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Evaluation of the efficacy of intravenous corticotherapy in preventing exacerbation of thyroid orbitopathy in patients with Graves' disease treated with radioactive iodine due to hyperthyroidism

Ocena skuteczności kortykoterapii dożylnej w prewencji zaostrzenia orbitopatii tarczycowej u osób z chorobą Gravesa i Basedowa leczonych radiojodem z powodu nadczynności tarczycy

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S u m m a r y

Introduction. Radioiodine treatment of thyrotoxicosis in Graves' disease patients may lead to orbitopathy progression. Oral glucocorticoid therapy is a standard method in prevention of eye changes exacerbation. The aim of this study was to evaluate the efficacy and safety of intravenous steroid therapy in prevention of orbitopathy exacerbation after ^{131}I treatment.

Material and methods. The study included 32 patients with Graves' disease and ophthalmopathy, treated with radioiodine due to thyrotoxicosis in 2010-2011 in the Department of Endocrinology CMKP. To prevent ophthalmopathy exacerbation, 16 patients (group 1) received intravenous methylprednisolone (4 weekly infusions of 250 mg), while the remaining 16 patients (group 2) were treated with prednisone (0.3-0.5 mg per kg of body weight for 4-5 weeks with dose reduction during 8 weeks). The groups were compared before and 1 month and 1 year after ^{131}I therapy in terms of severity of orbitopathy (NOSPECS classification) and its activity (using Clinical Activity Score – CAS), serum TSH receptor antibody (TRAb), the need for additional systemic steroid therapy due to exacerbation of eye changes and the occurrence of adverse events.

Results. Groups 1 and 2 did not differ significantly according to NOSPECS class, CAS, nor TRAb concentrations at baseline, after 1 month and after 1 year of treatment. In group 1, there were no side effects of corticosteroid therapy, while in group 2 two patients discontinued prednisone therapy – 1 because of depression, and 1 because of gastrointestinal disorders.

Conclusions. In compare to the commonly used oral prednisone, intravenous administration of methylprednisolone seem to be equally effective in the prevention of exacerbation of orbitopathy after radioiodine therapy and carries fewer side effects.

Key words: Graves' ophthalmopathy, radioiodine treatment, corticosteroids

S t r e s z c z e n i e

Wstęp. Leczenie radiojodem nadczynności tarczycy u chorych z chorobą Gravesa i Basedowa może prowadzić do zaostrzenia orbitopatii tarczycowej. Standardowo w zapobieganiu nasileniu zmian ocznych stosuje się steroidy doustnie. Celem pracy była ocena skuteczności i bezpieczeństwa stosowania steroidoterapii dożylnej jako prewencji zaostrzenia orbitopatii po leczeniu ^{131}I.

Materiał i metody. Badaniem objęto 32 osoby z chorobą Gravesa i Basedowa i orbitopatią tarczycową leczonych radiojodem w latach 2010-2011 w Klinice Endokrynologii CMKP z powodu nadczynności tarczycy. W ramach prewencji nasilenia zmian ocznych u 16 chorych (grupa 1) stosowano dożylnie metyloprednizolon (4 cotygodniowe wlewy po 250 mg), zaś pozostałych 16 osób (grupa 2) otrzymywało prednizon (0,3-0,5 mg na kg masy ciała przez 4-5 tygodni z redukcją dawki w ciągu 8 tygodni). Grupy porównywano przed oraz po upływie 1 miesiąca i 1 roku od leczenia ^{131}I pod względem ciężkości orbitopatii (wg klasyfikacji NOSPECS) i jej aktywności (z użyciem wskaźnika CAS), stężenia przeciwciał przeciwko receptorowi TSH (TRAb), konieczności stosowania dodatkowej steroidoterapii systemowej z powodu zaostrzenia zmian ocznych oraz występowania działań niepożądanych.

Wyniki. Grupy 1 i 2 nie różniły się istotnie między sobą pod względem klasy NOSPECS, wskaźnika CAS, ani stężeń przeciwciał TRAb zarówno wyjściowo, po 1 miesiącu, jak i po 1 roku leczenia. W grupie 1 nie obserwowano działań niepożądanych kortykoterapii, natomiast w grupie 2 u 2 osób odstawiono prednizon – u 1 z powodu depresji, zaś u 2 – dolegliwości ze strony przewodu pokarmowego.

