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A Comprehensive Study on the Blockage of Thyroid and Gastric Uptakes of ^{188}Re-perrhenate in Endovascular Irradiation Using Liquid-filled Balloon to Prevent Restenosis

Wan-Yu Lin,[1] Jih-Fang Hsieh,[2] Shih-Chuan Tsai,[3] Tzu-Chen Yen,[4] S. J. Wang[1] and F. F. Knapp, Jr.[5]

[1]DEPARTMENT OF NUCLEAR MEDICINE, TAICHUNG VETERANS GENERAL HOSPITAL, TAICHUNG, TAIWAN; [2]DEPARTMENT OF NUCLEAR MEDICINE, CHI-MEI FOUNDATION HOSPITAL, TAINAN, TAIWAN; [3]DEPARTMENT OF NUCLEAR MEDICINE, CHANGHUA, TAIWAN; [4]DEPARTMENT OF NUCLEAR MEDICINE, CHANG GUNG MEMORIAL HOSPITAL, TAIPEI MEDICAL CENTER AND SCHOOL OF MEDICINE, CHANG GUNG UNIVERSITY, TAIPEI TAIWAN; AND [5]NUCLEAR MEDICINE GROUP, OAK RIDGE NATIONAL LABORATORY, OAK RIDGE, TENNESSEE, USA

ABSTRACT. ^{188}Re-perrhenate has been reported effective in preventing restenosis after percutaneous transluminal coronary angioplasty. However, if the balloon ruptures, ^{188}Re-perrhenate is released into the circulation, causing high radiation dosing to the thyroid and stomach. In this study, we evaluated the effects of perchlorate or iodide given at different times and in different ways for blocking the uptake of ^{188}Re-perrhenate in the thyroid glands and the stomach to find the best method to apply clinically to reduce the radiation dose in case of balloon rupture. Sodium perchlorate, sodium iodide, or potassium iodide was given orally or intravenously to rats before, during, and after the injection of ^{188}Re-perrhenate. The rats were sacrificed and we calculated the concentration of ^{188}Re-perrhenate in various organs to evaluate the preblocking, mixed formula, and postblocking effects of perchlorate or iodide. Our data showed that the preblocking method effectively reduced the uptake of ^{188}Re-perrhenate in both the thyroid and the stomach. The mixed formula method also demonstrated good blocking effect. The postblocking method showed obvious depression of thyroid uptake of perrhenate but its blocking effect on the stomach was not satisfactory. NUCL MED BIOL 27;1:83–87, 2000. **© 2000 Elsevier Science Inc. All rights reserved.**

KEY WORDS. ^{188}Re-perrhenate, Intravascular irradiation, Beta particle, Restenosis, Blockage, Thyroid uptake, Gastric uptake

INTRODUCTION

Restenosis occurs in approximately 30–50% of cases after successful percutaneous transluminal coronary angioplasty (PTCA) and is the major factor limiting the long-term effectiveness of this procedure (11, 15, 19). Smooth muscle cell proliferation leading to neointima formation, elastic recoil, and late remodeling are the putative causes of restenosis of both first-time and previously dilated arteries (18, 25). Recently, several successful strategies employing endovascular irradiation of the dilated artery to prevent restenosis have been demonstrated in both animals and humans (10, 21, 22, 26). The major disadvantages of radioactive wires and stents are disposal problems and difficulty in centering (16). In contrast, liquid-filled balloons containing a beta-emitting radioisotope are self centering at all times (2). In addition, radioactive solutions for balloon inflation have other advantages such as ease of use with existing catheters and uniform dosing to the vessel walls.

A variety of beta-emitting radioisotopes can be prepared in a soluble form for use in a liquid-filled balloon. Among them, ^{188}Re is undoubtedly an excellent radiotherapeutic agent. The use of a ^{188}W/^{188}Re generator system is cost effective, because the ^{188}W parent has a long half-life of 69 days, resulting in a low cost per dose. The availability of a generator for ^{188}Re permits the on-site "milking" of the radioisotope, in the same fashion as Tc-99m, and can increase its clinical use (8). The short half-life (16.9 h) of ^{188}Re can effectively reduce the systemic radiation in the case of balloon rupture. The maximal beta energy of ^{188}Re is 2.12 MeV. The high beta energy may be important in the presence of calcified plaque in the lumen of vessels. In such cases, the attenuation and scatter of low energy beta particles would be of major concern with beta particle energies much less than 2 MeV. In addition, ^{188}Re is not a bone seeking radionuclide (23). Therefore, in the event of balloon rupture, significant bone marrow doses of beta radiation is not a concern, as it is when liquid phosphorus-32 or yttrium-90 are used.

