Preparation with Recombinant Human Thyroid-Stimulating Hormone for Thyroid Remnant Ablation with ^{131}I Is Associated with Lowered Radiotoxicity

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Preparation with recombinant human thyroid-stimulating hormone (rhTSH) for thyroid remnant ablation results in lower extrathyroidal radiation than does hypothyroidism. The objective of this prospective study was to compare the damage caused by ^{131}I (3.7 GBq) when these 2 preparations are used. **Methods:** Ninety-four consecutive patients who underwent total thyroidectomy and remnant ablation with 3.7 GBq of ^{131}I were studied. Thirty patients (group A) received rhTSH, and 64 (group B) were prepared by levothyroxine withdrawal. Damage to salivary glands, ovaries, and testes; hematologic damage; and oxidative injury were evaluated by measurement of serum amylase, follicle-stimulating hormone (FSH), complete blood count, and plasma 8-epi-$PGF_{2\alpha}$ before and after radioiodine. The 2 groups were similar in sex, age, and the results of baseline assessment. **Results:** The rate of successful ablation (stimulated thyroglobulin level < 1 ng/mL and negative findings on neck ultrasonography) was 90% in group A and 80% in group B. Considering only patients with a preablation thyroglobulin level greater than 1 ng/mL, these rates were 80% and 70.6%, respectively. Only 1 patient (3.3%) reported transient headaches with rhTSH. Elevated FSH levels after therapy were observed in 4 of 9 (44%) men in group A versus 16 of 18 (89%) in group B ($P < 0.03$), with a mean increase of 105% versus 236% ($P < 0.001$), respectively. In women, elevated FSH was observed in 1 of 13 (7.7%) patients in group A versus 6 of 30 (20%) in group B ($P = 0.4$), with a mean increase of 65% versus 125% ($P < 0.001$). Thrombocytopenia or neutropenia occurred in 2 of 28 (7%) patients in group A versus 12 of 56 (21.4%) in group B ($P = 0.1$), with a mean decrease of 20% versus 45% and 25% versus 52% ($P < 0.01$) for neutrophils and platelets, respectively. Hyperamylasemia and symptoms of acute sialoadenitis occurred in 11 of 30 (36.6%) versus 48 of 60 (80%) ($P < 0.001$) and in 9 of 30 (30%) versus 35 of 60 (58.3%) ($P = 0.01$), respectively. 8-Epi-$PGF_{2\alpha}$ was found to be elevated after ^{131}I in 14 of 25 (56%) patients in group A versus 45 of 45 (100%) in group B ($P < 0.001$), with a mean increase of 60% versus 125% ($P < 0.001$). **Conclusion:** The lower radiotoxicity with rhTSH, suggested in dosimetry studies, was confirmed in the present prospective investigation, and this advantage occurred without compromising the efficacy of treatment.

Key Words: thyroid cancer; remnant ablation; rhTSH

J Nucl Med 2008; 49:1776–1782
DOI: 10.2967/jnumed.108.050591

Total thyroidectomy followed by remnant ablation with ^{131}I is the initial therapy indicated for most patients with differentiated thyroid carcinoma (*1*). Factors against routine postoperative ablation are the uncertainty regarding the benefit for low-risk patients (*2*) and the undesired effects of this procedure. Rapidly occurring (weeks) and intense (low thyroxine) hypothyroidism has been inevitable until recently for ablation with ^{131}I, and although well tolerated, adverse effects of radioiodine, such as damage to the salivary glands (*3–5*), impaired gonadal function (*6–9*), oxidative injury (*10*), and even the risk of a secondary neoplasm (*1*), have been documented. The consequences of iatrogenic hypothyroidism (*11*) and adverse effects of ^{131}I may equal or even exceed the eventual benefits of ablation, particularly in low-risk patients (*1,2,12*).

The use of recombinant human thyroid-stimulating hormone (rhTSH), which is known to be efficient in remnant ablation (*13,14*) and has already been approved for this purpose in Europe, the United States, and Brazil, solves the problem of hypothyroidism. Regarding the adverse effects of radioiodine, the lower blood and whole-body radiation obtained with rhTSH (*15*) indicates a probable lower risk of toxicity with this preparation without compromising its efficacy (*14*).