Wnioski. W porównaniu z powszechnie stosowanym leczeniem doustnym prednizonem, dożylne podawanie metyloprednizolonu w ramach prewencji zaostrzenia orbitopatii po leczeniu radiojodem wydaje się równie skuteczne i obarczone mniejszą ilością działań niepożądanych.

Słowa kluczowe: oftalmopatia Gravesa, leczenie radiojodem, kortykosteroidy

INTRODUCTION

Therapy with radioactive iodine is currently the main method of radical treatment of hyperthyroidism in persons with Graves' disease, and absent or present accompanying orbitopathy (1). However, as a result of destruction of the thyroid gland caused by radioactive iodine, stimulation of the autoimmune process occurs, which relates to release of thyroid antigens (2, 3). It has been established that in 15-33% of persons with hyperthyroidism and coexisting active thyroid orbitopathy, treatment with ^{131}I may lead to exacerbation of eye lesions (4-6). Risk factors include: smoking (7), a high level of anti-TSH receptor antibodies (TRAb) (8), repeated treatment with ^{131}I as well as uncontrolled hypothyroidism after treatment with ^{131}I (9, 10). Normally, prophylaxis against intensification of the thyroid orbitopathy includes oral steroid therapy with prednisone (4, 6). In persons treated due to moderate or severe thyroid orbitopathy, intravenous administration of methylprednisolone in the form of repeated weekly infusions is more effective than oral treatment with prednisone. It also allows reducing the total dose of administered corticoids, which relates to less adverse reactions and better tolerance of treatment (11, 12).

The aim of this study is to evaluate the efficacy and safety of methylprednisolone use in the form of weekly intravenous infusions as prophylaxis against exacerbation of the thyroid orbitopathy after treatment with ^{131}I due to hyperthyroidism in persons with Graves' disease.

MATERIAL AND METHODS

The analysis included patients with Graves' disease and coexisting thyroid orbitopathy, treated with ^{131}I at the Clinic of Endocrinology of CMKP in 2010-2011 due to recurrent hyperthyroidism or hyperthyroidism resistant to conservative treatment. Subjects with moderate or severe orbitopathy, with a CAS (Clinical Activity Score) value of ≥ 3 (13) and patients treated in the past due to thyroid orbitopathy with intensive systemic steroid therapy or radiation treatment of the orbital cavities using the linear accelerator, were excluded from the study. Finally, 15 patients receiving systemic intravenous corticotherapy (group 1) underwent evaluation, and they were compared with a group of 15 patients selected according to gender, age and dose of ^{131}I and receiving routine oral treatment with prednisone (group 2). All subjects were informed about the potential consequences, adverse reactions and complications of treatment with ^{131}I and steroid prophylaxis, and they provided their written consents for the proposed treatment.

In group 1, methylprednisolone was used in a regimen of 4 weekly intravenous infusions in the dose of 250 mg of methylprednisolone (SoluMedrol) in 250 mL of 0.9% NaCl, and the first dose was administered on the same day when iodine isotope was administered. In group 2, according to the generally adopted regimen proposed by Barthalena et al. (4, 6), prednisone was used starting on the 1st day following administration of ^{131}I in the dose of 0.3-0.5 mg per kg of body weight over 4-5 weeks, then the dose was gradually reduced during the next 8 weeks.

The studied groups were compared before treatment, after 1 month and 1 year following treatment with ^{131}I in reference to severity and activity of orbitopathy, concentration of antibodies against the TSH receptor (TRAb), the necessity to use additional systemic steroid therapy due to exacerbation of eye lesions and the occurrence of side effects.

Severity of thyroid orbitopathy was evaluated with the NOSPECS classification (0 – No signs or symptoms; 1 – Only signs, no symptoms; 2 – Soft tissue involvement; 3 – Proptosis; 4 – Extraocular muscle involvement; 5 – Corneal involvement; 6 – Sight loss), and activity was evaluated with CAS (Clinical Activity Score) (1, 14, 15).

