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ORIGINAL ARTICLE

The effect of short-term treatment with lithium carbonate on the outcome of radioiodine therapy in patients with long-lasting Graves' hyperthyroidism

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Abstract
Objective The outcome of radioiodine therapy (RIT) in Graves' hyperthyroidism (GH) mainly depends on radioiodine (^{131}I) uptake and the effective half-life of ^{131}I in the gland. Studies have shown that lithium carbonate ($LiCO_3$) enhances the ^{131}I half-life and increases the applied thyroid radiation dose without affecting the thyroid ^{131}I uptake. We investigated the effect of short-term treatment with $LiCO_3$ on the outcome of RIT in patients with long-lasting GH, its influence on the thyroid hormones levels 7 days after RIT, and possible side effects.
Methods Study prospectively included 30 patients treated with $LiCO_3$ and ^{131}I (RI-Li group) and 30 patients only with ^{131}I (RI group). Treatment with $LiCO_3$ (900 mg/day) started 1 day before RIT and continued 6 days after. Anti-thyroid drugs withdrawal was 7 days before RIT. Patients were followed up for 12 months. We defined a success of RIT as euthyroidism or hypothyroidism, and a failure as persistent hyperthyroidism.
Results In RI-Li group, a serum level of Li was 0.571 ± 0.156 mmol/l before RIT. Serum levels of TT_4 and FT_4 increased while TSH decreased only in RI group 7 days after RIT. No toxic effects were noticed during $LiCO_3$ treatment. After 12 months, a success of RIT was 73.3% in RI and 90.0% in RI-Li group ($P < 0.01$). Hypothyroidism was achieved faster in RI-Li (1st month) than in RI group (3rd month). Euthyroidism slowly decreased in RI-Li group, and not all patients became hypothyroid for 12 months. In contrast, euthyroidism rapidly declined in RI group, and all cured patients became hypothyroid after 6 months.
Conclusion The short-term treatment with $LiCO_3$ as an adjunct to ^{131}I improves efficacy of RIT in patients with long-lasting GH. A success of RIT achieves faster in lithium-treated than in RI group. Treatment with $LiCO_3$ for 7 days prevents transient worsening of hyperthyroidism after RIT. Short-term use of $LiCO_3$ shows no toxic side effects.

Keywords Graves' hyperthyroidism · ^{131}I therapy · Lithium carbonate · Thyroid

Introduction

Graves' disease is the autoimmune thyroid disorder. Its onset is related to the interaction of genetic and environmental factors [1]. The primary clinical manifestation of the disease is Graves' hyperthyroidism (GH) characterized by the anti-thyroid stimulating hormone (TSH) receptor antibodies (TRAb) in serum and overproduction of thyroxine (T_4) and triiodothyronine (T_3) in the gland [2].

The initial therapeutic approach of GH with the anti-thyroid drugs (ATD) aims to reduce the production of thyroid hormones (TH). A relatively high relapse rate of GH after ATD withdrawal has reported in over 50% of treated patients [3]. It has recommended that if the ATD treatment fails after 18 months, the radioiodine therapy (RIT) or thyroidectomy should be applied [3–5]. The purpose of RIT is to destroy sufficient thyroid tissue by β^- particles emitted from radioiodine (^{131}I). It is not possible to determine an appropriate ^{131}I activity for achieving stable euthyroidism as the ideal outcome for GH. Therefore, hypothyroidism by lifetime thyroxine replacement therapy also represents a success of RIT [5]. The outcome of RIT mainly depends on the ^{131}I uptake and

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the effective half-life (EHL) of ^{131}I in the gland [6, 7]. The applied ^{131}I activity, TH levels, TRAb, pretreatment with ATD, age, or sex may also affect the efficacy of RIT [8–10].

