



Original article

Glucocorticoids safety administration in multiple sclerosis treatment: A focus on physicians' adherence to avoid side effect

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ABSTRACT

Introduction: The problems of GCs administration safety in MS patients have not been solved yet because of their side effects, absence of the alternative treatment for acute relapse onset and its rapid progression.

Aim: To analyze clinical and pharmaceutical aspects of GCs rational use in practical treatment of MS patients throughout studying of physicians' adherence to follow the recommendation of avoiding their side effects.

Material and methods: This is a retrospective study of 50 randomized MS case histories.

Results and discussion: Twenty two (44 %) of MS patients had clinical and anamnestic risk factors for GCs use. However, GCs have been prescribed in 27 cases (54 %) of current hospitalization, in 26 (52 %) of patients' anamnesis, and 38 (76 %) of patients, totally. During a hospital stage 44.44 % received pulse therapy, 59.26 % - oral GCs and 11.11 % - endolumbal administration. GCs were frequently used in MS onset during current hospitalization and in SPMS in pre-hospital period. Approximately 91 % with EDSS 5-6 were treated with GCs. We have observed possible side effects of GCs in 31.58 % among 38 MS cases treated with CGs, however, the patients have not been properly examined for their estimation. We have discovered that physicians paid more attention to prevention of gastrointestinal side effect of GCs (51.85 %), than osteoporosis. We also found 3 cases (11.11 %) of irrational combinations of GCs with NSAIDs.

Conclusions: GCs are frequently and effectively prescribed to MS patients, their side effects are still under proper control in clinical practice.

1. INTRODUCTION

Glucocorticoids (GCs) are considered reserve or unreplaceable medicines used in therapeutically difficult and sometimes desperate situations. They are effective in treatment of autoimmune diseases with unknown etiology, such as rheumatoid arthritis (RA), acute interstitial pneumonitis, multiple sclerosis (MS).^{1,2} GCs are widely used in allergic diseases, i.e. bronchial asthma, psoriasis, atopic dermatitis, etc.³⁻⁵ Furthermore, they are prescribed to prevent rejection after transplantation and to correct adrenal cortical hormone insufficiency.⁶ The mechanism of their actions is connected with suppression of immune reactions by lymphocytolysis, acceleration of immunoglobulins destruction, decrease of proinflammatory cytokines such as interleukin-2 production.²

The significance of GCs in clinical practice is impossible to underestimate. However, in some cases a number of side effects of GCs associated with a longterm usage or a high dose limit their prescriptions.⁷ The GCs therapy leads to osteoporosis, obesity, diabetes mellitus (DM), adrenal insufficiency, peptic ulcers and gastrointestinal bleeding, hypertension, behavior and cognitive changes, super infections due to immune suppression.^{8,9} Their side effect also are depended on route of administration and the drug, which exactly is used.

There are some recommendations for prevention and reduction of GCs' side effects.^{7,10,11} However, the question is whether physicians consider them in their daily practice.

We choose MS patients to analyze the side effect of GCs, considering their administration as a gold standard for acute relapse treatment.¹² Despite numerous studies of MS, GCs therapy remains the first-line in any of its clinical forms' aggravation. Not only it inhibits the autoimmune processes, but it is also used as a substitute therapy due to the development of GCs insufficiency in MS, which changes immunological reactivity by exacerbating allergic manifestations and promoting the process of demyelination.¹³ Although GCs has been used in MS treatment for years, the problems of their prescription in different types of MS course and prevention of their side effects have not been resolved yet.¹⁴

2. AIM

The aim of our study is to analyze clinical and pharmaceutical aspects of GCs' rational use in practical treatment of MS patients throughout studying of physicians' adherence to follow the recommendation of avoiding their side effects.

3. MATERIAL AND METHODS

This is a retrospective study of 50 MS case histories from 2007 to 2015. The cases were received by a randomized method at the Multiple Sclerosis Department of the State Institution 'Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine' in Ukraine.

In all cases anamnestic and physical examination data, as well as prescription lists have been analyzed. Administration of GCs at a prehospital stage and/or during the period of current hospitalization has been taken into consideration. The next issues were studying of presence of contraindications for GCs prescription, occurrence of possible side effects or adverse reactions, and use of non-advisable combination of GCs with other drugs in the observed case histories. We have also studied whether doctors follow the recommendations for prevention and reduction of GCs side effects. For statistics, we use absolute and percent data.