Before and during therapy, complete blood count, fasting glucose, concentration of sodium, potassium, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and total bilirubin were controlled.

The concentration of TSH, free thyroxine (fT4) and free triiodothyronine (fT3) were evaluated before treatment and then, every 4-8 weeks following treatment with ^{131}I, with the chemiluminescence method using an automatic analyzer Immulite 2000. Reference values for the respective hormones amounted to: TSH 0.4-4.0 μIU/mL, fT4 10.4-24.4 pmol/l, fT3 1.8-4.2 pg/mL. Concentrations of TRAb were evaluated with the ELISA test using Euroimmun Analyzer 1 (negative result: below 1.8 IU/mL, doubtful result: 1.8-2.0 IU/mL, positive result: above 2.0).

Results were subject to statistical analysis using tests for non-parametric functions: the Shapiro-Wilk

test for conformity, the Mann-Whitney test, Spearman's rank correlation coefficient and the Wilcoxon test for paired samples. A value of $p < 0.05$ was assumed as a statistically significant result.

RESULTS

The studied groups did not significantly differ in terms of gender, age, body weight, thyroid gland volume, dose of ^{131}I, activity of the thyroid orbitopathy evaluated with CAS and its intensity according to NOSPECS classification (tab. 1). The values of CAS and NOSPECS classification in both studied groups, before and after treatment with ^{131}I, are presented in table 2.

Medians of TRAb concentrations at baseline, after one month and after one year following treatment with ^{131}I in group 1 amounted to: 14.17 IU/mL (min. 3.55, max. > 40), 9.37 IU/mL (min. 2.04, max. > 40) and 2.05 IU/mL (min. 0.58, max. > 40), respectively, and in group 2: 10.72 IU/mL (min. 0.8, max. > 40), 7.16 IU/mL (min. 0.58, max. 25.82) and 2.62 IU/mL (min. 0.34, max. 23.44). There were no significant differences between both groups in terms of TRAb concentrations. However, a significant decrease in concentration of these antibodies was established in group 1, as well as in group 2, after one month and after one year following administration of radioactive iodine, comparing to baseline concentrations. In addition, a significant difference between TRAb concentrations was established in group 2 after one month and after one year following treatment (fig. 1).

No significant differences were established between studied groups after one month and after one year following treatment with ^{131}I in reference to CAS value, and degree of intensity of orbitopathy evaluated according to NOSPECS classification. In group 1, values of CAS after one year following therapy with radioactive iodine were significantly lower comparing to values observed at baseline and after one month following treatment ($Z = 2.803$, $p = 0.005$ and $Z = 2.023$, $p = 0.043$, respectively). In group 2, a significant difference was established between values of CAS before and after one year following therapy with radioactive iodine ($Z = 2.520$, $p = 0.012$). Comparing to baseline values, exacerbation of orbitopathy according to NOSPECS classification, was significantly reduced after one year in both studied groups (in group 1: $Z = 2.366$, $p = 0.017$; and in group 2: $Z = 2.665$, $p = 0.007$).

According to the regimen, all patients of group 1 received a total dose of 1.0 g of methylprednisolone. In group 2, the average dose of steroids received by a patient was significantly higher than it was in group 1 and it amounted to 1.37 ± 0.16 g per subject ($p < 0.001$). Due to the occurrence of adverse reactions in 2 persons of this group, using prednisone in these subjects was prematurely discontinued. During further observation, none of the studied patients revealed intensification of eye lesions, which would require administration of systemic steroid therapy.

Table 2. Distribution of values of CAS and classes according to NOSPECS in groups 1 and 2 at the baseline, 1 month after treatment and 1 year after treatment with ^{131}I.

	CAS			NOSPECS				
	0	**1**	**2**	**0**	**1**	**2**	**3**	**4**
Before treatment								
Group 1	6	6	4	0	4	3	2	7
Group 2	7	9	0	0	3	6	5	2
After 1 month								
Group 1	9	5	2	2	4	2	1	7
Group 2	11	5	0	2	3	4	5	2
After 1 year								
Group 1	13	3	0	4	4	0	2	6
Group 2	15	1	0	7	3	0	4	2

Table 1. Comparison of groups 1 and 2 before treatment with ^{131}I.