However, using the liquid-filled balloon method, the radioactive liquid in the balloon would be released into the circulation, resulting in unnecessary radiation doses to systemic organs if the balloon ruptured during the procedure, although the incidence is very rare (<0.1%). In addition, ^{188}Re is obtained as perrhenate (ReO_4^-), which is chemically similar to Tc-99m pertechnetate (ReO_4^-) (4) and is found to accumulate in the thyroid glands and stomach. Both the thyroid glands and the gastroenteric tract are sensitive to radiation. Because pertechnetate uptake in the thyroid, salivary glands, and stomach can be blocked using perchlorate (ClO_4^-) (14, 17), we assume that uptake of ^{188}Re-perrhenate in these organs also can be blocked by perchlorate or iodide. In this study, we evaluated the tissue biodistribution after various methods of blocking the uptake of ^{188}Re-perrhenate in the thyroid glands

Address correspondence to: Shih-Chuan Tsai, M.D., Department of Nuclear Medicine, Show Chwan Memorial Hospital, 542, Section 1, Chungshan Road, Changhua, Taiwan; e-mail: sctsai@show.org.tw

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and stomach to determine the best method to apply clinically to reduce the radiation dose to organs once the balloon ruptured.

MATERIALS AND METHODS

Preparation of ^{188}Re-perrhenate Solution

^{188}Re is generated by beta decay of tungsten-188, which can be produced by double neutron capture of enriched tungsten-186 target with high neutron flux ($>5 \times 10^{14}$ n/cm^2/s) (8). W-188 is produced by double neutron capture of ^{186}W. Elution of the ^{188}W/^{188}Re generator with normal saline provides solutions of carrier-free ^{188}Re sodium perrhenate ($NaReO_4$), with high yields (>80%) and low breakthrough ($<10^{-4}$%) of ^{188}Re-perrhenate solution. Both the radionuclide purity and radiochemical purity of the ^{188}Re-perrhenate solution exceeded 99%.

Animal Studies

Male Sprague-Dawley rats (250–300 g) were used in this study. The rats were fasted, but given free access to water, for a period of 24 h before the experiments.

Normal Controls

Ten rats were used to determine the normal tissue biodistribution of ^{188}Re-perrhenate. The rats were sacrificed at 30 min and 60 min (five in each group) after intravenous injection of approximately 3.7 MBq (0.1 mCi) ^{188}Re-perrhenate in a volume of 0.1 mL via the tail vein. The major organs including liver, lung, kidney, stomach, small intestine, and large intestine were taken out and weighed carefully. A section of the trachea containing the thyroid gland was removed, and the weight of the thyroid gland was calculated as 0.7% of the animal's weight. In addition, a 1-mL blood sample was drawn directly from the heart. Samples of different organs were counted in a well-type gamma counter (Packard Cobra II, Meriden, CT USA) to calculate resident activities in different organs. Tissue concentrations were calculated and expressed as percent injected dose per gram or per milliliter (%ID/g or mL).

Blocking Effect of Preadministration of Perchlorate or Iodide

Fifteen rats were used and were divided into three groups (five rats in each group). The preblocking effects of three formulas were evaluated: (1) potassium perchlorate 0.85 mg/100 g (600 mg/70 kg) given orally, (2) potassium iodide 1.03 mg/100 g (720 mg/70 kg) given orally, and (3) sodium iodide 0.93 mg/100 g (650 mg/70 kg) given intravenously. For oral administration, rats were provided with small pieces of rat chow on which had been adsorbed either potassium perchlorate or potassium iodide. For the intravenous administration, we used sodium iodide rather than potassium iodide to avoid the risk of arrhythmia, which might result from the intravenous injection of potassium. Thirty minutes after the rats consumed all of the rat chow or the iodide had been injected, 3.7 MBq (0.1 mCi) ^{188}Re-perrhenate were injected in a volume of 0.1 mL via the tail vein. The animals were sacrificed for biodistribution study 30 min later.