4. RESULTS AND DISCUSSION

We have discovered that the majority of MS patients received GCs, some of them had anamnestic data for GCs contraindication and others had signs of possible GCs side effects during hospitalization. We divided all the results according to the mentioned issues.

4.1. Present clinical and anamnestic factors in the observed cases that could be considered as contraindications for GCs prescriptions

We have learnt whether the following factors have been presented in case histories of the MS patients: obesity, hypertension, DM, osteoporosis, chronic gastritis and peptic ulcer, etc.

There were 5 (10%) patients with abnormal weight: 3 (6%) of them were overweight and 2 (4%) were obese. General cholesterol and its fractions' level have not been checked in the cases. Two (4%) patients had DM type 2. Blood glucose level baseline and after OTTG was checked only in 5 (10%) of total cases, while glycosylated HbA1c level was not defined in the patients at all. Hypertension was discovered in 7 (14%) of the studied cases (Table 1).

According to literature, GCs do not affect lipid profile,¹⁵ but has influence on glucose metabolism, increases blood pressure¹⁶ and leads to sinus bradycardia,¹⁷ gain weight and emotional instability.¹⁸ Thus, the GCs prescriptions should be debated in this clinical group of patients.

Chronic gastritis and peptic ulcer have been observed in 5 (10%) and 1 (2%) of patients, respectively (Table 1). Some researchers report that additional risk factors such as previous history of gastrointestinal events should also be considered as contraindication for GCs use.¹¹ Use of pulse therapy by methylprednisolone alone does not lead to gastric mucosal injury, but not together with nonsteroidal anti-inflammatory drugs (NSAIDs).¹⁹

There have been 13 (26%) of patients with persistent chronic infection which causes chronic inflammatory diseases such as tonsillitis, rhinosinusitis, pyelonephritis, saplingooforites, prostatitis, persistent mix infection in our research (Table 1). These chronic infections could be activated due to immunosuppression caused by GCs therapy.²⁰

There was no information about osteoporosis in the patients because bone mineral density (BMD) measurement

were absent. The literature sources show a significant influence of GCs on bone structures.²¹ Even though short course of pulse therapy by methylprednisolone seems to be safe, MS patients have additional risk of osteoporosis because of their inactivity.²² The researchers underline, BMD measurement of the MS patients should be taken before GCs treatment to determine those at high risk for osteoporosis,²³ and preventive or therapeutic agents should be given.²⁴

The patient were not properly checked for cardiovascular contraindications before starting pulse therapy by methylprednisolone despite on some authors had claimed of severe adverse effect on heart.^{9,16,17} First of all, nobody has been consulted by cardiologist and echocardiogram has not been done for anyone, despite of 8 (16%) patients have different changes in electrocardiogram. Repolarization disorder was found in 2 (4%) cases, bradycardia in 2 (4%) patients, tachycardia in 1 (2%) case, myocardial hypertrophy of left ventricular in 3 (6%) cases (Table 1). We believe the bradycardia and myocardial hypertrophy of left ventricular should be considered as contraindication for pulse therapy by methylprednisolone.^{16,17} Moreover, they were the same patients who have abnormal weight and hypertension.

Table 1. Clinical and anamnestic data, which could be considered as contraindication for of GCs prescription.

Possible contraindication for GCs prescriptions	Number of MS patients, n (%)
Overweight and obese	5 (10%)
DM type 2	2 (4%)
Hypertension	7 (14%)
Peptic ulcer and gastritis	6 (12%)
Persistent chronic infection	13 (26%)
Bradycardia	2 (4%)
Myocardial hypertrophy of left ventricular	3 (6%)
Total amount of patients, who might have contraindication	22 (44%)

A total number of patients with one or more clinical and anamnestic factors that could be interpreted as risk factors for the GCs use was 22 (44%). We suppose the real number of these patients was significantly higher due to the lack of necessary examination included in the case histories.