	Group 1					**Group 2**					**Z**	**p**
Gender (F/M)	**15/1**					**14/2**					**-0.28**	**0.78**
	Median	**Min**	**Max**	**25%**	**75%**	**Median**	**Min**	**Max**	**25%**	**75%**		
Age (years)	48.05	35.10	72.80	41.35	52.90	49.75	29.60	66.90	37.40	58.35	0.32	0.75
Body weight (kg)	72.00	56.00	103.00	61.00	77.00	63.50	51.00	95.00	58.00	77.70	1.00	0.32
Height (cm)	165.00	160.00	175.00	163.25	170.00	164.00	158.00	176.00	160.00	170.00	0.53	0.60
TSH (μIU/mL)	0.06	0.00	1.18	0.01	0.29	0.08	0.00	1.51	0.01	0.95	-0.72	0.47
fT4 (pmol/L)	16.85	9.49	24.70	14.59	20.08	17.35	9.78	31.30	12.60	23.00	0.21	0.84
fT3 (pg/mL)	4.03	2.79	6.65	3.24	5.16	4.05	2.45	8.31	3.41	5.05	-0.06	0.95
Thyroid gland volume (ml)	27.20	18.27	92.50	19.20	39.10	32.25	9.61	101.10	20.50	45.34	-0.47	0.64
Iodine capture T_{24} (%)	87.00	34.00	98.00	72.00	94.00	91.50	48.00	98.00	66.05	94.00	-0.49	0.62
Dose ^{131}I (mCi)	12.50	10.00	15.00	10.00	15.00	10.00	10.00	20.00	10.00	12.50	1.04	0.30
CAS	1.00	0.00	2.00	0.00	1.50	1.00	0.00	1.00	0.00	1.00	0.96	0.34
Class according to NOSPECS	3.00	1.00	4.00	1.50	4.00	2.00	1.00	4.00	2.00	3.00	0.89	0.38

