DEBATE

Radioiodine for Treatment of Graves' Disease in Pediatric Population: An Ideal Treatment

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Graves' disease is the most common cause of hyperthyroidism in the pediatric population, with a peak incidence in late childhood with a strong female.[1] Current treatment approaches involve antithyroid medications, surgery, and radioactive iodine, and these have been used for more than five decades.[2]

The past 50 years of treatment of Graves' disease in children has taught us many lessons. We now know that the majority of children and adolescents with Graves' disease will need definitive therapy, which can be capably achieved by surgery or radioactive iodine. Nevertheless, it is not uncommon for physicians to prescribe prolonged drug therapy. The issue of how long is too long and how we can best monitor and minimize potential toxic effects of antithyroid medication is one of the most important issues facing clinicians treating children with Graves' disease, and it dwarfs the debate of radioactive iodine *vs.* surgery. Operative mortality these days is rare, and we are not aware of any deaths directly related to the use of ^{131}I for the treatment of hyperthyroidism caused by Graves' disease in children. However, serious and fatal adverse events occur with antithyroid drug therapy, which, although uncommon, are not rare enough. New antithyroid medications with lower toxicity profiles than current antithyroid drugs (especially PTU) for the pediatric population are needed.

Central to considering treatment options in Graves' disease in the pediatric population is recognition of the fact that remission occurs in the minority of individuals with most authors reporting figures between 20 to 30%. Remission rates are even less in prepubertal than pubertal children, reaching only 15% of prepubescent children.[3] Presently it is not possible to accurately identify the small percentage of children who will achieve lasting remission, although remission is more likely when the thyroid is small at initial presentation.[4] Prolonged antithyroid drug therapy becomes mandatory when spontaneous remission of Graves' disease does not occur in order to, control the hyperthyroid state; however, prolonged antithyroid drug therapy does not appear to increase the likelihood of lasting remission. Studies by Greer et al metaanalysis by Weetman et al showed that the likelihood of remission of hyperthyroidism was similar when antithyroid medications were used for 6 or 36 months.[5,6]

An important concern related to antithyroid drug use in children is the occurrence of adverse side effects. Up to 25% of children will have minor side effects, including pruritus, hives, myalgias, small increases in liver enzymes, and leukopenia.[7] Up to 0.5% of PTU- or MMI-treated children will develop serious complications like fulminant hepatitis and severe bone marrow depression.[8] Published data about the risks of continuing medical therapy or changing to another medication after the occurrence of toxic reactions in children are limited. Considering the frequency of minor and major side effects, physicians will thus unexpectedly need to opt for alternative medications or definitive treatment in the midst of a course of drug therapy.

Surgery is the oldest form of definitive therapy of Graves' disease, and has the advantage that the hyperthyroid state resolves very quickly after surgery. Total thyroidectomy is generally considered as procedure of choice in order to prevent recurrence.[9] Critical importance in evaluating surgical outcome of Graves' disease is the experience of the surgical center and surgeon. The thyroidectomy complication rates reported in literature emanates from expert surgical centers and little is known about complication rates when surgery was performed by nonendocrine surgeons, and there are no comprehensive studies that have evaluated complication rates of thyroidectomy for Graves' disease in children. Acute complications after surgery in adults include hypocalcemia (40%), hematoma (2%), and recurrent laryngeal nerve paresis (2%).[10,11] Long-term complications include hypoparathyroidism (1%) and recurrent laryngeal nerve injury (2%).[12]

Although not mentioned as a complication, surgery is universally associated with neck scars, which teenagers and young adults often try to hide with necklaces, scarves, and high collars. Hypertrophic scars after thyroidectomy, requiring medical or surgical treatment, occur as well. Associated with surgery are postoperative pain and discomfort and time lost from school and activities.

Radioactive iodine therapy of Graves' disease was introduced more than 60 years ago, and it is estimated that more than one million individuals have been treated with ^{131}I for hyperthyroidism.[13] The use of radioactive iodine has been detailed for more than 1200 children.[14] Patients as young as 1 year of age have been treated with ^{131}I with excellent outcomes. These studies have reported remission rates that exceed 95%, with very rare complications.

^{131}I doses are typically calculated to deliver the desired amount of radiation based on gland size and radioactive iodine uptake.[15] Some centers administer to all patients the same fixed dose of ^{131}I with excellent outcome.[16] When children are treated with more than 200 to 250 Gy (~220 to 275 μCi/gm), hypothyroidism is achieved in nearly 95% of patients.[17] Few acute adverse responses to ^{131}I therapy of Graves' disease have been described.[18] In adults, transient nausea has been reported after radioiodine administration, and mild pain over the thyroid gland may develop 1 to 3 days after a therapeutic dose. These side effects are self-limited and respond to treatment with nonsteroidal anti-inflammatory agents.

Thyroid storm has been reported rarely to develop 1 to 14 days after ^{131}I treatment 19, with patients with severe thyrotoxicosis and very large goiters at highest risk. If antithyroid medication is stopped too soon before treatment with ^{131}I and the thyroid is large, thyroid hormone stores will be replenished and increase the risk for thyroid storm.[19] Discontinuing antithyroid medication 5 days before ^{131}I is administered is sufficient.[20] Symptoms of hyperthyroidism can be readily controlled when antithyroid medication is stopped by β-blocker therapy.