The objective of the present study was to compare the damage caused by ^{131}I (3.7 GBq) during remnant ablation in patients prepared with rhTSH versus those who undergo levothyroxine withdrawal.

Received May 30, 2008; revision accepted Aug. 7, 2008.
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MATERIALS AND METHODS

Patients

We studied 94 consecutive patients, seen between August 2003 and December 2006, who underwent total thyroidectomy without lymph node metastases apparent during surgery, had macroscopically complete tumor resection, and fulfilled the following inclusion criteria: age between 18 and 65 y, no associated comorbidities, a well-differentiated tumor no larger than 5 cm and with no extensive extrathyroidal invasion (*16*), a postoperative clinical examination and chest radiograph showing no signs of metastases, and negative for antithyroglobulin antibodies.

^{131}I Therapy

All patients received 3.7 GBq (100 mCi) of ^{131}I for remnant ablation without undergoing pretreatment whole-body scanning. Preparation with rhTSH was offered to all 94 patients, although none of the patients presented a contraindication for iatrogenic hypothyroidism or an apparent incapacity for endogenous thyroid-stimulating hormone elevation (*17*). After the patients were informed that rhTSH has still not been approved for ablation and that there is no formal indication for this preparation, 30 patients opted for levothyroxine withdrawal. In 34 of the 64 remaining patients, acquisition of rhTSH was not feasible. Thirty patients (group A) received 0.9 mg of rhTSH for 2 consecutive days followed by ^{131}I administration on the third day. All these patients signed a consent form approved and required by the Ethics Committee of Santa Casa de Belo Horizonte because the use of rhTSH for ablation had not yet been approved in Brazil when the study was performed. The remaining 64 patients (group B) were prepared by levothyroxine withdrawal for 3–4 wk.

The subjects received instructions regarding limiting exposure to environmental iodine and using a low-iodine diet for 2 wk before ^{131}I therapy (*18*). For women of child-bearing potential, a negative serum human chorionic gonadotropin pregnancy test was required. When presenting with intestinal constipation, the patients were told to drink a lot of water and were given a laxative to adequately eliminate ^{131}I. The patients were advised to frequently chew gum, which was made freely available. Hormonal therapy was reintroduced 48 h after radioiodine administration in patients who underwent levothyroxine withdrawal.

All patients, except 2 in group B, underwent whole-body scanning 7 d after ^{131}I administration. Five patients showed ectopic cervical uptake (lymph node) on posttherapy whole-body scanning (2 in group A and 3 in group B).

Study Protocol

The subjects were evaluated approximately 8–10 wk after thyroidectomy during levothyroxine use and also immediately before the administration of ^{131}I to exclude those who were already showing basal changes in the parameters studied. The exclusion (clinical and laboratory) criteria are shown in Table 1. Four, 3, 21, 4, and 7 patients were excluded from the evaluation of damage to salivary glands, testes, ovaries, hematologic injury, and oxidative injury, respectively, for the reasons shown in Table 1. The patients included in the study were investigated according to the protocol summarized in Table 2.

Outcome of Ablation

Six to 12 mo after ablation, the patients were reevaluated by measurement of stimulated thyroglobulin with the same preparation as that used for ablation and neck ultrasonography. Ablation was considered to be successful when the stimulated thyroglobulin level was less than 1 ng/mL and neck ultrasonography showed no abnormalities.

Assays

Amylase was measured in serum by the purine nucleoside phosphorylase kinetic method, with a reference value of up to 104 U/L. Follicle-stimulating hormone (FSH) was determined using the IRMA FSH MAIAclone kit (BioChem Immuno Systems), with an intra- and interassay variability of 1.2%−3.5% and 2%−5.4%, respectively, and a reference value of up to 14 IU/L for men and for women in the follicular phase of the cycle (time of measurement). Leukocytes (neutrophils), platelets, and red blood cells were counted in an automated flow cytometer, and samples showing alterations in any of the series were reevaluated.