After an unexpected observation that lithium salts cause sedation in guinea pigs, lithium carbonate ($LiCO_3$) was introduced in 1949 for stabilizing the mood in patients with bipolar psychoses [11]. It has been noticed that long-term treatment with $LiCO_3$ in some patients induced goiter [12]. Studies have shown that $LiCO_3$ inhibits the discharge rate of ^{131}I from the thyroid [13] and blocks release of TH from the gland in both normal and hyperthyroid subjects [14]. It has also been shown that $LiCO_3$ treatment for 14 days prolongs the thyroidal EHL of tracer doses of ^{131}I [15]. Accordingly, the effect of $LiCO_3$ on RIT outcome in GH was analyzed by several studies [16–24]. Some of them showed a higher cure rate in patients treated with ^{131}I plus $LiCO_3$ than in patients treated with ^{131}I alone [16–20], while others contradicted the beneficial effect of $LiCO_3$ on the overall RIT outcome [21–24]. Treatment with $LiCO_3$ (6–21 days), its daily dose (750–900 mg), the beginning of the treatment before RIT (3–12 days), ATD withdrawal before RIT (3–5 days), and the applied ^{131}I activities differed among the studies [16–19, 23]. The impact of $LiCO_3$ on RIT outcome was mainly examined in patients with a recent onset of GH [16–18]. Concerning these studies, we chose 7-day treatment with $LiCO_3$ (started 7 days after ATD withdrawal and 1 day before RIT) in a daily dose of 900 mg and applied 296–444 MBq of ^{131}I-Na doses in order to improve efficacy of RIT.

The aim of this prospective study was to investigate the effect of short-term treatment with $LiCO_3$ on the outcome of RIT in patients with long-lasting GH, its influence on the thyroid hormone levels 7 days after RIT, and possible side effects. The effect of age, duration of GH, TRAb, technetium-99m pertechnetate ($^{99m}TcO_4^-$) thyroid uptake (^{99m}TcTU), and the applied ^{131}I activities on the outcome of RIT in both groups were also studied.

Materials and methods

Study design

We prospectively included 60 patients with recurrent and long-lasting GH. Thirty patients were treated with ^{131}I and $LiCO_3$ (RI-Li group) while 30 patients with ^{131}I alone (RI group). All patients were subjected to the same conditions of preparation to RIT and followed up for 12 months. The uncertain outcome of the study was approved by the Committee for postgraduate studies at the Faculty of Medicine Niš (reference number 04-835/12). The study was conducted from April 2012 to March 2016 at the Center of Nuclear Medicine, Clinical Center of Niš, Serbia. The patients were received detailed information about the procedure, possible outcome, and safety factors.

Eligibility criteria

The inclusion criteria were: both sexes aged 20–70 years, TRAb at the onset of GH, failure of ATD therapy, and absent or moderately present Graves' ophthalmopathy (GO). We also included the patients with the gland size estimated by palpation as a grade 0 (normal-sized, invisible), grade 1 (slightly enlarged, visible), and grade 2 (moderately enlarged, highly visible). The exclusion criteria were: thyroid nodules suspicious for malignancy, severe GO, previous treatment with ^{131}I, thyroidectomy, amiodarone or $LiCO_3$, psychiatric or renal diseases.

Patients

The study included 49 females and 11 males aged 30–69 years (52.6 ± 9.05 year). The disease lasted longer than 2 years in 55 of 60 patients (range 7 months to 30 years). All patients were treated with ATD for 1–24 months to the remission of disease (8.62 ± 4.57 month). Values of ^{99m}TcTU ranged from 0.50 to 21.5% (8.59 ± 5.12%).

Methods

After achieved remission, the ATD therapy was discontinued 7 days before RIT. The ^{99m}TcTU test was performed 1 day before RIT (normal value 0.30–3.00%). We applied intravenously 74 MBq of $^{99m}TcO_4^-$ and after 20 min the thyroid uptake was measured by a Siemens e-cam gamma camera equipped with a low energy collimator. Thyroid uptake of $^{99m}TcO_4^-$ was calculated as the ratio of the thyroid counts and the net syringe counts that were both corrected for the background counts, radioactive decay of ^{99m}Tc, and attenuation of γ-photons in the air.

