

# Pulse glucocorticoid therapy in neuroimmune disorders

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**ABSTRACT** - The goals of this review were to examine published data concerning glucocorticoid pulse therapy in general, as well as evidence-based treatment regimens in several neurological disorders. The aim of pulse therapy is achieving a stronger and more rapid therapeutic effect, and decreasing the need for long-term use of steroids. It is supposed that the action of supra pharmacological doses of glucocorticoids is mediated through nongenomic actions within the cell. Only in multiple sclerosis there is enough evidence from relatively large randomized controlled trials (class I evidence) for the efficacy of pulse therapy, so that it can be recommended as first-line therapy (recommendation level A). More information is needed to define the specific diseases to be treated and the optimal timing of pulses to obtain maximal benefit.

**Key words:** pulse glucocorticoid therapy, nongenomic glucocorticoid effects, multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, diabetic proximal neuropathy

## INTRODUCTION

Due to their anti-inflammatory and immunosuppressive action, glucocorticoids are among most frequently used medications. They have been in clinical practice for more than 55 years, and today oral route of administration of small but efficient doses is preferred, usually with a maximal dose of 1 mg of prednisone *per* kg of body weight, or 100 mg of prednisone daily. Very high doses of methylprednisolone administered intravenously were for the first time used in order to prevent renal transplant rejection. Afterwards, a series of reports on successful usage of glucocorticoid mega doses in autoimmune diseases followed. However, there is

evident discrepancy between long-standing and frequent usage of glucocorticoids and a shortage of quality evidence about their action, together with precise instructions concerning dosing regimen, duration of treatment, choice of medication and administration route. Frequently, the method of their utilization is based on empirical evidence; so it is not surprising that both oral and intravenous regimens often vary from one affiliation to another.

In this article, the most important information from the available scientific papers about the

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mechanisms of action of pulse glucocorticoid therapy and its application in neuroimmune disorders has been summarized.

## GENOMIC AND NONGENOMIC ACTION OF GLUCOCORTICOIDS

Glucocorticoids exhibit their pharmacological effects in two ways. Classic genomic mechanisms are well known – as lipophilic substances, they easily pass through the cell membrane and bind to cytoplasmic glucocorticoid receptors, then migrate to nucleus, and through binding with DNA initiate or inhibit transcription of certain genes and consequently influence synthesis of different proteins, such as cytokines and inflammatory mediators. These processes take a relatively long time; the genomic effect develops after at least 30 minutes, often even after several hours. However, glucocorticoids can exhibit immediate action in terms of seconds to minutes *via* nongenomic mechanisms of action. Nongenomic actions are not related to gene transcription *via* receptor binding – they are the result of binding to specific cell membrane receptors or direct interactions with biologic membranes (1,2). The mechanisms of nonspecific nongenomic effects were explained by Buttgerit *et al.* in a series of studies exploring direct effects of glucocorticoids on the energy metabolism of rat thymocytes that were stimulated with concanavalin-A. It was shown that high concentrations of methylprednisolone changed the physical and chemical qualities of cell membrane by intercalating in it, which caused inhibition of Na and Ca transport through the membrane with a subsequent decrease of free calcium ion concentration in the cytoplasm and decline in the production of ATP (3). Direct effect on the membrane of mitochondria is exhibited through increased proton transport and a distur-

bance in oxidative phosphorylation (4,5). Due to these prompt effects on immune cells, their activation is obstructed, which leads to rapid immunosuppression. Most likely, there is also a rapid induction of apoptosis of immune cells (6). The genomic mechanisms are developed with low doses of glucocorticoids – it was found that with a 100-200 mg of prednisone dose, all of the glucocorticoid receptors were occupied and an increase in the genomic effect could not be caused by further dose increase. Nongenomic effect is developed with high concentrations and it is an important mechanism of the therapeutic effect of pulse glucocorticoid therapy (Fig. 1).