Plasma 8-epi-$PGF_{2\alpha}$ was measured by a specific enzyme immunoassay (Cayman Chemical) after extraction and purification by chromatography. The mean value plus 2 SDs was 22 pg/mL for a control group consisting of 24 (16 women and 8 men) healthy nonsmoking individuals aged 18–65 y (mean, 45 y) without known

TABLE 1
Exclusion Criteria

Parameter evaluated for damage	Exclusion criterion	No. of patients excluded
Salivary glands	History of salivary gland disorders	0
	Use of anticholinergic drugs	1
	Report of recurrent or persistent pain or enlargement of salivary glands	1
	Hyperamylasemia before ^{131}I administration	3
Ovaries	History of oophorectomy, chemotherapy, or pelvic radiotherapy	0
	Increased FSH before ^{131}I	20
Testes	History of chemotherapy, orchiepididymitis, cryptorchidism	1
	Varicocele or infertility	1
	Increased FSH before ^{131}I	1
Hematologic	Known hematologic disease	0
	Neutrophils $<$ 1,800/mm^3	2
	Platelets $<$ 150,000/mm^3	1
	Hemoglobin $<$ 12 g/dL	1
Oxidative	Diabetes	0
	Smoker	7

TABLE 2
Study Protocol

Parameter evaluated for damage	Test	Time of evaluation
Salivary glands	Serum amylase	Immediately before and 48 h after ^{131}I*
	Enlargement or pain in salivary glands	2 and 7 d after ^{131}I
Ovaries	Serum FSH	Immediately before and 6 mo after ^{131}I*
Testes	Serum FSH	Immediately before and 6 mo after ^{131}I*
Hematologic	Blood count	Immediately before and 30, 45, and 60 d after ^{131}I
Oxidative	Plasma 8-epi-$PGF_{2\alpha}$	Immediately before and 4 d after ^{131}I*

*Significant increases in levels of amylase (*4,5*), FSH (*6–9*), and 8-epi-$PGF_{2\alpha}$ (*10*) after ^{131}I were seen at these times.

disease and not using any medications. For values of approximately 5, 10, and 30 pg/mL, the intraassay variability was 3%, 3.2%, and 2.9%, respectively, and the interassay variability (interval of 2 wk) was 5%, 5.3%, and 4.5%, respectively. The detection limit calculated for 20 samples with a known zero concentration of 8-epi-$PGF_{2\alpha}$ was 1.3 pg/mL. The blood samples were prepared with 2% ethylenediaminetetraacetic acid and 1 mg of acetylsalicylic acid per milliliter and were immediately centrifuged, and plasma was extracted and stored at 70°C until the time of analysis, which occurred within a maximum of 2 wk (*10*).

Thyroglobulin was measured by a radioimmunometric assay (ELSA-hTG; CIS Bio International), with a functional sensitivity of 1 ng/mL. Antithyroglobulin antibodies were determined by a chemiluminescent assay (Nichols Institute Diagnostics), with a detection limit of 1 IU/mL and a reference value of up to 2 IU/mL.

Imaging Methods

Ultrasonography was performed with a linear multifrequency 10-MHz transducer. All suspected lesions apparent on ultrasonography (*19*) were evaluated by ultrasonography-guided fine-needle aspiration biopsy.

Statistical Analysis

Results are expressed as mean ± SD or as percentage. Means were compared between groups by the Student t test or the nonparametric Mann–Whitney U test. The Fisher exact test or χ^2 test was used to detect differences in the proportion of cases. A P value of less than 0.05 was considered to be significant.

RESULTS

The characteristics of the patients included in group A (rhTSH) and group B (levothyroxine withdrawal) are shown in Table 3. Uptake in the thyroid bed was no more than 2% in any patient.

Outcome of Ablation

The thyroglobulin level during levothyroxine therapy was no more than 1 ng/mL in any patient 6–12 mo after ablation. Ablation was successful (stimulated thyroglobulin level < 1 ng/mL and negative neck ultrasonography findings) in 27 of 30 patients of group A (90%) and in 51 of 64 of group B (80%) (not significant [NS]). Considering only patients with a thyroglobulin level greater than 1 ng/mL immediately before ^{131}I administration, the rates were 80% in group A (12/15) and 70.6% in group B (24/34) (NS).

Adverse Effects

Only 1 patient (3.3%) reported a transient adverse effect (headache) with rhTSH during the period between the first injection and 1 wk after the second application.

For each assessment (Table 4), application of the exclusion criteria resulted in 2 groups (rhTSH vs. hypothyroidism), and these groups were also always similar in sex and age.