Treatment with $LiCO_3$ started 1 day before RIT by administering orally 300 mg every 8 h. The treatment lasted for 7 days. Before ^{131}I-NaI application, the serum level of lithium was measured (reference interval 0.300–1.30 mmol/l) (Flame Photometer IL945). Patients were obliged to report the side effects during treatment. Serum levels of sodium (Na), potassium (K), chlorine (Cl), bicarbonates (Bic), calcium (Ca), magnesium (Mg), urea (U), and creatinine (Cr) were determined 1 day before and at the end of $LiCO_3$ treatment (Olympus AV680 analyzer, USA).

Serum levels of TSH, total T_4 and T_3 (TT_4, TT_3), free T_4 and T_3 (FT_4, FT_3), and TRAb were determined on the day of RIT. We repeated the measuring of TSH and TH 7 days after that (LKB-Wallac Clinic Gamma1272, Finland).

The dose of ^{131}I-NaI was orally applied. It was determined concerning the gland size, i.e., 276, 370, and 444 MBq for

grade 0, 1, and 2, respectively. Patients were followed up for 12 months. The serum levels of FT_4, FT_3, and TSH were measured after 1, 3, 6, 9, and 12 months. The success of RIT was defined as biochemically confirmed euthyroidism or hypothyroidism for 12 months and the failure as persistent hyperthyroidism.

Data analysis

The continuous variables are presented as mean ± standard deviation (SD) or mean ± standard error (SE) and median if required, and categorical variables as absolute numbers or percentage. Kolmogorov–Smirnov test is used to determine whether the values of continuous variables were normally distributed or not. Student's *t* test for independent samples (normally distributed values) and Wilcoxon rank-sum test (non-normally distributed values) are used to assess the differences in patient's baseline characteristics between groups. Chi-square test and Fisher's exact test (if one cell in 2 × 2 table has the value less than 5) are used to compare categorical variables and therapeutic outcome among the groups. A repeated measure ANOVA is used to estimate the differences in mean values of variables measured before and after treatment within the groups. Logistic regression analysis is used to identify the independent variables that contribute to the prediction of the unfavorable modality of the dependent variable. Kaplan–Meier survival analysis is performed to estimate the cure time of disease and comparison between groups is assessed with the log-rank test. We considered the *P* value of <0.05 as significant. A statistical analysis is performed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago IL, USA).

Results

The patient`s baseline characteristics of both groups on the day of RIT are shown in Table 1. They had similar age, duration of GH and ATD therapy, TRAb level and ^{99m}TcTU before RIT, and received the same dose of ^{131}I-NaI. The mean free and total TH as well as TSH serum levels did not differ between the groups (Table 1). However, TT_4 and FT_4 serum levels significantly increased while TSH level decreased 7 days after RIT in patients treated with ^{131}I alone (Table 2). In contrast, there were no considerable changes in TT_4, FT_4, and TSH levels in RI-Li group, except decreased TT_3 level (Table 2). Also, 7 days after RIT only mean FT_4 serum level significantly differed among the groups (19.1 ± 6.93 vs. 12.7 ± 3.80 nmol/l, $P < 0.001$). The worsening of GO was not noticed for 12 months.

Table 1 Baseline characteristics of patients treated only with ^{131}I and ^{131}I with $LiCO_3$ before radioiodine therapy