Although the potential of worsening ophthalmopathy has been reported in a small percentage of adults who have received ^{131}I, this is an uncommon problem in children. In prospective studies of children, worsening of eye disease has not been observed after ^{131}I therapy.[21,22] Recent study by El-Kaissi S, concluded that Radioiodine therapy RAI therapy for Graves' disease did not increase the risk of progression or development of ophthalmopathy in patients with mild or no eye disease at baseline.[23] When profound Graves' ophthalmopathy is present, adjunctive low dose (0.2 mg/kg) prednisone therapy for 6 weeks has been shown to prevent the worsening of eye disease after ^{131}I.[24]

The thyroid gland is unique in its developmental sensitivity to malignancy after radiation exposure. Individuals older than 20 years of age do not have an increased risk of thyroid cancer when exposed to low-level thyroid irradiation.[25,26] Detractors of ^{131}I therapy point to the increased rates of thyroid cancer and thyroid nodules observed in young children exposed to radiation from nuclear fallout at Hiroshima or after the Chernobyl nuclear reactor explosion. However, these data do not directly apply when assessing risks of ^{131}I therapy. The risk of thyroid neoplasms is greatest with exposure to low level external radiation (0.1-25 Gy; ~ 0.09-30 μCi/gm) not with the higher doses used to treat Graves' disease. It is also important to note that iodine deficiency and exposure to nuclides other than ^{131}I may have contributed to the increased risk of thyroid cancer in the young after the Chernobyl reactor explosion.[27] Supporting this concept, thyroid cancer rates were not increased in more than 3000 children exposed to ^{131}I at the Hanford nuclear reactor site in an iodine replete region.[28] Increased thyroid cancer rates were also not seen in 6000 children who received ^{131}I diagnostically.[29]

The cooperative thyrotoxicosis therapy follow-up study also showed that thyroid neoplasms developed in children treated with lower, rather than higher, doses of ^{131}I. Thyroid adenomas developed in 30% of 30 children treated in one center with low doses of ^{131}I estimated to result in thyroid exposure of 25 Gy (~ 30 μCi/gm).[30] Yet when children were treated with higher doses of ^{131}I (100-200 Gy; ~ 110-220 μCi/gm), the incidence of thyroid neoplasms was not increased.[31]

Antithyroid drugs are preferred to radioactive iodine therapy by some clinicians, assuming that thyroid cancer risk is less after drug therapy than after radioactive iodine. The cooperative thyrotoxicosis therapy follow-up study, however, found that the incidence of thyroid carcinomas in more than 10 to 20 years of follow-up was 5-fold higher in individuals treated with thioamide drugs than in patients treated with ^{131}I, and it was 8-fold higher than in patients treated surgically.[31]

Outcomes after ^{131}I treatment of more than 1200 children and adolescents treated with higher doses of radioiodine for Graves' disease have been reported.[32] The duration of follow-up in these studies ranged from less than 5 to 15 years, with some subjects followed for more than 20 years. These studies have not revealed an increased risk of thyroid malignancy. The longest follow-up studies of

children recently treated with ^{131}I come from Read et al.[33] When more than 100 patients were surveyed nearly four decades after receiving radioactive iodine, no adverse events or deaths could be attributed to ^{131}I therapy.[33]

Although radioactive iodine is being used in progressively younger ages, it is not known if there is an age below which high-dose ^{131}I therapy should be avoided. Risks of thyroid cancer after external irradiation are highest in children younger than 5 years of age and progressively decline with advancing age. If there is residual thyroid tissue in young children after radioactive iodine treatment, there is a theoretical risk of thyroid cancer. It may therefore be prudent to avoid radioactive iodine therapy in children younger than 5 years.

The literature contains data on 500 offspring born to approximately 370 subjects treated with ^{131}I for hyperthyroidism during childhood and adolescence. The incidence of congenital anomalies reported among the offspring of patients treated with radioiodine does not differ from the incidence in the general population. In addition, there was no increased prevalence of congenital anomalies in the offspring of 77 patients treated for thyroid cancer in childhood with 80-700 mCi of ^{131}I.[34] There is no evidence of an increased rate of birth defects in survivors of the Hiroshima and Nagasaki atomic bomb blasts who were exposed to higher levels of external irradiation of the gonads than are associated with radioactive iodine therapy.[35,36]

In addition to thyroid cancer, potential influences of ^{131}I therapy on other cancers need to be considered. Follow-up from the large cohort of the cooperative thyrotoxicosis therapy follow-up study did not find increased risks of leukemia in the ^{131}I-treated group, as compared with the drug- and surgery-treated groups.[37] No increase in overall cancer mortality was seen in the ^{131}I-treated patients either.[38] Total-body radiation doses after ^{131}I vary with age, and the same absolute dose of ^{131}I will result in more radiation exposure to a young child than to an adolescent or adult. At 0, 1, 5, 10, and 15 years of age and in adulthood, respective total body radiation doses are 11.1, 4.6, 2.4, 1.45, 0.90, and 0.85 rem per mCi of ^{131}I.[39] Based on the Biological Effects of Ionizing Radiation Committee V (BEIR V) analysis of external radiation exposure, the theoretical risk of cancer death after acute radiation exposure is 0.16% per rem for children and 0.08% per rem for adults, although there is uncertainty associated with these projections.[40] At present, there is no good dosimetric information regarding ^{131}I use in children with Graves' disease to assess actual total body exposure and the long-term theoretical risks associated with this exposure, especially in young children.

CONCLUSION

When considering definitive therapy, there is ample data that address the long-term outcome of radioactive iodine therapy in children. These data have yet to reveal substantive acute or long-term consequences of this method of selective thyroid ablation. Properly administered, radioactive iodine remains an ideal form of treatment for Graves' disease in the pediatric population.

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