TABLE 3
Characteristics of Groups A and B

Characteristic	Group A (rhTSH; n = 30)	Group B (hypothyroidism; n = 64)
Age (y)	45 ± 9.5	44 ± 11
Sex	Female: 20; male: 10	Female: 44; male: 20
Histologic type	Papillary: 27; follicular: 3	Papillary: 58; follicular: 6
Tumor size (cm)	2.7 ± 0.7	2.5 ± 0.6
Minimal extrathyroidal invasion	6 (20%)	14 (22%)
Tumor size ≤ 2 cm	10 (33.3%)	23 (36%)
Tumor size > 2 and ≤ 4 cm	11 (36.6%)	21 (33%)
Tumor size > 4 cm or extrathyroid invasion	9 (30%)	20 (31.2%)
Interval between thyroidectomy and ablation (d)	102 ± 21	106 ± 18
TSH immediately before ^{131}I administration (mIU/L)*	118 ± 28.5	85 ± 23

*$P < 0.05$.

TABLE 4
^{131}I-Related Adverse Effects in Groups A and B

Outcome	Group A (rhTSH)	Group B (hypothyroidism)	*P*
Elevated FSH 6 mo after ^{131}I			
Men	4/9 (44.4%)	16/18 (89%)	0.03
Women	1/13 (7.7%)	6/30 (20%)	0.4
Mean increase of FSH			
Men	105%	236%	<0.001
Women	65%	125%	<0.001
Hyperamylasemia 48 h after ^{131}I*	11/30 (36.6%)	48/60 (80%)	<0.001
Symptoms of acute sialoadenitis up to 7 d after ^{131}I*	9/30 (30%)	35/60 (58.3%)	0.01
Thrombocytopenia (<100,000/mm^3) or neutropenia (<1,500/mm^3) (lowest count) up to 60 d after ^{131}I†	2/28 (7%)	12/56 (21.4%)	0.1
Mean decrease of neutrophils (considering lowest count)‡	20%	45%	<0.01
Mean decrease of platelets (considering lowest count)‡	25%	52%	<0.01
Increased 8-epi-$PGF_{2\alpha}$ 96 h after ^{131}I	14/25 (56%)	45/45 (100%)	<0.001
Mean increase of 8-epi-$PGF_{2\alpha}$	60%	125%	<0.001

*All symptomatic patients presented with concomitant hyperamylasemia. No cause other than salivary gland damage was suspected for increase in serum amylase in any patient.

†One patient showed platelet count of less than 75,000/mm^3 and other-neutrophil count of less than 1,000/mm^3. Thrombocytopenia or neutropenia was observed 30, 45, and 60 d after ^{131}I administration in 4, 8, and 2 patients, respectively.

‡Lowest platelet count was observed 30, 45, and 60 d after ablation in 20, 44, and 20 patients, respectively. Lowest neutrophil count was observed 30, 45, and 60 d after ablation in 16, 40, and 28 patients, respectively.

We observed no difference in FSH, amylase, or blood cell count before and 24 h after the second injection of rhTSH in group A, or before and 3–4 wk after levothyroxine withdrawal in group B, with the results obtained immediately before ^{131}I administration being defined as baseline. Serum FSH levels in men and women were similar in the 2 groups before ^{131}I (6.5 ± 1.5 IU/L vs. 6.1 ± 1.6 IU/L [NS] and 5.2 ± 1.4 IU/L vs. 5.5 ± 1.6 IU/L [NS], respectively), as were amylase levels (56 ± 20 U/L vs. 52 ± 18 U/L [NS]). Basal platelet and neutrophil counts were normal and also similar (mean of 276,500/mm^3 vs. 281,200/mm^3 [NS] and 2,320/mm^3 vs. 2,420/mm^3 [NS], respectively), as were mean hemoglobin levels (14 g/dL in both groups). Plasma 8-epi-$PGF_{2\alpha}$ levels were elevated (>22 pg/mL) before ^{131}I in 3 of 28 (10.7%) patients in group A versus 14 of 59 (23.7%) in group B (P = 0.24). Restriction of the evaluation to patients with normal basal levels showed similar values in the 2 groups. The behavior of these markers after ^{131}I therapy is shown in Table 4.