4.2. Study of GCs administration ways in MS patients during current hospitalization and at the prehospital stage

GCs have been prescribed in 27 (54%) cases during current hospitalization, and in 26 (52%) of prehospital stage. The total number of patients treated with GCs was 38 (76%) (Table 2).

During the current hospital treatment, the patients have received GCs in three schemes. Almost half of them were prescribed intravenous pulse therapy by methylprednisolone (solumedrol) 500–1000 mg daily for 3–5 days (Table 2).

Actually, the use of pulse therapy allowed to effectively relieve severe recurrence in relapsing-remitting type of MS (RRMS) and rapid progression rates in secondary progressive type (SPMS). This contributes to a significant regression of 'neurological deficit' and to prolonged clinical remission in RRMS, or it leads to stabilization in MS onset.^{12,25,26}

Another 16 patients received oral methylprednisolone (Medrol) in dose 40–80 mg for alternating scheme every other day (Table 2). One patient was treated with oral methylprednisolone after finishing pulse therapy to achieve therapeutic effect. According to the literature sources, oral administration of GCs shows the most effective results in RRMS patients with relapses of moderate severity with Expanded Disability Status Scale (EDSS) 3–4. At the MS onset, this tactics leads to stabilization with a partial regression. In general, oral administration of GCs is less effective than pulse therapy in acute period.^{14,27}

We observed some new methods for GCs application of endolumbal injection of dexamethasone (dexazone) in 3 (11.11%) patients (Table 2). It is provided by neurologists from the State Institution 'Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine'. They proved the effectiveness and expediency of this administration in severe cases of MS prodromal forms, proceeding mainly with spinal symptoms.¹³

Table 2. Number of GCs prescriptions depending on the way of administration.

GCs therapy	Total number of GCs prescription	Pulse therapy	Oral administration	Endolumbal injection
Prehospital stage	26 (52%)	19 (73.08%)	13 (50.00%)	1 (3.84%)
Current hospitalization	27 (54%)	12 (44.44%)	16 (59.26%)	3 (11.11%)
Both pre- and hospital	38 (76%)	26 (68.42%)	22 (57.89%)	4 (10.52%)

The average duration of MS in investigated cases was 9.54 ± 8.32 years. MS onset was diagnosed in 9 (18%) of patients, and an aggravation was found in 41 (82%) of patients. Maximal duration of MS took 27 years. Anamnestic data show the GCs pulse therapy applied in 19 (73.08%) cases. Oral GCs administration at prehospital stage was found in 13 (50%) patients. At prehospital stage, mostly methylprednisolone was used. However, we found prescription of oral prednisolone in 3 (11.52%) cases and oral dexamethasone in 4 (15.36%) cases retrospectively. Endolumbal administration of GCs was in anamnesis of 1 patient (3.84%). Analysis of general GCs prescriptions at hospital and prehospital stages shows the pulse therapy in 68.42% of total GCs prescriptions in MS patients, and oral GCs administration found in 57.89%, respectively (Table 2).

The researchers reported of GCs longterm treatment effectiveness in intravenous pulse therapy by high dose methylprednisolone. It is associated with a significant disability risk progression reduction for 5 years in RRMS, while oral

continuous low dose prednisolone is not correlated with any risk reduction in disability progression for 18 months. Risk of experiencing at least one exacerbation at the end of follow-up is not significantly reduced with GCs therapy.²⁸

4.3. Study of GCs prescription frequency in MS cases depending on course and 'neurological deficit' severity

Total 50 cases were split into groups due to the clinical course of MS to study the condition of GCs prescriptions. There were 9 (18%) MS onset cases, 33 (66%) of the RRMS cases and 8 (16%) of the SPMS cases. Patients with primary-progressive type of MS (PPMS) were not considered in our research as there were few of them.

The GCs were prescribed during current hospitalization to 77.77% of MS onset patients, 51.51% of RRMS and 37.50% of SPMS cases (Table 3). As we see, GCs were most frequently used in hospital period in the group of MS onset patients. Anamnestic data show the most frequent GCs prescriptions at the prehospital stage in SPMS patients. Particular attention was paid to 3 patients with MS onset, treated with GCs before hospitalization. These were cases with repeated hospitalization during a short period. The cases might evidence unsuccessful previous GCs therapy of the MS onset with repeated prescription.