Blocking Effect of Mixing Sodium Iodide with ^{188}Re-perrhenate

Five rats were used and each received an injection via the tail vein of 0.1 mL of the mixed formula, which contained 3.7 MBq (0.1 mCi) ^{188}Re-perrhenate and 0.93 mg/100 g of sodium iodide. The rats were sacrificed for biodistribution study 30 min after the injection.

Blocking Effect of Postadministration of Perchlorate or Iodide

Fifteen rats were used and were divided into three groups (five rats in each group). The postblocking effects of three formulas were evaluated: (1) potassium perchlorate 0.85 mg/100 g (600 mg/70 kg) given orally, (2) potassium iodide 1.03 mg/100 g (720 mg/70 kg) given orally, and (3) sodium iodide 0.93 mg/100 g (650 mg/70 kg) given intravenously. Twenty minutes after injecting 0.1 mL of 3.7 MBq (0.1 mCi) ^{188}Re-perrhenate, two groups of rats were given either potassium perchlorate or potassium iodide orally. The third group of rats was given sodium iodide intravenously 30 min after ^{188}Re-perrhenate injection. The rats were sacrificed for biodistribution study 1 h after injection of ^{188}Re-perrhenate.

RESULTS

The tissue concentrations of ^{188}Re-perrhenate in preblocking, mixed formula, and postblocking groups are shown in Table 1. The concentration levels of radioactivity were significantly higher in both the thyroid gland and the stomach. The uptake of ^{188}Re-perrhenate in other organs was low (below 2 %ID/g).

Blocking Effect on Thyroid Uptake of ^{188}Re-perrhenate

PREBLOCKING EFFECT. In the control group, mean thyroid uptake of perrhenate was 63.88% (ID/g) 30 min after injection (Fig. 1). The thyroid uptake of ^{188}Re-perrhenate dropped significantly when perchlorate or iodide was given 30 min before the injection of ^{188}Re-perrhenate. The thyroid uptake levels were 15.63%, 22.97%, and 31.02% in $NaClO_4$ group, NaI group, and KI group, respectively. Administration of $NaClO_4$ orally 30 min before the injection of ^{188}Re-perrhenate had the best blocking effect.

MIXED FORMULA EFFECT. Thyroid uptake decreased significantly from 63.88% to 24.29%.

POSTBLOCKING EFFECT. In the control group, mean thyroid uptake of perrhenate was 54.21% 1 h after injection. When either KI (orally) or NaI (intravenously) was administered 30 min after intravenous injection of ^{188}Re-perrhenate, the thyroid uptake of perrhenate dropped significantly. The thyroid uptake levels were 20.74% and 14.82% in KI group and NaI group, respectively. NaI administered intravenously 30 min after injection of ^{188}Re-perrhenate showed better blocking effect on thyroid uptake.

Blocking Effect on Stomach Uptake of ^{188}Re-perrhenate

PREBLOCKING EFFECT. In the control group, mean gastric uptake of perrhenate was 10.67% 30 min after injection (Fig. 2). The gastric uptake of ^{188}Re-perrhenate dropped significantly when perchlorate or iodide was given 30 min before the injection of ^{188}Re-perrhenate. The gastric uptake levels were 2.76%, 6.22%, and 7.64% in the $NaClO_4$ group, NaI group, and KI group, respectively. Administration of $NaClO_4$ orally 30 min before the injection of ^{188}Re-perrhenate had the best blocking effect.

MIXED FORMULA EFFECT. The mixed formula showed good blocking effect. The gastric uptake of ^{188}Re-perrhenate decreased from 10.67% to 3.89%.

TABLE 1. Effects on Tissue Concentrations in Rats Using Preblocking, Mixed Formula, and Postblocking Methods