	RI group	RI-Li group	*P*
Female|male (*n*)	24|6	25|5	0.739
Age (year)	51.3 ± 9.23[a]|36–67[b]	53.9 ± 8.83[a]|30–69[b]	0.270
GH duration (year)	6.05 ± 4.38[a]|0.75–21[b]	7.02 ± 5.67[a]|0.58–30[b]	0.539
GH ≥2 years (*n*)	27	28	1.000
GO (%)	43.3	40.0	0.793
ATDTh (month)	8.75 ± 5.31[a]|1–24[b]	8.48 ± 3.76[a]|2–18[b]	0.841
TRAb (mU/l)	5.29 ± 7.12[a]	5.63 ± 4.11[a]	0.133
^{99m}TcTU (%)	9.87 ± 5.61[a]	7.31 ± 4.30[a]	0.052
FT_4 (nmol/l)	16.8 ± 7.86[a]	14.1 ± 5.71[a]	0.173
FT_3 (pmol/l)	6.75 ± 1.53[a]	6.81 ± 1.54[a]	0.874
TT_4 (nmol/l)	129 ± 36.3[a]	144 ± 46.3[a]	0.072
TT_3 (nmol/l)	3.09 ± 0.73[a]	3.41 ± 1.22[a]	0.830
TSH (mU/l)	0.860 ± 0.889[a]	0.894 ± 0.631[a]	0.530
Grade 0 (*n*)	4	2	0.671
Grade 1 (*n*)	21	23	0.559
Grade 2 (*n*)	5	5	1.000
^{131}I-NaI dose (MBq)	398 ± 46.1[a]	392 ± 41.3[a]	0.578

ATDTh duration of ATD therapy before remission of GH

[a]Mean ± SD

[b]Range

Lithium serum level was within the reference interval before RIT (0.571 ± 0.156 mmol/l; range 0.400–0.990 mmol/l). We did not notice the toxic side effects of lithium during the 7-day treatment. Comparison of electrolytes, urea, and creatinine levels 1 day before (all in normal ranges) and after the 7-day treatment with $LiCO_3$ showed no significant changes (Table 3).

A higher percentage of cured patients was in RI-Li than in RI group (Fig. 1). The median cure time was shorter in the RI-Li group (1st month) than in RI group (3rd month) [mean ± SE 1.00 ± 0.00 month, CI (95%) 1.00–1.00 vs. 2.77 ± 0.426 month, CI (95%) 1.94–3.61; $P = 0.000012$]. Hypothyroidism was achieved faster in RI-Li (in five patients after 1 month) than in RI group (in eight patients after 3 months) but still, two of 22 patients in RI-Li group who were euthyroid after 1 month remained euthyroid 12 months after RIT. In contrast, all cured patients in RI group became hypothyroid after 6 months (Fig. 2).

Age, duration of GH, TRAb, and ^{99m}TcTU (Table 4) did not have a predictive role for permanent hyperthyroidism 12 months after RIT in both groups. Despite that, we identified the dose of ^{131}I-NaI as a predictor of RIT failure only in RI group (Table 4). Also, the applied 370 and 444 MBq activities of ^{131}I were appropriate to successfully cure more patients in RI-Li than in RI group for 12 months (Table 5).

Table 2 Thyroid hormones and TSH serum levels in patients treated only with ^{131}I and ^{131}I with $LiCO_3$ on the day of radioiodine application and 7 days after that

	RI group			RI-Li group		
	Day 0 (mean ± SD)	Day 7 (mean ± SD)	*P*	Day 0 (mean ± SD)	Day 7 (mean ± SD)	*P*
FT_4 (nmol/l)	16.8 ± 7.86	19.1 ± 6.93	0.008	14.1 ± 5.71	12.7 ± 3.80	0.173
FT_3 (pmol/l)	6.75 ± 1.53	6.73 ± 1.96	0.962	6.81 ± 1.54	6.51 ± 1.49	0.301
TT_4 (nmol/l)	129 ± 36.3	152 ± 44.9	0.001	144 ± 46.3	146 ± 45.1	0.362
TT_3 (nmol/l)	3.09 ± 0.73	3.15 ± 0.85	0.703	3.41 ± 1.22	2.69 ± 1.25	0.001
TSH (mU/l)	0.860 ± 0.889	0.508 ± 0.717	0.004	0.894 ± 0.631	0.855 ± 0.689	0.533