Table 3. Number of GCs prescriptions depending on clinical course of MS.

GCs therapy	MS onset (n = 9)	RRMS, (n = 33)	SPMS (n = 8)
Prehospital stage	3 (33.33%)	18 (54.54%)	5 (62.5%)
Current hospitalization	7 (77.77%)	17 (51.51%)	3 (37.5%)
Both pre- and hospital	8 (88.88%)	23 (69.69%)	7 (87.5%)

Next, we study GCs prescriptions frequency depending on 'neurological deficit', which was estimated by EDSS. There were 7 (14%) cases with EDSS 1–2, 32 (62%) with EDSS 3–4, and 11 (22%) with EDSS 5–6 from total 50 cases.

Table 4 shows that the most frequent prescription of GCs was in patients with maximum EDSS 5–6. Approximately 90% of the patients with the severest 'neurological deficiency' have received GCs at the prehospital stage, and 80% – during current hospitalization. This also proves the efficiency of the GCs.

Table 4. Number of GCs prescriptions depending on EDSS.

GCs therapy	Number of GCs prescriptions in different EDSS		
	1–2, (n = 7)	3–4, (n = 32)	5–6, (n = 11)
Prehospital stage	3 (42.86%)	13 (40.62%)	10 (90.91%)
During current hospitalization	4 (57.14%)	14 (43.75%)	9 (81.81%)
Both hospital and prehospital period	6 (85.71%)	22 (68.75%)	10 (90.91%)

4.4. Control of GCs side effects occurrence in MS patients

GCs remain the most powerful and effective medication for acute exacerbations and severe cases of MS with high EDSS. Thus, the MS patients have to take them for a long time, repeat the scheme of treatment and change one of GCs to another. This undeniably leads to the side effect occurrence, which is indication for GCs discontinuation. Withdrawal syndrome might be common in such situations.²⁵ The biggest problem is absence of the pharmacological group that could totally replace GCs in MS exacerbation treatment.

Scientists continue to search for solution to the problem of GCs side effects. Recently it has been reported about new classes of medicines: selective glucocorticoid receptor agonists and modulators (SEGRAMs), which might replace GCs in future MS treatment.²⁹ However, there is still not enough clinical research on this issue. Doctors are more likely to continue the 'therapy of despair', than start thinking about possible side effects of GCs.

There were 38 patients (76%) in our study, who have received GCs at the prehospital stage and during current hospitalization. We found neither any information on registration of GCs side effects, nor withdrawal of medicine due to the side effects' registration. However, we have carefully studied clinical and anamnestic data of patients who have ever received GCs therapy.

We suppose that signs of GCs side effects might occur in 12 cases (31.58%) among 38 patients who have received GCs therapy both at a prehospital stage and in current hospitalization (Table 5). There were 4 cases, in which patients noted that they had increased blood pressure recently. It might be explained by the age of patients over 40 years. However, one of them was 30 years old. Another possible side effect was gaining weight by 2 patients, who believed that overweight was the result of GCs therapy. Two patients reported on becoming DM due to longterm GCs therapy. We observed chronic inflammatory diseases aggravation such as acute pyelonephritis, acute rhinopharyngitis, subacute rhinitis in 3 cases in one week after the start of pulse therapy by solumedrol in hospital. One patient refused to receive GCs, which might also be due to some unidirectional side effects of GCs (Table 5).

Table 5. Possible side effect of the GCs.

Signs of possible side effects	Number of patients GCs treated	Data source
Increased blood pressure	4 (10.53%)	Anamnestic data
Weight gain	2 (5.26%)	Anamnestic data
DM onset	2 (5.26%)	Anamnestic data
Aggravation of chronic infection	3 (7.89%)	Clinical data
Refusal of the GCs	1 (2.63%)	Clinical data
Total	12 (31.58%)	

Our data on possible side effect of GCs in 31.58% of MS cases correspond to another research, where side effects of GCs have been observed in 38.2% of RA patients.³⁰ Among MS patients from NARCOMS registered 17% indicated serious adverse effects after a long-period of GCs treatment, the majority completed treatment; only 0.8% stopped therapy because of adverse effects.³¹ In our study nobody was refused the GCs therapy.