## GLUCOCORTICOID PULSE THERAPY

Pulse therapy is defined as the application of suprapharmacological doses intermittently over a short time period. Pulse glucocorticoid therapy is defined as therapy with 250 mg or more of prednisone or its equivalent in one pulse. The increased clinical effect of pulse therapy compared to the usual doses of glucocorticoids is explained by nongenomic mechanisms; when high doses are used, alongside with genomic, the nongenomic effects occur, which leads to a faster and more pronounced therapy response. These findings encourage the use of pulse glucocorticoid therapy in acute exacerbations of immune diseases, but it is also successfully used in chronic autoimmune disorders. The goal of pulse therapy is to achieve a more rapid and efficient therapeutic effect together with a reduced need for long-term administration of high glucocorticoid doses, which results in a lower frequency of unwanted effects. The relative potencies of nongenomic and classic genomic effects are very different. For pulse therapy, a strong nongenomic effect is desired, with a balance between genomic and nongenomic potency, so methylprednisolone (MP) and dexamethasone are preferred (7,8). The dosage regimen is not standardized. A dosage of 500-1000 mg MP (10-20 mg/kg) or 50-200 mg of dexamethasone (2-5 mg/kg) is commonly used. Furthermore, the length of treatment and the frequency of pulses for different disorders have not been defined. Pulse therapy is generally well tolerated. The classic side effects of long-term therapy are typically not expected (9). Most often, redness of the face, metallic taste in mouth, insomnia, mild edema and mood changes are experienced. Although it is believed that pulse therapy with MP does not lead to a change in bone density, Hauge-

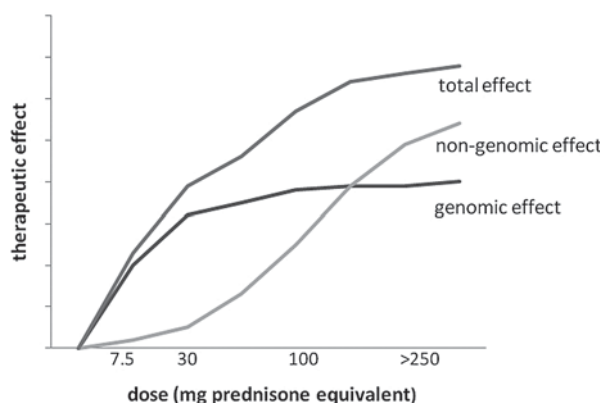


Fig. 1. Therapeutic effect of pulse glucocorticoid therapy.

berg *et al.* report that pulse therapy in patients with different rheumatologic disorders leads to a notable loss of bone mass. Interestingly, the loss was most profound during the first 6-12 months of therapy, and parallel administration of bisphosphonates had a favorable effect (10). In a study on 539 subjects with systemic lupus erythematosus, Zonana-Nacach *et al.* did not find relationship between intravenous MP therapy and avascular hip necrosis; the only statistically significant association was established between pulse therapy and cognitive dysfunction (11). Although pulse therapy is generally safe, cases of sudden death, cardiac arrhythmia and cardiac arrest have been described; most often when the infusion was administered very rapidly (9,12). Therefore, short infusions are not recommended; slow infusion (2 hours) is safer because a sudden electrolyte imbalance is avoided. The first pulse therapy ought to be under close medical supervision due to the possibility of anaphylaxis, psychosis, pancreatitis, hepatitis, seizures and blood pressure changes. During and after therapy, monitoring of cardiac rhythm, blood pressure, blood glucose and electrolytes is required. Contraindications for pulse glucocorticoid therapy include systemic infection, unregulated arterial hypertension, psychosis, drug hypersensitivity, and active peptic ulcer.

## PULSE THERAPY IN MULTIPLE SCLEROSIS

Numerous studies have proved the efficacy of MP intravenous pulse therapy in the management of acute multiple sclerosis relapse (level A recommendation). A significant reduction of contrast enhancing lesions on MR images has been demonstrated, although this effect is transient, i.e. prevention of new active lesions is not possible. The occurrence of new inflammatory activity is probably dependent on the dose and length of treatment (13,14). However, optimal dosing regimen (considering clinical efficacy and unwanted effects) has not yet been fully established. Great variability exists in terms of doses, duration of treatment and ways of its termination. Applied doses of MP in different studies vary from 500 mg (15), 15 mg/kg (16), 1000 mg (17,18) up to 2000 mg in a single pulse. Today, a generally accepted treatment is 500 to 1000 mg daily over 3-5 days (19). Occasional studies that compared the efficacy of different doses of MP provide evidence in favor of larger doses. Oliveri *et al.* compared the efficacy of 500 mg and 2000 mg of IV MP over the course of five days.