Day 0 day of RIT, *Day 7* 7 days after RIT

Table 3 Serum levels of electrolytes, urea, and creatinine before and after the 7-day-long treatment with $LiCO_3$

	b-$LiCO_3$ (mean ± SD)	a-$LiCO_3$ (mean ± SD)	*P*
Na (mmol/l)	141 ± 3.71	140 ± 3.40	0.566
K (mmol/l)	4.66 ± 0.369	4.59 ± 0.368	0.375
Cl (mmol/l)	104 ± 2.85	104 ± 2.72	0.359
Bic (mmol/l)	24.4 ± 1.24	24.2 ± 1.08	0.165
Ca (mmol/l)	2.42 ± 0.152	2.43 ± 0.116	0.598
Mg (mmol/l)	0.922 ± 0.120	0.932 ± 0.171	0.680
U (mmol/l)	4.86 ± 0.835	5.18 ± 1.49	0.228
Cr (mmol/l)	70.8 ± 13.4	71.1 ± 16.7	0.615

b-$LiCO_3$ before $LiCO_3$ treatment, *a-$LiCO_3$* after $LiCO_3$ treatment

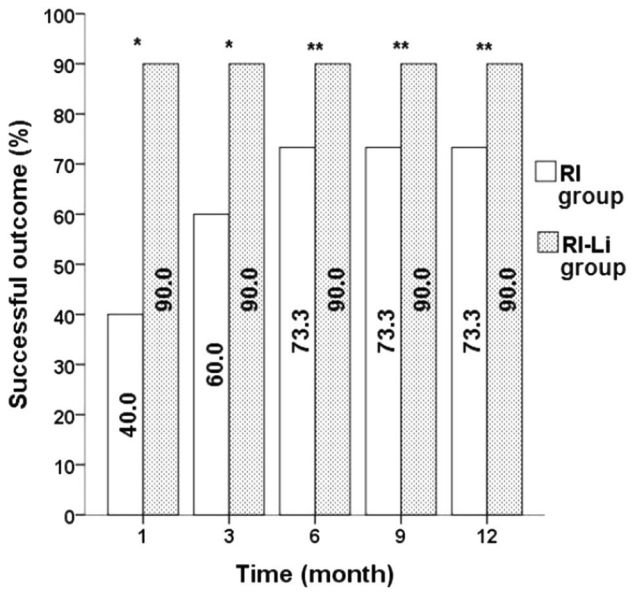

Fig. 1 Comparison of successful RIT outcome for 12 months among the patients' groups treated only with ^{131}I and ^{131}I with $LiCO_3$; $*P < 0.0001$, $**P < 0.01$

Discussion

Radioiodine therapy is effective, safe, and inexpensive for the treatment of GH [5]. The β^- particles of ^{131}I induce thyroid cell destruction in proportion to the quantity of radionuclide accumulated in the gland. The disease should transiently exacerbate after RIT because of the larger release of TH from the damaged gland [8]. Many factors may have the effect on RIT outcome in GH [6–10], but the most influential are ^{131}I uptake and EHL of ^{131}I in the gland [6, 7]. The reduced thyroid iodine pool, faster ^{131}I turnover rate, and shorter EHL of ^{131}I follow Graves' hyperthyroidism. Hence, any attempt to prolong EHL of ^{131}I in the gland may lead to improvement of RIT effectiveness.

Lithium carbonate is primarily used for the treatment of bipolar affective disorders, and its long-term administering may affect the thyroid function [25]. Dunkelmann et al. [26] showed that lithium enhanced the ^{131}I half-life by 60.0%, and increased the applied thyroid radiation dose by 39.0% but did not affect the thyroid ^{131}I uptake when was administered 885 mg/day for 2 weeks. These properties seem beneficial for RIT. Lithium carbonate was rarely utilized to improve the efficiency of RIT. It is not appropriate for the treatment of GH but only in the patients with very short EHL [26], for preventing transient exacerbation of the disease after ATD withdrawal before RIT [17] or in patients who do not tolerate ATD [27].