Follow-up

By the last assessment (June 2008), normalization of FSH had occurred in 20 of 27 patients with elevated levels of this hormone 6 mo after ablation, and platelet and neutrophil counts had also returned to normal in 10 of 12 patients with early neutropenia or thrombocytopenia after ^{131}I administration. Six of the 7 patients who continued to show elevated FSH and the 2 patients with persistent hematologic alterations belonged to group B. Hyperamylasemia persisted in only 2 patients, also from group B, and recurrent or persistent pain or xerostomia was observed in 4 patients (1 from group A and 3 from group B). All these patients showed elevated amylase levels or acute sialoadenitis after ablation.

DISCUSSION

In low-risk patients, postoperative ^{131}I has been based on the lower recurrence rate and even a lower mortality observed in the Ohio series (*20*), on the improvement in the specificity of thyroglobulin, and on the early detection of metastases by posttherapy whole-body scanning (*20*). In contrast, not all investigators have confirmed the benefit of adjuvant therapy with ^{131}I in this group (*2*), with this therapy resulting in 2 relevant problems, the need for iatrogenic hypothyroidism (*11*) and radioiodine toxicity (*1,3–10*). With respect to the latter, a low activity (1.1–1.85 GBq [30–50 mCi]) is applied to minimize the adverse effects of radioiodine. Although 2 recent randomized studies confirmed the equivalent efficacy of low ^{131}I activities both during hypothyroidism (*21*) and after rhTSH (*22*), some authors still question whether the efficacy is the same as that obtained with 3.7 GBq (*23*). Preparation with rhTSH is known to result in lower blood and whole-body radiation than does hypothyroidism (*15,24–28*). The most likely explanation is a difference in the clearance of ^{131}I, which is lower during hypothyroidism because of a reduction in the renal glomerular filtration rate (*14,15*). We are unaware of any published studies that specifically evaluated radiotoxicity in patients treated with rhTSH versus hypothyroidism.

With respect to patients prepared by levothyroxine withdrawal for several weeks, our results agree well with the literature. After the administration of approximately 3,700 MBq (100 mCi), studies have reported hyperamylasemia

(>200 U/L) in 40% of patients (*5*), a significant increase of serum amylase levels in more than 80% (*4*), and acute sialoadenitis in 30%−50% (*5,29,30*). The lack of a significant and concomitant increase in pancreatic enzymes and the presence of symptoms of sialoadenitis, but not of pancreatitis, in patients with postradiation hyperamylasemia (*31,32*) confirm that the increase in amylase results from salivary gland injury. Administration of 3,700 MBq (100 mCi) has also resulted in an increase in FSH in all men 6 mo after therapy (*7*) but in only 28% of women (*8*). Regarding hematologic toxicity, Lima et al. (*33*), using an activity of 9.25–13 GBq (250–350 mCi), observed mild or moderate thrombocytopenia and neutropenia on some occasions up to 60 d after therapy in 45% and 50% of patients, respectively. When administering an average of 7.6 GBq, Haynie and Beierwaltes (*34*) reported reduced values in one of the series (red blood cells, leukocytes, or platelets) in 48% of 152 patients. A radiation dose of less than 2 Gy in the blood is also known to result in only minimal and transient thrombocytopenia and leukopenia (*35*), as observed in the present study. Therefore, we believe that the present results have not under- or overestimated ^{131}I toxicity.

The isoprostane 8-epi-$PGF_{2\alpha}$ is generated after free radical–mediated peroxidation of arachidonic acid, and some properties render this compound a reliable indicator of oxidative stress in vivo (*36*): it is a specific product of lipid peroxidation, a stable compound, and present in detectable quantities in all normal biologic fluids and tissues; its formation increases dramatically in vivo after several oxidant injuries; its levels are not affected by dietary lipid content; and commercial kits are available for its measurement. 8-Epi-$PGF_{2\alpha}$ is mitogenic, is a vasoconstrictor, and displays a potential proaggregation effect on human platelets, and elevated concentrations are observed in conditions such as smoking, hypercholesterolemia, diabetes, advanced age, atherosclerosis-associated diseases, and chronic lung disease (*10*). Wolfram et al. showed a dose-dependent increase in 8-epi-$PGF_{2\alpha}$ levels in the plasma, serum, and urine of patients undergoing radioiodine therapy (*10*). An invariable increase in plasma 8-epi-$PGF_{2\alpha}$, 100% on average, was reported after the administration of 2.96 GBq (80 mCi) (*10*), in good agreement with our results.