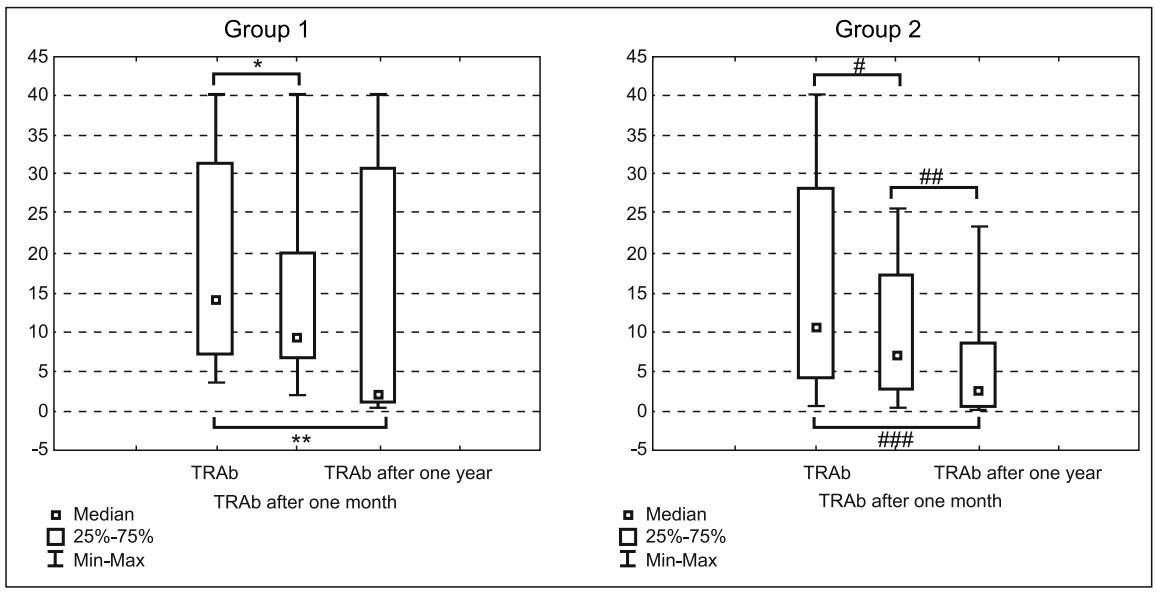

Fig. 1. Concentration of TRAb (IU/mL) in subjects with Graves' disease and coexisting thyroid orbitopathy before treatment, 1 month after and 1 year after treatment with ^{131}I combined with prophylactic systemic steroid therapy (group 1 – methylprednisolone, intravenous; group 2 – prednisone, oral). The Wilcoxon matched pairs test: * – Z=2.12, p = 0.034; ** – Z = 2.07, p = 0.038; # – Z = 3.52, p < 0.001, ## – Z = 3.15, p = 0.002; ### – Z = 2.84, p = 0.004.

Before implementation of prophylaxis with corticosteroids, 3 subjects suffered from type 2 diabetes mellitus 2, and 1 subject – with glucose intolerance – all of them were assigned to group 1. During administration of methylprednisolone, no exacerbation in terms of glycemic control was observed in these patients, as well as no significant changes in concentration of glycated hemoglobin. However, another 3 patients (1 of group 1 and 2 of group 2) revealed abnormal fasting glucose level. Moreover, in medical interviews, the studied subjects revealed: depression (2 subjects of group 1 and 1 of group 2), hypertension (4 subjects of group 1 and 4 of group 2), gastric ulcer disease (3 subjects of group 1 and 1 of group 2), gastritis (1 female patient of group 1), gastroesophageal reflux (3 subjects of group 2) and varicose veins (1 female patient of group 2). In the group receiving intravenous pulses of methylprednisolone, it was not necessary to modify treatment regimen due to adverse reactions. However, among subjects using oral steroid therapy, 2 subjects required lowering of the dose and duration in administration of prednisone – in one case, due to intensification of symptoms of depression, and in the second case, due to gastrointestinal symptoms. None of the subjects revealed a significant increase in aminotranspherase and total bilirubin concentrations.

Analysis of data obtained one year after treatment with ^{131}I revealed a positive correlation between the occurrence of hyperthyroidism and concentration of TRAb ($r = 0.531510$, $p < 0.05$) and the value of CAS ($r = 0.436436$, $p < 0.05$), as well as negative correlation between the occurrence of hypothyroidism and concentration of TRAb ($r = -0{,}503361$, $p < 0.05$).

DISCUSSION

Based on many previously published studies, it has been demonstrated that therapy with radioactive iodine in hypothyroidism in patients with Graves' disease is connected with an increased risk of exacerbation of existing active thyroid orbitopathy (4-6). In case of inactive orbitopathy, this risk is insignificant; it also seems that treatment with radioactive iodine only occasionally leads to the de novo occurrence of orbitopathy. As a result of the thyroid gland destruction caused by radioactive iodine, exacerbation of autoimmune process occurs, with increased concentration and activity of TRAb antibodies and activation of T lymphocytes (2, 16). The percentage of patients who revealed a decline in level of TRAb antibodies within 5 years following treatment with ^{131}I is significantly lower comparing to persons treated with thyreostatic drugs or undergoing thyroidectomy (16). The results we obtained indicate that a combination of radiotherapy with oral, as well as with intravenous corticotherapy leads to a significant decrease in concentrations of TRAb, not only after one month, but also after one year following administration of ^{131}I (fig. 1).

Exacerbation of the thyroid orbitopathy relates to approximately 15% of patients within the first 6 months following treatment with ^{131}I, but in about 5% of patients, a persistent orbitopathy is observed, which require additional steroid therapy (4-6). It was demonstrated that short-term, 3-month, prophylactic use of oral glucocorticoids almost completely eliminates the risk of exacerbation of eye lesions (4, 6). It seems that also shorter, 1-2-month corticosteroid therapy may be sufficient in this case.

