



A Narrative Review on Pulse Therapy in Dentistry: Rhythm of Relief

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Abstract

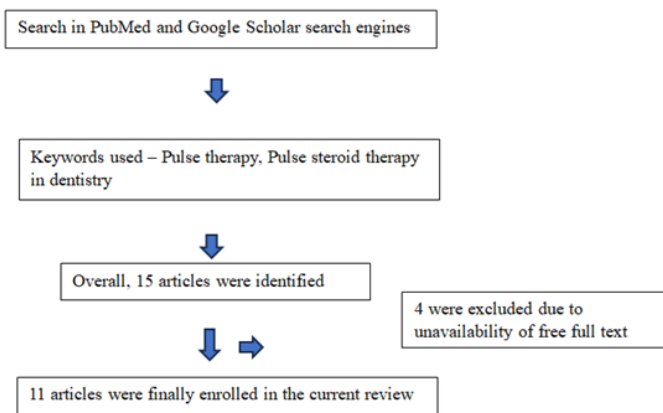
Pulse therapy is supra therapeutic administration of drugs in intermittent manner. This therapy provides excellent treatment response by enhancing therapeutic effects with reduced side effects. It is used in dentistry for many inflammatory and autoimmune disorders. An extensive search of all materials was carried out related to this topic on the PubMed and Google Scholar search engines with keywords such as pulse therapy, pulse steroid therapy in dentistry in the title alone and 11 articles were selected based on suitability with current review objectives and analysed. This review tends to focus on various available pulse therapies with dosages, indications, contraindications and protocols for administering in detail.

Keywords: Pulse dose, Pulse steroid therapy, Immunosuppressants, Dentistry

Introduction

Pulse therapy means the administration of large (suprapharmacologic) doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects.¹ In order to achieve graft survival right after a kidney transplant, Kountz and Cohn first proposed the idea of pulse therapy in 1969. This involved transfusing a large dosage of steroids straight into the renal graft through the renal artery. Dr. JS Pasricha introduced pulse treatment to India in 1981 in an effort to treat a patient suffering from severe Reiter's disease.² In dentistry, it is used to treat a variety of autoimmune and inflammatory conditions³.

Material and Methods



Drugs Used in Pulse Therapy¹

- a) Corticosteroids
- b) Immunosuppressives
- c) Antifungals
- e) Antibiotics

Pulse Steroid Therapy

Methylprednisolone and dexamethasone are the corticosteroids most frequently used in pulse therapy.⁴

Methylprednisolone and dexamethasone are broadly disseminated throughout the tissues, have a high bioavailability, and are mainly bound to serum albumin.

After intravenous injection, both medicines have a high unbound "free" concentration and are only weakly bound to transcortin.⁵ In contrast to hydrocortisone, methylprednisolone is a strong, intermediate-acting anti-inflammatory drug that has a low propensity to cause water and sodium retention. It has a 12-36-hour biological half-life and 1.25 times the potency of prednisolone.⁶ The half-life of dexamethasone, a fluoride glucocorticoid, is 36-72 hours. With a modest equipotent volume, a negligible mineralocorticoid action, and virtually no tendency to retain salt, it is 6.7 times more potent than prednisolone.⁷

Dosage and Administration

Since there are no rules about how often or when to administer the intravenous pulses, they can be

administered as single boluses, daily boluses for three consecutive days, or on alternate days for a maximum of twelve days. Up to a maximum dosage of 1 g, methylprednisolone is given at a dose of 20-30 mg/kg (500-1000 mg/m²) every pulse. The dosage of dexamethasone is 4-5 mg/kg (100-200 mg) per pulse.⁸ The initial infusion time was 10 to 20 minutes, based on research conducted on healthy persons. However, delivery over 1-3 hours is advised because fast infusions are known to be linked to a higher risk of hemodynamic abnormalities. The corticosteroid preparation is dissolved in 150-200 ml of 5% dextrose and infused intravenously, slowly over 2-3 hours.⁵

Mechanism of Action

Research indicates that the pharmacologic effects of high doses of steroids produced by pulse corticosteroid therapy differ qualitatively from those of lesser doses. Only at cell concentrations that can be reached by the largest oral or intravenous dosages of glucocorticoids have it been demonstrated that high doses of these hormones suppress NFkappa activity (transrepression).⁹ Steroids breakdown in the cell membrane in very high concentrations, increasing membrane stability and decreasing non-genomic cell function.