Although not evaluated in the present study because of the obviously insufficient number of patients and follow-up time, 10 y after therapy 3 more cases of leukemia and 57 more cases of solid malignant tumors than expected would occur per 10,000 patients treated with 3,700 MBq (100 mCi) of ^{131}I during hypothyroidism (*1*). Because this risk is also proportional to the radiation that reaches extrathyroidal tissues (*37*), preparation with rhTSH would have a favorable impact on this highly undesired effect.

The present study was not randomized, a fact that does not exclude the possibility of bias. However, the selection of patients for the use of rhTSH was not based on parameters known to influence radiotoxicity, and the groups receiving the 2 preparations were similar in sex, age, and baseline parameters. In addition, the patients originated from the same center. Thus, possible differences between groups in evaluation of the results, including the technique and the observer, are unlikely.

The radiation reaching the tissues was not directly measured. Using MIRD (*38*), the estimated radiation in testes and ovaries would be 85 mGy and 140 mGy, respectively, when 3,700 MBq (100 mCi) of ^{131}I are administered during euthyroidism (as for the preparation with rhTSH). Specific studies on thyroidectomized patients during hypothyroidism suggest that the same activity would result in a testicular radiation of 86 mGy (*39*) to 120 mGy (*40*); the radiation in the ovaries would be much higher than estimated by MIRD (*9*), and an average radiation of 740 mGy would be obtained for the salivary glands (*41*). Interstudy comparison is inappropriate because of differences in the characteristics of the patients, in the preparation protocol, in the assessment techniques, and between examiners. In a randomized study involving similar groups (rhTSH vs. hypothyroidism) and a uniform assessment, Hanscheid et al. (*15*) reported that the radiation in blood after 3,700 MBq (100 mCi) of ^{131}I was 0.62 Gy during hypothyroidism and 0.4 Gy for rhTSH, with this finding also suggesting a lower tissue irradiation when the latter preparation is used. Because tissue irradiation correlates with the ^{131}I activity administered, the relationship between the latter and the increase in FSH (*42*), amylase (*4*), and 8-epi-$PGF_{2\alpha}$ (*10*) levels and the reduction in blood cell count (*37*) supports the hypothesis that the magnitude of changes in these markers in fact reflects radiation reaching the respective tissues (*43*).

The fact that we observed no difference in FSH, amylase, or blood cell count before and after levothyroxine withdrawal, together with the finding of similar basal levels (immediately before ^{131}I) in the 2 groups, permits us to exclude the possibility that hypothyroidism itself influenced the results. Other studies confirm that hypothyroidism results in no or only a mild increase in serum amylase (*44*), FSH (*42*), and 8-epi-$PGF_{2\alpha}$ levels (*45*). Although the increase in these markers is not a specific radiation-induced damage, the exclusion of other causes of tissue injury and the temporal relationship permit us to conclude that the alterations observed can be attributed exclusively to radiation.

To our knowledge, only a single study has compared rhTSH and hypothyroidism in terms of radiation in blood and in whole body and also reported the efficacy of these preparations: no difference in the ablation rate (*14,15*). The patients included in our study were also evaluated regarding the success of ablation, and no difference was observed between preparations, a finding confirming that the lower toxicity of ^{131}I with rhTSH occurs without compromising the efficacy of treatment.

After confirmation of the efficacy and approval of rhTSH for remnant ablation, the next step is to define the preparation of choice. The prevention of iatrogenic hypothyroidism is the main and best-known advantage of rhTSH. Short exposure to elevated thyroid-stimulating hormone, reducing the risk of

tumor growth, is another potential advantage (*11*). The lower toxicity associated with rhTSH has been supported by dosimetry studies (*15*) showing lower radiation in the blood and whole body, and now by the data of the present prospective study. This advantage occurs without compromising the efficacy of treatment. These findings favor rhTSH as the preparation of choice for thyroid remnant ablation and probably the only acceptable choice in low-risk patients for whom the benefits of ^{131}I are controversial (*2*) and for whom the undesired effects of this treatment need to be minimized.

CONCLUSION

The lower radiotoxicity with rhTSH, suggested in dosimetry studies, was confirmed in the present prospective investigation, and this advantage occurred without compromising the efficacy of treatment.

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