In treatment of thyroid orbitopathy, intravenous corticosteroid therapy in the form of periodically repeated

pulses, due to better treatment effects and better safety of use, is currently preferred comparing to oral steroid therapy (11-13, 17-19). The most common treatment regimen includes administration of 12 weekly intravenous pulses of methylprednisolone, but the first 6 of them in the dose of 500 mg each, and the next 6 – in the dose of 250 mg each (11). Total administered dose of methylprednisolone during this therapy is 4.5 g. It is significantly lower than the recommended upper limit amounting to 8 g. Results of retrospective studies published until now indicate that using such regimen of intravenous steroid therapy in thyroid orbitopathy leads to improvement in eye lesions in 80-90% of patients, and administration of prednisone – in 50-60% of patients (17-19).

In our study, the group receiving intravenous methylprednisolone did not significantly differ from the group receiving oral prednisone in terms of concentrations of TRAb, value of CAS, or NOSPECS classification. None of the studied patients revealed exacerbation of eye lesions requiring corticosteroid therapy. Therefore, it seems that using repeated pulses of methylprednisolone is also effective in prophylaxis of exacerbation of the thyroid orbitopathy following treatment with ^{131}I, as the currently popular regimen of oral corticotherapy.

Steroid therapies, both intravenous and oral, are connected with many serious adverse reactions, which include i.a.: liver failure (mainly observed after exceeding a total dose of 8 g), activation of viral hepatitis, exacerbation of hypertension, diabetes mellitus, peptic ulcer disease, osteoporosis, infectious diseases, cataract and glaucoma (11, 17, 19). As a result of use of corticosteroids, exacerbation of depression, psychosis and even suicide attempts were also observed. In addition, chronic, daily use of corticosteroids may lead to secondary adrenal insufficiency. It was not proven that intravenous corticosteroid therapy in the form of repeated weekly pulses gave such effect.

Despite higher number of patients with past or current diseases, which may exacerbate during use of steroids, none of the subjects of group 1 (receiving methylprednisolone) revealed a need for modification of doses or therapy regimen. However, in group 2 using oral steroids, it was necessary to discontinue this treatment in 2 female patients. It suggests that adverse reactions occur more rarely while using the regimen we proposed, but due to the low number of subjects in the studied groups, drawing reliable conclusions is impossible.

It was proven that uncontrolled hypothyroidism, as a consequence of treatment with radioactive iodine, is an additional significant risk factor for exacerbation of orbitopathy (9, 10). In our material, hypothyroidism developed in 6 subjects from the group using intravenous methylprednisolone and in 6 subjects taking oral steroid therapy. In the majority of cases, it was effectively controlled by substitution treatment with L-thyroxine from the subclinical phase. Only 2 subjects revealed a short-term decrease in fT3 and fT4 concentration below the normal level. None of these patients demonstrate exacerbation of the thyroid orbitopathy.

Our material revealed that hypothyroidism was negatively correlated with a concentration of TRAb antibodies determined one year after treatment with ^{131}I. It may be explained as decresase of amount of thyroid tissue as source of autoantigens. As it was expected, concentration of TRAb was positively correlated with hyperthyroidism maintained over one year following therapy with ^{131}I. In case of use of thyroid ablation with radioactive iodine as a complementary treatment to total thyroidectomy in patients treated with immunosuppressants due to Graves' orbitopathy, treatment effects were more beneficial than in case of using thyroidectomy alone (20). It may encourage using an aggressive treatment with radioactive iodine in order to eliminate as much thyroid tissue as possible as a source of antigens, even for the price of controlled development of hypothyroidism.

CONCLUSIONS

Obtained results demonstrate that the method of intravenous administration of corticosteroids in the form of weekly infusions, which was evaluated in this paper, may turn out to be as effective as the previously generally used regimen of oral glucocorticoid therapy as prophylaxis against exacerbation of orbitopathy after treatment with radioiodine. Use of a lower total dose of corticoids during treatment and pulse administration seems to increase safety and improve tolerance of treatment, which is especially important in case of prophylactic actions. Therefore, it seems to be justified to conduct further studies on the efficacy and safety of the proposed treatment regimen.

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