Overall, the effects of corticosteroid pulses seem to involve down regulating immune cell activation and the generation of proinflammatory cytokines, which results in decreased adhesion molecule expression and decreased neutrophil migration into inflamed areas.^{9,10}

Rationale for The Use⁵

1. The goal of pulse therapy is to reduce the requirement for long-term steroid administration while achieving faster and stronger efficacy.
2. It has repeatedly been observed that the toxicity is lower than that of oral prednisone taken daily.

3. A significant anti-inflammatory impact is obtained right away when corticosteroids are given as pulses.
4. Inflammatory damage is reduced since there is a quicker clinical recovery from symptoms than with oral medication. After one pulse, the clinical improvement lasts for roughly three weeks, and the hypothalamic-pituitary axis is not suppressed for an extended period of time.
5. It has a favorable risk/benefit ratio and is quite effective at reducing inflammation in the short run.

Indications¹¹

It is indicated in severe diseases flares or exacerbations, resistant cases or patients with comorbidities where corticosteroids seem to be contraindicated.

1. Pemphigus Vulgaris
2. Lichen Planus
3. Systemic Sclerosis
4. Systemic Lupus Erythematosus
5. Dermatomyositis
6. Pyoderma Gangrenosum
7. Toxic Epidermal Necrolysis
8. Steven Johnson's Syndrome
9. Sarcoidosis
10. Systemic Vasculitis

Contraindications

Systemic infections, including fungal sepsis, uncontrolled hypertension and known hypersensitivity to steroid preparation.⁸ Pregnant, lactating and unmarried patients.³

Regimens¹¹

1. Dexamethasone cyclophosphamide pulse therapy (DCP)
2. Dexamethasone azathioprine pulse therapy (DAP)
3. Dexamethasone methotrexate pulse therapy (DMP)
4. Methyl prednisolone pulse therapy (MPPT)
5. Cyclophosphamide pulse therapy
6. Oral minipulse corticosteroid therapy

7. Topical Corticosteroid pulse therapy

Dexamethasone Cyclophosphamide Pulse Therapy (DCP)¹⁰

DCP Therapy is Divided into four Phases

1st phase

For three days in a row, a gradual intravenous infusion of 100 mg of dexamethasone in 5% dextrose over two hours is started, along with a 500 mg infusion of cyclophosphamide on one of those days.

Until no new lesions develop in between pulses, DCPs are performed every 28 days.

On the remaining days, cyclophosphamide 50 mg/day is administered orally. During this phase, the patient may develop recurrences in between the DCPs and conventional doses of oral corticosteroids can be given to achieve quicker clinical recovery. After the skin and mucous membrane lesions have subsided completely and the additional medications are withdrawn, the patient is considered to have entered phase II.

2nd phase

Phase of remission while on therapy. DCP schedule is given for duration of 9 months.

3rd phase

Monthly pulses are terminated and oral cyclophosphamide is continued for duration of 9 months.

4th phase

Treatment is stopped and patients are followed-up for next 10 years.

Modifications of DCP Therapy

There are following modifications of DCP therapy

Dexamethasone Azathioprine Pulse Therapy [DAP]

Cyclophosphamide is known to induce amenorrhea and oligo/azoospermia. During the first three phases, 50 mg of azathioprine was administered daily in place of cyclophosphamide for unmarried individuals.

Dexamethasone Methotrexate Pulse Therapy [DMP]

Cyclophosphamide was substituted with 7.5 mg of methotrexate taken orally on a weekly basis throughout the initial three stages of pulse treatment.

DMP is instituted in patients who are unable to complete Phase I even after 12 pulses (1 year) of DCP or DAP therapy.

DCP Therapy in Children

DCP therapy can be given to patients of all ages but the doses have to be reduced to half for children below the age of 12 years.

DCP Therapy in Systemic Diseases

Individuals with diabetes require administration of 10 units of soluble insulin for each 500 ml container of 5% dextrose mixed in the same infusion. In addition, patient's regular treatment for diabetes mellitus is continued. Similarly, patients having concomitant diseases such as hypertension and tuberculosis must receive the respective medication. In cases of severe infection, the pulse may be postponed for one or two weeks until the infection is managed effectively.¹⁰

Urinary complications linked to cyclophosphamide can be avoided by incorporating an extra pack of 500ml of 5% dextrose when 500 mg of cyclophosphamide was introduced into the drip on the second day of the DCP.

