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Is High Dose Radioactive Iodine-131 More Effective Than Low Dose Iodine-131 In The Therapy Of Patients With Hyperthyroidism?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not high dose radioactive iodine-131 is more effective than low dose iodine-131 in the therapy of patients with hyperthyroidism.

STUDY DESIGN: The review included three primary English language studies that were peer reviewed articles published in 2003, 2010 and 2011.

DATA SOURCES: This paper evaluates three randomized control trials (one prospective randomized and two comparative randomized) looking at the effectiveness of high dose and low dose radioactive iodine-131 for the treatment of hyperthyroidism.

OUTCOMES MEASURED: Each study examined patients being treated with high or low dose radioactive iodine-131. The outcomes measured include 1) incidence of failed treatment that required further therapy 2) patients that maintained a euthyroid state 3) patients needing therapy for hypothyroidism caused by the radioactive therapy. The measurements were evaluated with laboratory values as well as a 5- point scoring system and clinical symptoms of hyperthyroidism and hypothyroidism. Statistical evaluation is based on p-values and NNT.

RESULTS: Three randomized controlled trials were included in this review. Results from *Leslie et al.* 2003, found that low dose regimen is as effective as high dose regimen. The conclusion and statistical analysis of *Pusuwan et al.* 2011, found that high dose regimen would be more effective than low dose regimen. Lastly, the *Thientunyakit et al.* 2010, study found that neither dose regimen was shown to be more effective in the treatment of hyperthyroidism.

CONCLUSION: All three of the randomized trials in this EBM review contradicted findings in the other. That being said, at this time there is no conclusive evidence to support whether high or low dose radioactive iodine regimen is more effective in the treatment of hyperthyroidism. There has to be continued research and development in this field of study to better determine a dose regimen that is effective in managing patients with this disease.

KEY WORDS: Iodine-131, Hyperthyroidism, Comparison, Treatment

INTRODUCTION

Radioactive iodine was introduced as a means for treatment of hyperthyroidism in 1941 by Hertz and Roberts in the United States.¹ Radioactive iodine treatment has since been widely accepted as the gold standard for treatment of hyperthyroidism for over 50 years and is preferred over surgery or anti-thyroid medications.¹ This form of therapy is primarily for patients that are in a hyperthyroid state and have medical complications associated with it or are symptomatic from this state. This form of treatment is relatively safe, simple and effective, but there still is a great deal of controversy surround the amount of radiation that the patient should receive to reach maximum efficacy.² The different theories for most effective dosing ranges from low dose verses high dose regimens. The dose regime is attained from calculated doses or fixed doses of iodine-131. With regards to low dose the treatment theory is to maintain a euthyroid state at least one year.^{1,2,3} High dose theory is to induce a state of hypothyroidism followed by hormone replacement maintenance. Calculations to determine the dose regimen takes into account gland size, presence of nodularity and results of a radioactive iodine uptake and scan.³ Another controversial theory is that of a fixed dose. This is when an institution uses a fixed dose method and treats everyone with the same dose no matter the severity of their hyperthyroidism. Another issue with deciding which method to use is that there is only about a 60% predictive rate for estimating euthyroidism in a patient receiving iodine-131 treatment.^{2,3} In the United States, the use of iodine-131 at a therapeutic level requires careful planning and patient education in regards to protecting the public from potentially harmful ionizing radiation that is released and excreted from the body.

Hyperthyroidism is a disease state characterized by excessive production of thyroid hormones T3 and T4 by the thyroid which causes an increase in metabolic activity of the body.

It is estimated that about 3% of the world's population is affected by hyperthyroidism.³ This can be measured with TSH and T3/T4 measurements and symptom profiles of patients.

Hyperthyroidism can be broken up into primary, secondary and tertiary forms. The classification of the disease state is determined by the anatomical location of where the hyperthyroid state originates. It is estimated that about 60-80% of primary hyperthyroidism is associated with Graves' disease.² Hyperthyroidism may be associated with any age, sex and race. However, it is most common in women over the age of 60.¹ Symptom profiles used to diagnose hyperthyroidism include fatigue, tremor, palpitations, diaphoresis, exophthalmos, increased appetite and weight loss. An increase of thyroid hormone can also exacerbate comorbidities especially cardiac in nature which can be fatal if left untreated.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not high dose radioactive iodine-131 is more effective than low dose iodine-131 in the therapy of patients with hyperthyroidism.