Presented results are in agreement with some results of our previous report obtained in a small number of patients with long-lasting GH [20]. We confirmed an increase of TT_4 and FT_4 serum levels and a decrease of TSH level 7 days after RIT only in patients treated with ^{131}I alone. This phenomenon that occurs several days after RIT as a repercussion of gland irradiation was absent in patients treated with $LiCO_3$. Other studies also reported this first protective effect of lithium whether it was given with [14, 16, 18] or without ^{131}I [28–30]. Thus, in patients with recent onset of GH (≤6 months) treated with ^{131}I plus $LiCO_3$ (900 mg/day for 12 days), Bogazzi et al. [18] showed that FT_4 serum level did not change significantly after RIT. They reported that FT_4

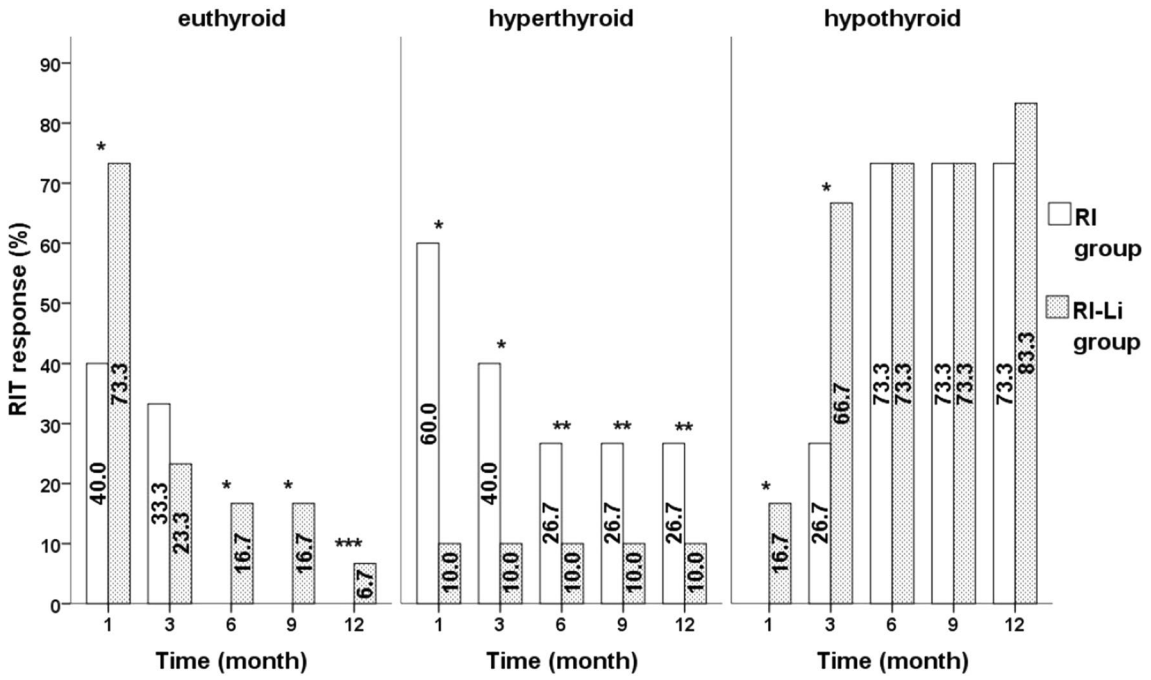

Fig. 2 Comparison of radioiodine therapeutic response for 12 months among the patients' groups treated only with ^{131}I and ^{131}I with $LiCO_3$; *$P < 0.0001$, **$P < 0.01$, ***$P < 0.05$

Table 4 Influence of the risk factors on a failure of radioiodine therapy after 12 months in patients treated only with ^{131}I and ^{131}I with $LiCO_3$

	RI group			RI-Li group		
	P	OR	CI (95%)	*P*	OR	CI (95%)
Age	0.629	1.042	0.882–1.231	0.384	1.077	0.911–1.274
GH duration	0.150	1.260	0.920–1.726	0.576	1.074	0.837–1.378
TRAb	0.235	1.108	0.936–1.313	0.463	0.857	0.568–1.294
^{99m}TcTU	0.480	1.100	0.844–1.435	0.918	0.985	0.734–1.321
^{131}I-Na dose	0.021	8.308	1.383–49.9	0.195	0.425	0.116–1.552

OR odds ratio, *CI* confidential interval

Table 5 Comparison between ^{131}I-NaI dose and radioiodine therapy response for 12 months in patients treated only with ^{131}I and ^{131}I with $LiCO_3$