	%ID/g								
	Blood	**Liver**	**Kidney**	**Heart**	**Lung**	**Thyroid**	**Stomach**	**Small intestine**	**Large intestine**
Pre-blocking									
Control	1.5 ± 0.12	0.64 ± 0.02	0.94 ± 0.07	0.58 ± 0.02	0.95 ± 0.08	63.88 ± 8.11	10.67 ± 2.43	0.59 ± 0.09	0.40 ± 0.03
$NaClO_4$ ral	1.66 ± 0.17	0.69 ± 0.08	1.06 ± 0.14	0.67 ± 0.12	1.01 ± 0.12	15.63 ± 2.06	2.76 ± 0.49	0.46 ± 0.04	0.40 ± 0.04
NaI IV	1.64 ± 0.06	0.66 ± 0.05	1.06 ± 0.04	0.58 ± 0.07	0.92 ± 0.08	22.97 ± 3.88	6.22 ± 0.86	0.74 ± 0.32	0.55 ± 0.17
KI orally	1.55 ± 0.18	0.63 ± 0.07	0.92 ± 0.13	0.56 ± 0.08	0.89 ± 0.15	31.02 ± 6.85	7.64 ± 1.49	0.69 ± 0.19	0.46 ± 0.06
Mixed formula									
NaI	1.62 ± 0.13	0.68 ± 0.06	0.88 ± 0.11	0.55 ± 0.03	0.86 ± 0.10	24.29 ± 4.86	3.89 ± 0.81	0.50 ± 0.06	0.43 ± 0.08
Post-blocking									
Control	0.99 ± 0.10	0.40 ± 0.03	0.66 ± 0.04	0.33 ± 0.04	0.56 ± 0.05	54.21 ± 11.28	12.27 ± 2.00	0.44 ± 0.19	0.28 ± 0.02
KI oral	0.98 ± 0.06	0.36 ± 0.02	0.56 ± 0.06	0.35 ± 0.04	0.54 ± 0.04	20.74 ± 2.35	7.48 ± 1.20	0.36 ± 0.04	0.28 ± 0.03
NaI IV	1.23 ± 0.14	0.48 ± 0.05	0.77 ± 0.09	0.44 ± 0.07	0.66 ± 0.10	14.82 ± 5.22	9.69 ± 1.02	0.58 ± 0.23	0.35 ± 0.05

Note: Data are the average of 5 tissue samples.

POSTBLOCKING EFFECT. In the control group, mean gastric uptake of perrhenate was 12.27% 1 h after injection. When either KI (orally) or NaI (intravenously) was administered 30 min after intravenous injection of ^{188}Re-perrhenate, the gastric uptake of perrhenate dropped. The gastric uptake levels were 7.48% and 9.69% in the KI group and NaI group, respectively. KI administered orally 30 min after injection of ^{188}Re-perrhenate had a better blocking effect on gastric uptake.

DISCUSSION

Both the thyroid gland and the gastrointestinal tract are very sensitive to radiation. The association of radiation exposure to the thyroid gland with the subsequent development of thyroid nodules and hypothyroidism is well-recognized (3, 5, 12). Radiation is also reported to be associated with an increase in acute gastrointestinal toxicity during rectal adjuvant therapy, most notably an increased incidence of diarrhea (13, 20). Therefore, unexpected radiation doses to the thyroid gland and gastrointestinal tract would be the major drawback to using ^{188}Re-perrhenate in endovascular irradiation with a liquid-filled balloon to prevent restenosis because the balloon could rupture during the procedure, although the incidence of such rupture is very rare (<0.1%).

The biologic distribution of pertechnetate is altered by pretreatment of the patient with perchlorate (ClO_4^-) (24), a monovalent anion of approximately the same size as technetium pertechnetate