METHODS

Randomized control studies were selected on the basis of comparison of high verses low dose of radioactive iodine-131. The studies included subjects who presented with hyperthyroidism to the institution conducting the trial. The exclusion criteria included pregnant patients, patients that randomly converted to euthyroidism, patients lost to follow up, children less than 18 years old, patient refusal, physician refusal or patients previously treated with iodine-131.^{1,2,3} The outcomes measured in these studies included persistent/recurrent hyperthyroidism, sustained euthyroidism and advancement to hypothyroidism.^{1,2,3} Treatment

success was considered sustained euthyroidism or induced hypothyroidism. Under these criteria, there were three randomized controlled comparative trials that were identified and included in this evidence based review.

An extensive search utilizing PubMed and CINAHL was completed using the key words of “iodine-131”, “hyperthyroidism”, “comparison” and “treatment” to select relevant articles. All of the articles utilized in this review were published in peer reviewed journals and printed in English. The studies were also selected based on relevance and importance of the outcomes to the patient (POEMs). The included studies were RCTs that were published in 2003, 2010 and 2011 with participants that were diagnosed with hyperthyroidism and underwent radioactive iodine-131 therapy. Exclusion criteria included: pregnancy, patients who randomly converted to euthyroidism, patients lost to follow up, children less than 18 years of age, patients that had a prior treatment with radioactive iodine-131 and patient or physician refusal. The summary of the statistical data was reported as p-values and NNTs.

Table 1. Includes the demographics of the patients included in the RCTs.

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
<i>Pusuwan et al.</i> (2011)	Prospective RCT	145	41 +/- 14 years	Patients referred to the Division of Nuclear Medicine Faculty of Medicine Siriraj Hospital who had not yet received radioactive iodine treatment-naïve patients.	Patients younger than 18 years old. Pregnancy or lactating patients. Previously treated with iodine-131 or surgery. Patients refusing treatment. Patients lost to follow up.	5	High dose vs. Low dose iodine-131 therapy.

<i>Thientunyakit et al.</i> (2010)	Comparative evaluation RCT	144	41 +/- 14 years	All Hyperthyroid patients referred to the Nuclear Medicine Department, Songklanagarind University.	Patients that had previously been treated with radioactive iodine. Eleven were excluded due to loss of follow up. Five became euthyroid before treatment.	16	Calculated vs. Estimated high and low dose iodine-131 therapy.
<i>Leslie et al.</i> (2003)	Prospective RCT	88	41 +/- 14 years	All patients being referred to the Nuclear Medicine Department at St. Boniface General Hospital for first treatment of Grave's Disease hyperthyroidism.	Patient preference for same day therapy. Patients from remote locations. Patient or physician refusal. Patients that were treated with iodine-131 prior.	0	Low-adjusted dose vs. High-adjusted dose.

OUTCOMES MEASURED

The outcomes measured were patient-oriented evidence that matters (POEMS). To help measure subjective data, several clinical assessments were used to measure the outcome of the RCTs. *Thientunyakit et al.* 2010, managed this by evaluating a 5-point scoring system of clinical presentation for hyperthyroidism, symptomatic profile of fatigue, tremor, palpitations, diaphoresis, gland size or exophthalmos.³ Reversely a 5-point clinical scoring system for hypothyroidism post- treatment included swelling, bloating, constipation and cold sensation.³ Hypothyroidism and hyperthyroidism symptoms were then correlated with biochemical

laboratory measurements of TSH and T3/T4. *Leslie et al.* 2003, evaluated physical exam and clinical symptoms most notably gland size and ophthalmopathy, and correlated symptomatology with biochemical laboratory examination. *Pusuwan et al.* 2011, utilized a clinical evaluation of cardiac complications, glandular size and goiter, nausea and thyroiditis to monitor patients pre and post therapy.¹ These clinical evaluations were also compared and correlated with biochemical TSH and T3/T4 levels.

RESULTS

Three comparative RCTs were evaluated with patients undergoing treatment with radioactive iodine -131. The comparative evaluation was based on high dose iodine and low dose iodine. All studies utilized similar processes with slight variations in each study. The three studies have similar inclusion and exclusion criteria (see Table 1 above). All studies used nuclear medicine departments and certified physicians to conduct the therapy process.^{1,2,3} This provided maximum safety and accuracy when calculating or estimating treatment doses. Follow up was conducted by trained personnel to ensure patient safety.