	296 MBq			370 MBq			444 MBq		
Month	RI ur|sr (n)	RI-Li ur|sr (n)	*P*	RI ur|sr (n)	RI-Li ur|sr (n)	*P*	RI ur|sr (n)	RI-Li ur|sr (n)	*P*
1th	3|1	1|1	1.000	11|10	2|21	0.002	4|1	0|5	0.048
3rd	0|4	1|1	0.333	8|13	2|21	0.0003	4|1	0|5	0.048
6th–12th	0|4	1|1	0.333	4|17	2|21	0.403	4|1	0|5	0.048

ur unsuccessful RIT response, *sr* successful RIT response

level increased in patients treated with ^{131}I alone reaching a peak between 3 and 5 days after RIT ($P < 0.0001$ for both times). Carlson et al. [29] found 26.0–45.0% inhibition of TT_4 disappearance rate in hyperthyroid patients treated only with lithium for 6–7 days but without any change in TT_4 disappearance slope in euthyroid individuals. In our study, mean TH serum levels and TSH level before and 7 days after RIT did not differ among the groups except the difference in mean FT_4 level. Bogazzi et al. [18] also found a higher mean FT_4 level in patients who received only ^{131}I than in

patients who received ^{131}I and $LiCO_3$. In the present study, mean TT_3 level decreased significantly in RI-Li group 7 days after RIT which was not noticed in our previous report [20]. Similarly, Temple et al. [28] found that TT_3 serum level fell somewhat more than TT_4 level after lithium administering. So, they postulated that lithium might inhibit the conversion of thyroxine to triiodothyronine.

The use of $LiCO_3$ is accompanied by controversies for the treatment of bipolar affective disorders because of life-long dose monitoring and the appearance of both acute and chronic side effects [25, 31]. Lithium carbonate has a simple pharmacokinetics, and after an oral administering reaches a peak of serum concentration for 4–12 h. It thoroughly distributes into interstitial fluid and ultimately slowly enters into the intracellular fluid [32]. Lithium exclusively excretes via the kidneys and any acute or chronic disturbance of the excretion increases its serum concentration and may become toxic [31, 32]. The pathophysiology of renal, parathyroid, and thyroid dysfunctions during its long-term use is unclear [33]. We showed no side toxic effects of lithium for 7 days of use. Mean serum levels of electrolytes, urea, and creatinine before and after 7-day treatment were similar. There are insufficient reports on $LiCO_3$ side effects when its short-term use (400–900 mg/day) with ^{131}I is combined. The studies of Turner et al. [15] and Bogazzi et al. [18] reported that the side effects of $LiCO_3$ were not relevant. In other studies, only one of 54 patients had mild nausea [16] or insignificant appearance of nausea and neck sensitivity [17]. We noticed that $LiCO_3$ supporting RIT had no impact on GO. To our knowledge, only one study reported that the patients had no worsening of GO for 12 months after RIT [16].