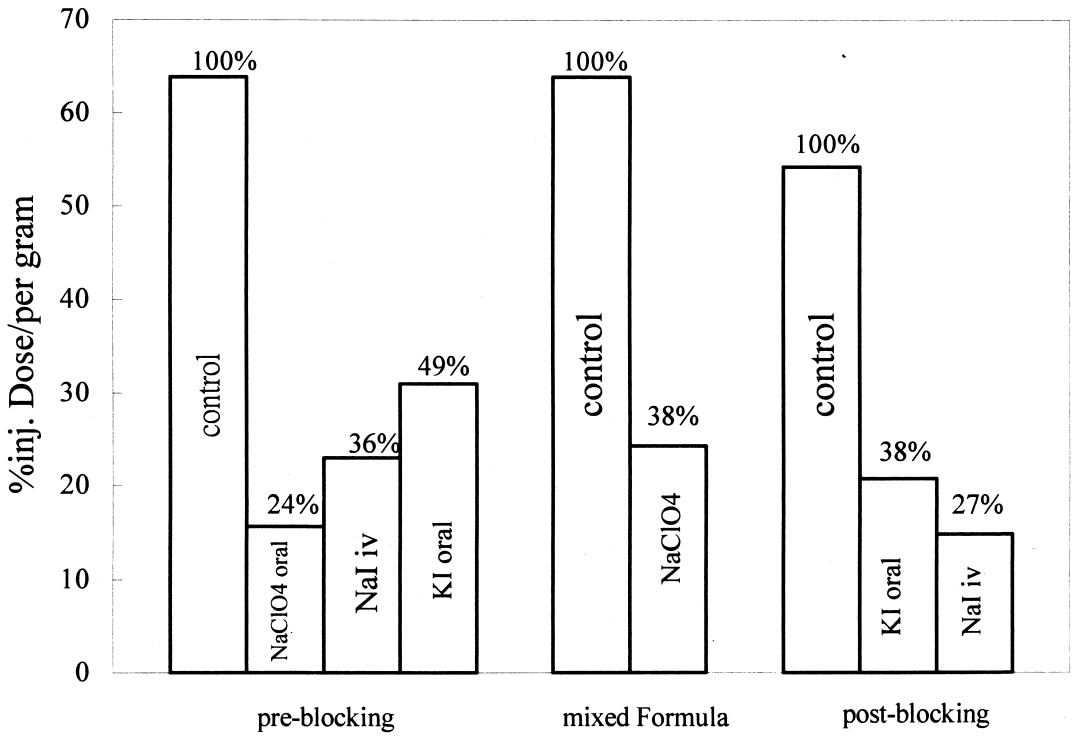

FIG. 1. The effects of preblocking, mixed formula, and postblocking methods on blockage of thyroid uptake of ^{188}Re-perrhenate in rats. iv = intravenous.

