels of TSH despite on THW protocol.[17,18] These patients would invariably have bulkier disease (higher Tg levels) and falsely have "poorer" clearance compared to those on THW protocol. The majority of patients in the rhTSH group (85.7%, 12 out of 14 patients) in our study have significant

metastatic disease (either residual disease in thyroid, cervical nodes, lungs, or bone) and were given higher doses of I-131. Nevertheless, the data from this study need to be interpreted with caution due to the small sample size.

CONCLUSION

Based on the study, the minimum fluids required to achieve permissible level for release in the fastest time in patients undergoing high dose I-131 therapy regardless of protocol is 2,148 mL/day. The knowledge of the amount of fluid needed aids clinician to evidently advise their patient on the minimum amount of fluid to consume and enable them to plan the utilization of their isolation wards to treat more patients.

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Conflicts of interest

There are no conflicts of interest.

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