We showed the remarkable effect of $LiCO_3$ on RIT outcome in patients with long-lasting GH. Lithium-treated patients were cured more rapidly (27/30 patients were euthyroid or hypothyroid after 1 month) than those treated only with ^{131}I-NaI (12/30 patients were euthyroid after one and 22 patients were hypothyroid after 6 months). Although the daily dose of $LiCO_3$, duration of treatment and its beginning before RIT, and the applied ^{131}I activities [16–24] differed among studies, our results are in agreement with the results of some other studies [16–19]. The cited studies [16–18], except the study of Martin et al. [19], included patients with recent onset of GH. After 5 days of ATD withdrawal, Bogazzi et al. [16] treated a newly diagnosed GH patients with $LiCO_3$ for 6 days (900 mg/day) starting on the day of ^{131}I application (521 ± 148 and 556 ± 141 MBq in RI and RI-Li group, respectively). After 1 year, the success of RIT was 72.0% in RI and 83.0% in RI-Li group ($P = 0.02$). Martin et al. [19] showed the success in 93.1% of patients treated with ^{131}I-NaI (500 MBq) and $LiCO_3$ for 10 days (800 mg/day, starting 3 days before RIT), as well in 83.5% of patients treated only with ^{131}I-NaI ($P = 0.049$). This improvement of RIT efficiency occurs due to the extension of EHL of ^{131}I in the gland by $LiCO_3$ [13–15, 26] and the increment of radiation dose in the thyroid [18]. However, others showed that $LiCO_3$ did not affect the outcome of RIT [21–24]. Two studies [21, 22] explained such result by a high cure rate in both groups and a small number of treated patients. Also, Bal et al. [23] reported that a success of RIT was 71.6% in RI-Li and 70.5% in control group after 12 months ($P > 0.05$). In that study, ATD withdrawal was 3–4 days before RIT, the treatment with $LiCO_3$ started on the day of RIT (900 mg/day for 21 days), and the low doses of ^{131}I-NaI in both groups (196 ± 55.5 and 211 ± 59.2 MBq) were applied. Comparison of the designs and results of the cited studies show that the insignificant effect of $LiCO_3$ on RIT outcome occurs when a low dose of ^{131}I-NaI was applied [23], or when the treatment with $LiCO_3$ started on the day of RIT [16, 23]. In the second case, the effect of $LiCO_3$ on the follicular cells level is diminished probably due to it slowly entering the intracellular fluid [32], and its incomplete accumulation in the tissue before ^{131}I was applied.

The important finding of our study is that the number of euthyroid patients slowly decreases in the lithium-treated group, but not all cured patients become hypothyroid for 12 months. On the contrary, the number of euthyroid patients who did not receive $LiCO_3$ rapidly declines and all of them become hypothyroid for 6 months. That may suggest a protective effect of $LiCO_3$ on preventing early induction of hypothyroidism.

Age, duration of GH, TRAb, and ^{99m}TcTU were not determined as predictors of permanent GH in both groups. It is not possible to establish a direct connection between the risk factors and genetic susceptibility because of presence and interaction of several of these factors in a patient before the onset of disease [1]. Despite that, the dose of ^{131}I-NaI had a predictive role in RIT failure only in RI group. Finally, comparison of the RIT response and the applied ^{131}I activities points that the short-term treatment with $LiCO_3$ provides the success of RIT in more patients with the low doses of ^{131}I-NaI. This finding could confirm that $LiCO_3$ increases radiation dose in the gland and leads to a higher level of tissue irradiation. To our knowledge, only Martin et al. [19] showed that the ^{131}I activity, gender, and age correlated with a high probability of successful treatment of GH with ^{131}I and $LiCO_3$, although, they applied the high doses of ^{131}I-NaI in both groups (510–597 and 537–595 MBq).

Conclusion

Although the patients with GH should not be treated with ATD more than 18 months, it is often disregarded in clinical practice. Generally, the long-lasting GH and comorbidities make it difficult to apply the radioiodine or surgical therapy for the finally cure of the disease. Lithium carbonate as an

adjunct to ^{131}I is rarely used in daily practice except for preventing transient worsening of the disease after RIT and mainly in patients with newly diagnosed GH. Despite that, our perspective study included the patients with long-lasting GH who were treated with relatively low doses of ^{131}I-NaI. The study indicates that the short course of $LiCO_3$ treatment in combination with ^{131}I has the beneficial effect on RIT outcome in these patients. A successful outcome is achieved faster in lithium-treated patients than in those treated with ^{131}I alone. Lithium carbonate prevents transient worsening of hyperthyroidism after ^{131}I application. The treatment with $LiCO_3$ for 7 days is safe in patients with normal renal function and serum electrolytes levels. Also, age, duration of GH, TRAb, and ^{99m}TcTU have no influence on RIT outcome in patients treated and not treated with $LiCO_3$, but the dose of ^{131}I-Na has a predictive role for a failure of RIT in patients treated only with ^{131}I.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were by the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its letter amendments or comparable ethical standards.

Informed consent Informed consent has obtained from all individual participants included in the study.

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