Note that all of the studies that were evaluated contained dichotomous data. Statistical calculations used included numbers needed to treat (NNT) and p-values.

The study performed by *Leslie et al.* 2003, compared radioactive iodine-131 doses in the treatment of Graves' Disease. Patients were first stratified based on their radioactive iodine uptake at four hours and were then randomized into one of four groups (high-fixed, low-fixed, high-adjusted and low-adjusted). Only high and low-adjusted dose arms of the study were examined in this review. A total of 43 patients were examined (low-adjusted, n=22; high adjusted n=21) and completed the study.² All of the patients in the stratified group received the

same therapy. The low-adjusted group received a dose of 2.96 MBq (megabequerel) (80 μ Ci(microcurie))/g of thyroid tissue adjusted for 24-hour uptake percentage.² The high-adjusted group received 4.44 MBq (120 μ Ci)/g of thyroid tissue adjusted for 24-hour uptake percentage.² Most patients received antithyroid medication before treatment. This medication was discontinued 5 days prior to therapy. Systemic beta-blockers were not discontinued during therapy for cardiac protection.² Patients were then examined to evaluate if they failed therapy and remained hyperthyroid or if therapy was successful and they converted to hypothyroid or remained euthyroid. Evaluation consisted of clinical evaluation of symptoms with physical exam and biochemical laboratory evaluation.² The study also has a result of a NNT of 17.

Table 2. Created from *Leslie et al.* 2003 Table 3.

P-value= 0.05	Low-adjusted	High-adjusted
Hyperthyroid	4 (18%)	5 (24%)
Euthyroid	0 (0%)	4 (19%)
Hypothyroid	18 (82%)	12 (57%)
Totals	22 (100%)	21 (100%)

The study by *Thientunyakit et al.* 2010, was a comparative study of two different dosing protocols of radioactive iodine-131 in the treatment of hyperthyroidism. The study included 128 patients; these patients were randomly placed in the separate arms of the study. One group contained 67 patients who received doses estimated by palpation alone, (100 μ Ci/ g of thyroid tissue for diffuse goiter and 200 μ Ci/ g of thyroid tissue for nodular goiter).³ There was a maximum dose of 30 mCi (milicurie) set for these patients.³ The second arm of the study

contained 61 patients and they were dosed with calculated method using palpation and 24-hour uptake percentage.³ In this study most patients received antithyroid medication before the therapeutic dose of iodine-131 was administered. These drugs were then discontinued at least 10 days before the date of therapy. Beta-blockers were not stopped for the therapy. The patients were followed up to one year using a 5-point clinical symptom model as mentioned above and biochemical studies to correlate.³ The results at one year of induced hypothyroidism in estimated verses calculated were 48% to 52%, respectively.³ The results of persistent or recurrent hyperthyroidism were 55% vs. 45%, respectively.³ The results for euthyroidism were 52% vs. 48%, respectively.³ With this data it can be observed a p-value of 0.185. The NNT for this study was 10.

Table 3. Key Statistical Values of the RCT being reviewed.

	p-value	CER	EER	RBI	ABI	NNT
<i>Leslie et al. (2003)</i>	0.05	18%	24%	86.7%	6%	17 patients
<i>Pusuwan et al. (2011)</i>	0.008	48%	30%	37.5%	-18%	-5 Patients
<i>Thientunyakit et al. (2010)</i>	0.185	45%	55%	22.2%	10%	10 patients

CER= control adverse event, EER= experimental adverse event, RBI= relative benefit increase, ABI= Absolute benefit increase, NNT= numbers needed to treat.

Pusuwan et al. 2011, conducted a prospective randomized study comparing the efficacy of high and low dose iodine-131 treatment for hyperthyroidism. This particular study took 150 patients and randomly placed them into a high dose and low dose group.¹ Any patients that were taking antithyroid medication were taken off of the medication 5-7 days prior to the therapy. The patient's gland size was measured using a 24-hour uptake percentage. A calculation was used with a formula of 150 $\mu\text{Ci/g}$ of thyroid tissue for the high dose arm and 100 $\mu\text{Ci/g}$ of thyroid tissue.¹ The study used the theory that failed therapy was maintained or recurrent

hyperthyroidism and successful treatment was defined as euthyroid state or hypothyroid state. Patients were followed one year by clinical symptomatology were specifically evaluated for nausea, heart failure and arrhythmias from increased metabolic activity and thyroiditis with biochemical evaluation via TSH and T3/T4.¹ The success rate at one year was 70% for the high dose group and 52% for the low dose group with a p-value of 0.027.¹ When doing statistical a statistical analysis on the trial it was found to have a p-value of 0.008.¹ The NNT was calculated to be -5.