Larger dose was significantly more efficient in reducing the number of contrast enhancing lesions 30 and 60 days after therapy, i.e. it showed a stronger and longer effect on maintaining the integrity of blood-brain barrier after clinical relapse (20). Animal studies also showed results that were in favor of ultrahigh doses. It was proved that high doses of MP induced apoptosis of T cells in serum and *in situ* in experimental autoimmune encephalomyelitis. This effect was directly proportional to the dose (10 and 50 mg/kg MP) and severity of the disease, i.e. in a severe disease due to a more pronounced damage of the blood-brain barrier, the same dose caused a stronger effect than in a mild form of the disease. A dose of 1 mg/kg was ineffective in all disease forms (6). These data justify the use of higher doses of MP (2 g) or duration of treatment longer than 3 days with 1 g MP in cases of insufficient therapy response to lower doses.

Frequently, once the pulse therapy has been finished, oral corticosteroid therapy is initiated for a shorter period of time in smaller, gradually decreasing doses. It was used differently by different authors. This method of treatment was not proven to be effective (21).

Since 1990, oral administration of high doses of MP has been analyzed and in most studies it proved to be as efficient as intravenous application (22,23). Pulse therapy in multiple sclerosis is well tolerated and usually accompanied by transient side effects. There is no evidence for osteoporosis development in repeated pulse therapy in multiple sclerosis (24).

## PULSE THERAPY IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Chronic inflammatory demyelinating polyneuropathy (CIDP) is historically described as a polyneuropathy that responds to corticosteroids. In CIDP, according to EFNS guidelines, intravenous immunoglobulins are indicated (level A recommendation) or glucocorticoids (level C recommendation – no large controlled studies were performed) (25). In an attempt to achieve a faster therapeutic effect and lessen the side effects of long-term corticosteroid therapy, pulse therapy was analyzed in both smaller and larger controlled studies. So far, there is no solid evidence in favor of pulse therapy, but the conclusion of existing studies is that it is as effective as immunoglobulins, but cheaper, and that



it has less unwanted side effects compared to classic glucocorticoid therapy (26,27). However, unlike pulse therapy in a multiple sclerosis relapse, here the pulse therapy is applied long-term, repeatedly. For this reason, side effects are more pronounced than in MS treatment. In long-term use, osteoporosis is possible and prevention is needed.

Dosing regimen of pulse therapy differs from author to author. Lopate *et al.* in a retrospective study found the recovery of patients to be the same when treated with pulse intravenous MP, oral prednisone or immunoglobulins. Treatment was started with 1000 mg MP for 3-5 consecutive days, followed by 1000 mg once a week for 4 weeks and then a gradual decrease in the frequency of pulses and doses was carried out, depending on the patient clinical state (26). Muley *et al.* in an open prospective study successfully applied pulse oral MP 500 mg a week for 3 months, followed by a decrease of pulse dose by 50-100 mg every three months, depending on the patient clinical state (27). When pulses of high doses of dexamethasone were applied (40 mg orally on 4 consecutive days of every month for 6 months), remission was achieved as with oral prednisone therapy (28). The same group of patients were followed long-term in a prospective cohort study. The results suggest advantages of pulse dexamethasone therapy due to faster recovery, somewhat longer remission and fewer unwanted side effects when compared with oral prednisolone treatment (29). Nobile-Orazio *et al.* compared the efficacy and tolerability of six-month therapy with IV immunoglobulins and IV MP (500 mg daily for 4 consecutive days each month). In the MP group, a more frequent discontinuation of therapy was noted due to intolerability and weak efficacy, but on the other hand, MP caused longer remission compared to immunoglobulin (30).

## PULSE THERAPY IN MYASTHENIA GRAVIS

Glucocorticoid therapy of myasthenia gravis has some peculiarities compared to other conditions. Namely, when initiating therapy, a transient deterioration in about 50% of myasthenia patients is noted, and among those, 6%-10% can have serious deterioration, which can lead to a myasthenic crisis (31,32). Current view is that initiating therapy with low doses and with a gradual increase reduces the risk of deterioration, and in an outpatient setting mild forms of the disease are preferably initially treated with a low dose of prednisolone (33). If immunosuppression is needed, glucocorticoids