Registration of the GCs side effects should be proved by certain methods of control. Nevertheless, we have discovered absence of blood glucose level data baseline and after OTTG in 90% of total case histories, glycosylated hemoglobin level in 100%, blood cholesterol level in 85%, BMD measurement in 100%, Echocardiography in 100% of the all cases. Thus, it becomes obvious why no side effects have been reported in investigated cases. In general, we have found out that the MS patients under study were extremely rarely consulted by related specialists. There were consultation of otorhinolaryngologist in 13 (26%), internist in 19 (38%), cardiologist in 0%, dermatologist in 0%, gynecologist in 1 (2%), urologist in 0%, ophthalmologist in 27 (54%), vertebrologist in 1 (2%), endocrinologist in 1 (2%) and gastroenterologist in 0% of studied cases. This also limited both registration of GCs side effects and prevention of risk for GCs prescriptions.

We absolutely agree with researchers, who think that physicians must pay attention to risks of the side effects related to GCs treatment and be familiar with guidelines to manage them.¹¹

4.5. The search for evidence of the physicians' tendencies to prevent GCs side effects

We have discovered GCs in 27 (54%) lists of prescription during the current hospitalization. The doctors pay attention to side effects from gastrointestinal tract, which often occur in GCs treatment.^{11,19,32} They use anti-secretory and antacid medicines in 14 (51.85%) cases of GCs prescription. The most 'popular' was combination of aluminum hydroxide and omeprazole in 9 (33.33%) cases. In some cases, there was also prescription of ranitidine, lansoprazole, magnum hydroxide.

However, we observed irrational combinations of GCs with NSAIDs in 3 cases (11.11%) and with nicotinic acid in one case (3.7%), which could increase gastrointestinal side effects. The number of irrational combinations is high in our study, but it is still lower than in another research, where the irrational prescription of GCs with NSAIDs was 22.3% of RA patients.³⁰

We found prescriptions of some unusual combinations of GCs with spironolactone in 12 cases (44.44%). Some authors have reported that spironolactone has an anti-inflammatory effect, which has been preclinically studied.³³ The spironolactone-based composition has been recently patented for treatment of MS.³⁴ However, the combination of GCs with spironolactone is to be studied in future research.

Finally, we did not notice the physicians' adherence to prevent the development of osteoporosis. The American College of Rheumatology recommends using calcium and vita-

min D for as long as the patient receives GCs.¹⁰ We have not found any prescription of these medications in case histories.

There is strong evidence for prevention and treatment of osteoporosis and the use of proton pump inhibitors in GCs treatment.³⁵ The researchers advise to investigate presence of comorbidities and to evaluate the risk factors of GCs side effects occurrence. During GCs therapy, monitoring of body weight and waist circumference, blood pressure, blood glucose, lipid profile, BMD, electrocardiogram control, and vaccinations should be provided.³⁶ Irrational combinations should be avoided.^{30,32}

5. CONCLUSIONS

GCs prescriptions could not be underestimated in MS treatment due to high effectiveness in MS relapses and in 'neurological deficiency' progression. They have been prescribed to 76% of MS patients. On the other hand, this can cause a large number of GCs side effects, such as hypertension, glucose metabolism impairment, weight gain, osteoporosis, gastropathy, aggravation of chronic infection and others. This indicates the necessity to have a strict GCs safety administration control at before-, during- and after-prescription stages. Check-ups to prevent and treat GCs side effects are poorly provided by physicians, that is shown a lack of clinicians' compliance with the evidence-based guidelines. First of all, incomplete MS patient's examination does not reveal the full list of possible risk factors for GCs use and occurrence of side effects at an early stage. Secondly, preventive GCs effect pharmacotherapy is weakly prescribed: gastropathy is avoided in half of cases, but osteoporosis – in none.

Clinical perspectives

Our research allowed us to look deep insight into the conditions of GCs safety administration in MS treatment. We tried to indicate the main issues of the incorrect tactics of the GCs prescription. We believe our study will help physicians-practitioners to avoid GCs side effects more effectively. The anticipation of GCs side effects in physicians' daily practice is the right way to GCs safety administration.

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