DISCUSSION

There have been limited studies done on the effectiveness of high versus low does radioactive iodine-131 on patients with hyperthyroidism. Even though this has been the gold standard therapy for over 50 years¹, many debate the differences in dose determination. It is thought that this form of therapy is safe and effective but the most appropriate dose remains controversial when aiming to get a patient to a euthyroid state. However, maintaining euthyroidism maybe an ineffective goal in managing patients with iodine-131 because a large percentage of this population treated converts to hypothyroidism. The RCTs used considered iatrogenic hypothyroidism a successful treatment of hyperthyroidism, but for many practioners this is still argued as being unsuccessful. This is because hypothyroidism can be managed easily and the replacement hormone is fairly inexpensive. However, many patients do not want the burden of thyroid replacement hormone and periodic medicine management. In *Leslie et al.* 2003, and *Thientunyakit et al.* 2010, it was noted that the ability to predict the clinical outcome is only about 60% and shows the difficulty in the decision to pick high or low dose therapy for any given patient.^{2,3} In the trial done by *Thientunyakit et al.* 2010, the calculated dose and the estimated high and low dose groups had surprising similar outcomes and proved the low ability

to predict the clinical outcome of this procedure. The other studies carry clinically significant p-values, showing if the patient would receive an adjusted low dose of radioactive iodine-131 they have an increased chance of failed therapy and subsequently would remain hyperthyroid. This would cause them to be clinically symptomatic following the 5-point scoring system and in need further treatment and subsequently more radiation, time and cost to the patient. Another aspect of clinical consideration is if you treat the patient and they in fact do become hypothyroid then they will require thyroid replacement hormone to avoid harmful hypothyroid sequela. These complications are also mentioned in the 5-point scoring system for hypothyroidism.

There are notable limitations in all three trials used in this review which demonstrate that more research needs to be done to better assess the dosing methods of iodine-131. For example all three trials had a low number of patients enrolled in the comparative studies.^{1,2,3} The ability to have a large number study is difficult because of the nature of the data being collected. There are theorized inherent risks of ionizing radiation; therefore, this limits the number of participants of this type of analysis. Each study reported that most patients were on antithyroid medication for a period of time before therapy. It is still unknown how much this can actually affect the uptake and efficacy of iodine-131 in the destruction of thyroid tissue. This could cause changes in patient preparation and outcome post-therapy. It is also mentioned that with different clinicians there could be a difference in estimated gland size when the thyroid is palpated. This can change dose amounts and cause outcome to vary as well. With these considerations in three RCTs reviewed, there needs to be many more studies in the evaluation of dose calculation and amount of iodine-131 that is used to treat hyperthyroidism.

As a final consideration, it is essential to follow patients with an iatrogenically induced hypothyroid state. There needs to be close follow up and management of these patients. It is

possible to have long term debilitation and sequela involved with hypothyroidism.³ Practitioners need to be diligent and manage this condition closely so the patient can live a full life without comorbidities caused by the iodine-131 therapy.

CONCLUSION

After reviewing all three trials in this selective EBM review, the evidence is inconclusive and contradictory as to whether high or low dose radioactive iodine-131 is more effective in treatment of hyperthyroidism. Each study gives different outcomes and statistical data to whether high, low, adjusted or fixed doses are the best. The United States needs more research and development in this area of medicine to better understand the clinical outcomes it holds. This is evident with two of the studies being conducted in Thailand and the other being done in Canada. This information indicates the need for future research on the best way to dose patients to achieve positive outcome for the patient. The prognosis of patients with hyperthyroidism is good. However, ongoing research should be considered to identify a way to lengthen the time patients are in a euthyroid state. This will lower the chance of potentially harmful and unpleasant sequela from recurrent hyperthyroidism or induced hypothyroidism. This can also cut down the annual healthcare cost of retreatment courses, diagnostic tests, multiple office visits and thyroid replacement hormone therapy.

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