are the first therapeutic choice in this condition (level of evidence IV – efficacy has not been proved in case control studies) (34). There are ever more scientific reports on the advantages of pulse therapy with MP in myasthenia gravis – fewer side effects, faster recovery and even less pronounced disease deterioration on therapy initiation have been reported. It is somewhat paradoxical that mega doses are used in order to have less side effects, but this proved to be true according to many papers on this topic. Namely, with this type of treatment, a lower long-term maintenance dose is required, which reduces the frequency of unwanted side effects. Better results are notably achieved in older patients, who due to their age and comorbidities often do not tolerate long-term corticosteroid therapy well (35). Still, a lack of highly rated studies prevents reaching evidence-based recommendations. Also, there are no recommendations on the dose of a single pulse or dosage regimen. Pulse therapy with MP was applied in different ways by different authors: intermittently 20-30 mg/kg without a maintenance dose in pediatric patients with myasthenia whose condition was not sufficiently controlled by oral prednisone therapy (36); 2000 mg every five days until improvement, followed by 30 mg oral prednisone with gradual dose decrease (37); 2000 mg on two consecutive days, with the duration of improvement of 4-14 weeks (38); and plasmapheresis with 1000 mg IV MP administered after plasmapheresis and for the next two days in the morning, long term maintenance dose 5-15 mg prednisone (35). We successfully applied pulse therapy with IV MP as initial therapy in four female patients (1000 mg MP for three consecutive days or 500 mg MP for four to five consecutive days), and also on four occasions in patients who were on smaller doses of glucocorticoids, but experienced exacerbation of the disease. No deterioration of the disease after therapy initiation was observed. Nevertheless, additional studies are required to evaluate long-term efficacy and safety of this type of therapy in myasthenia gravis.

## PULSE THERAPY IN PROXIMAL DIABETIC NEUROPATHY

Clinical and histopathological studies appearing in the 1990s pointed to the immune mechanisms in the etiopathogenesis of this condition (microvasculitis of vasa nervorum) and justified the use of immunosuppressive and immunomodulatory therapy in this disease. Still, an optimal therapy for these patients has not yet been established, partly

so because this condition tends to resolve spontaneously. There are numerous reports on a beneficial action of immunomodulatory and corticosteroid therapy on positive sensory symptoms and faster recovery (39). In a retrospective study with 500 mg IV MP on two consecutive days every two weeks during three months, Kilfoyle *et al.* report a prompt effect on pain reduction and slower effect on motor deficit recovery (40). In an abstract from 2006, Dyck *et al.* report results from a double-blind placebo controlled study on 75 patients with IV MP (significant pain reduction was noted, but without a statistically significant difference in final recovery) (41). Nevertheless, a Cochrane meta-analysis from 2009 does not find evidence in randomized controlled trials that would support immunotherapy application in this condition (42). An updated Cochrane review from 2012 still does not report any new evidence that could contribute to a recommendation for corticosteroid use in this condition (43).

## CONCLUSION

Administration of very high doses of glucocorticoids (above 250 mg MP) exhibits, apart from genomic action, an additional nongenomic action, which results in a faster and stronger therapy response. In multiple sclerosis relapse, pulse therapy alone is sufficient to achieve remission, but in the majority of patients with a chronic autoimmune disease such as CIDP or myasthenia gravis, due to transience of the initial positive effect of pulse therapy, pulse therapy alone is not enough to achieve remission. For this reason, initial pulse therapy is usually followed by long-term application of smaller glucocorticoid doses or pulse therapy is repeated long-term. Apart from multiple sclerosis relapse, so far there is no evidence from highly ranked studies, which would enable making recommendations for this therapy in neuroimmune conditions. All studies on this topic agree that pulse therapy results in fewer unwanted side effects compared to classic glucocorticoid therapy, although this is not yet supported by prospective randomized controlled studies. The treatment with corticosteroids remains an art, balancing the severity of the individual patient's disease, concurrent medical issues, and clinical experience.

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## Pulsna glukokortikoidna terapija kod neuroimunoloških poremećaja

**SAŽETAK** - Cilj ovoga pregleda je bio je istražiti objavljene podatke koji se odnose općenito na pulsnu glukokortikoidnu terapiju, kao i režim liječenja utemeljen na dokazima u različitim neurološkim bolestima. Pulsnom terapijom postiže se brži i snažniji terapijski učinak uz smanjenje potrebe za dugoročnom steroidnom terapijom. Pretpostavlja se da se djelovanje suprafarmakoloških doza glukokortikoida razvija putem negenomskih mehanizama u stanici. Jedino u multiploj sklerozi postoji dovoljno dokaza na temelju relativno velikih randomiziranih kontroliranih studija o učinkovitosti pulsne terapije (klasa dokaza I.), tako da se može preporučiti kao prva linija terapije (preporuka razine A). Potrebni su dodatni podaci da bi se definirao način liječenja u pojedinim bolestima i optimalna primjena pulseva za postizanje maksimalnog učinka.

**Ključne riječi:** pulsna glukokortikoidna terapija, negenomsko glukokortikoidno djelovanje, multipla skleroza, miastenija gravis, CIDP, proksimalna dijabetična neuropatija