The use of supportive medications includes administering oral calcium at a dosage of 500 mg daily during the initial three phases, as well as a monthly injection of vitamin D3 at lakh units during the first two phases.

II. Pasricha et al. instituted three modifications in the DCP regimen. These were:

1. Emphasis on thorough cleaning of the skin, scalp and oral cavity even when there were lesions
2. Use of oral antibiotics and anti-candida drugs helped to clear up/prevent the superadded infections

3. Simultaneous use of oral corticosteroids in doses sufficient to control the disease activity led to quick healing of the lesions and a psychological benefit to the patient.

The modifications shortened the duration of phase I to 3-4 months in most of the patients.³

Methyl Prednisolone Pulse Therapy (MPPT)

Methylprednisolone is given in doses ranging from 20 to 30 mg/kg (500 to 1000 mg/m²) for each pulse treatment, with the upper limit set at 1 g.²

Cyclophosphamide Pulse Therapy

Cyclophosphamide is administered intravenously in pulse doses of 500 to 1000 mg/m² over a one-hour period. Since only a fraction of the drug metabolizes during its first journey through the liver, its bioavailability is nearly 100 percent.²

Oral Mini Pulse Corticosteroid Therapy

Patients undergoing pulse therapy must be closely observed in a hospital environment due to the administration of high drug doses intravenously; however, this level of monitoring is not necessary for those with only oral lesions. To address this issue, a novel treatment approach known as oral mini pulse therapy (OMP) was developed two decades ago. This method enhances patient adherence and reduces the likelihood of both immediate and long-term adverse effects linked with corticosteroid use. Betamethasone is prescribed orally at a dosage of 10 mg once a week for conditions such as vitiligo and lichen planus, yielding varying results. The 10 mg dose of betamethasone is divided into two equal doses taken on two successive days each week and is gradually reduced until total remission of the lesions is achieved.²

Topical Corticosteroid Pulse Therapy

Topical corticosteroid pulse therapy comprises of intermittent use of super-potent corticosteroids.

Prolonged continuous therapy with such agents in patients with psoriasis results in certain side-effects whereas intermittent therapy may achieve beneficial effects for maintenance of remissions with an advantage of diminishing the side effects. Clobetasol propionate (0.05%) is primarily administered as a weekly topical regimen consisting of three consecutive applications spaced 12 hours apart, specifically for psoriasis.²

Protocol for High Dose Intravenous "Pulse" Steroids Administration⁵

Before starting therapy

The patient should be free from any systemic infections before administration of corticosteroids. Minor upper respiratory tract, gastrointestinal or skin infections are not a contraindication to therapy.

Blood pressure must be controlled using appropriate drugs.

Obtain total and differential white cell counts, and blood level of sugar, urea, creatinine, sodium and potassium.

During and following therapy

Careful record of heart rate, respiratory rate and blood pressure every 15-30 minutes should be maintained. If an arrhythmia is suspected, the infusion is discontinued; an ECG and blood levels of sodium, potassium, calcium and magnesium are obtained and abnormalities are rectified.

Careful screening for occurrence or exacerbation of infections.

Estimate blood levels of sugar and electrolytes every other day.

Pulse Therapy with Antifungals

Antifungal medications such as itraconazole and fluconazole are utilized to manage both superficial and deep fungal infections. The regimen for itraconazole consists of 400 mg per day for one week each month over the course of three months.²

Pulse Dosing of Antibiotics

The concept of pulse dosing is an innovative method for administering antibiotics that generates increased levels of the antibiotic early within the dosing period. Currently, this pulse dosing technique is under development for drugs like metronidazole. By splitting the antibiotic dose and delivering it in a pulsatile manner, it may allow the target bacteria to be exposed to high concentrations of the antibiotic at different stages in their growth cycle, thus focusing on the most susceptible bacteria.²

Conclusion

Since 1986, pulse therapy has revolutionized the management of various life-threatening conditions. When administered for suitable conditions and diseases, substantial intravenous doses of corticosteroid are overall less harmful than ongoing steroid therapy at reduced dosages. However, there is no evidence that they can independently cure or alter the long-term outcomes of diseases. Additional details are necessary to identify the exact conditions to treat, the best corticosteroid, immunosuppressant, antifungal or antibiotic to utilize in pulse therapy and the ideal timing for administering pulses to prevent chronic toxicity and achieve the greatest advantage.

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