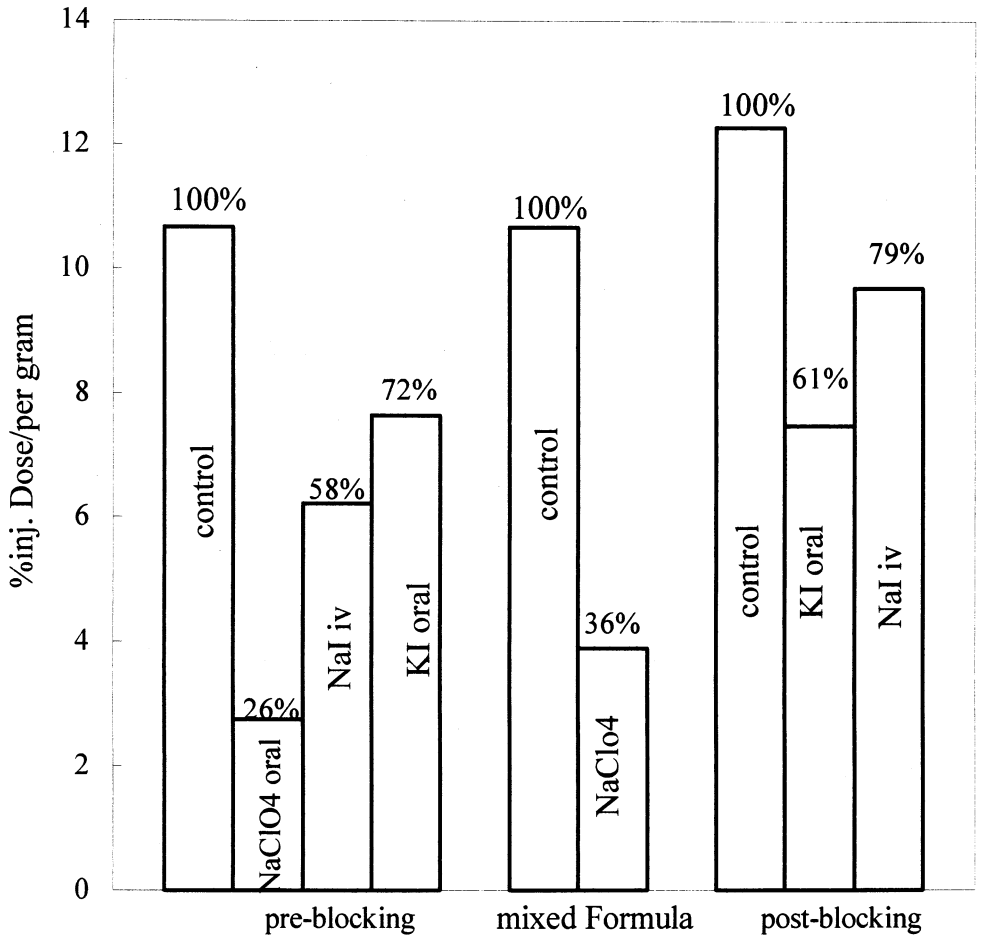

FIG. 2. The effects of preblocking, mixed formula, and postblocking methods on blockage of gastric uptake of ^{188}Re-perrhenate in rats. iv = intravenous.

(TcO_4^-). Perchlorate blocks the uptake of pertechnetate in the thyroid gland, salivary glands, choroid plexus, and gastric mucosa by competitive inhibition. In addition, ingestion of foods rich in iodine, such as seafood, also may decrease thyroid uptake of iodine or pertechnetate for up to 15 days (6). Clinically, a perchlorate discharge test can detect a disturbance in the iodine pathway of the thyroid. The test is based on the fact that perchlorate is trapped by the thyroid and displaces iodide ions that have not been organized (1). Moreover, perchlorate has also been used in a gastrointestinal bleeding study to block gastric uptake of free 99mTc-pertechnetate after *in vivo* labeling of red cells (7). Because the chemical properties of rhenium and technetium are similar (4), it is reasonable to assume that the uptake of ^{188}Re-perrhenate in the thyroid and stomach can be reduced by perchlorate.

Our results showed that pretreatment with perchlorate or iodide via oral intake or intravenous injection could effectively reduce the uptake of perrhenate in both the thyroid gland and the stomach. Moreover, oral intake of sodium perchlorate before injection of ^{188}Re-perrhenate had the best blocking effect: Thyroid uptake was reduced by 75% (from 66.88% to 15.63%) and gastric uptake was reduced by 74% (from 10.67% to 2.76%) within 30 min. However, from the viewpoints of clinical practice and cost-effectiveness, it does not seem worthwhile to pretreat all patients with perchlorate or iodide because the incidence of balloon rupture is very rare.

The blocking effect of mixed formula on thyroid and gastric uptakes of perrhenate was good. It effectively reduced thyroid and gastric uptakes by 62% and 64%, respectively. The mixed formula is a good method to reduce the radiation doses to the thyroid and the stomach in case of balloon rupture because pretreatment is not required and preparation of the mixed formula is very simple.

The reductions in thyroid uptake were also good with oral KI or intravenous NaI after the injection of ^{188}Re-perrhenate. The reductions were 62% for KI and 73% for NaI. In contrast, the blocking effect on gastric uptake was limited by iodide either via oral intake or vein injection. The reduction was only 40% for KI given orally and 21% for NaI given intravenously. The radiation doses to the thyroid gland and the stomach would be higher using the postblocking method than the preblocking or mixed formula methods, because the thyroid and stomach would have accumulated a significant amount of perrhenate before the iodide or perchlorate could be given and take effect.

The effectiveness of oral administration of perchlorate in reducing whole body radiation caused by ^{188}Re-perrhenate has been reported by Kotzerke *et al.* (9). In their study, patients received 600 mg perchlorate orally 15 min after injection of 80–100 MBq ^{188}Re-perrhenate. The radiation can be reduced from 2.000 mGy MBq^{-1} to 0.069 mGy MBq^{-1} in lower large intestine wall, from 0.430 mGy MBq^{-1} to 0.067 mGy MBq^{-1} in the stomach, and from 1.100 mGy MBq^{-1} to 0.067 mGy MBq^{-1} in the thyroid gland. The reduction is obvious. According to our study, both the preblocking

and mixed formula methods should achieve better effectiveness than the postblocking method.

In conclusion, our data suggest that (1) oral pretreatment of the patients with sodium perchlorate has the best blocking effect on the uptake of ^{188}Re-perrhenate in the thyroid gland and stomach, (2) mixed formula (mixed ^{188}Re-perrhenate and sodium iodide) also have a good effect on reducing radiation dose to the thyroid and the stomach, and (3) once the balloon is ruptured, the postblocking method should be applied to patients who have not already received a prevention procedure.

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