

REVIEW ARTICLE

Pulse Therapy in Dentistry: A ReviewNikhat Mukhtar Gazge¹, Balaji P.²**ABSTRACT**

Corticosteroids are an important class of naturally occurring and synthetic steroid hormones which have widespread uses in dentistry. Pulse therapy was introduced to overcome their serious side effects and requirement of long term maintenance doses. Pulse therapy means the administration of supra-pharmacologic doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects. In India, it was first described by Pasricha and Ramji in 1981. The various drugs, apart from corticosteroids that are used in pulse therapy include antifungals, antivirals and antibiotics. The aim of this review article is to highlight the various regimens used in corticosteroid pulse therapy, their indications, contraindications, adverse effects and modifications to treat conditions associated with oral and maxillofacial region.

Keywords: Corticosteroid pulse therapy, Drug pulse therapy, Pulse therapy, Pulse drug therapy

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INTRODUCTION

Human beings have been suffering from various inflammatory and autoimmune diseases since ancient times. With the increasing awareness of the public towards oral diseases, the number of medically compromised patients visiting oral physicians has enormously

increased. Hence, oral physicians should be aware of the different classes of drugs available to treat such patients. Corticosteroids, being an important class of naturally occurring and synthetic steroid hormones, have well known uses in such conditions. However, due to their serious side effects and requirement of long term maintenance doses, pulse therapy was introduced.

Pulse therapy refers to discontinuous intravenous infusion or oral dosing of high-dose glucocorticoids in short bursts.¹ Pulse therapy is employed as a treatment modality in various autoimmune disorders which will be mentioned later in the article. Theoretically, pulsing of corticosteroids should provide quick and effective elimination of the disease when compared to the traditional oral doses of the drug. Apart from this, it will also lead to a reduction in the required long term maintenance doses of corticosteroids due to which the side effects will be minimized.² Figure 1 depicts a timeline showing the milestones in pulse therapy.

DRUGS USED IN PULSE THERAPY

There are many classes of drugs that are employed in pulse therapy: corticosteroids, immunosuppressives, antifungals, antivirals and antibiotics.

PULSE CORTICOSTEROID THERAPY

Usually high doses of prednisone (>250mg) or its equivalent per day is given as a discontinuous IV infusion. This can be given as a single daily bolus for 3 days in a row or on alternate days for 12 days. However, there is no mention of any specific guidelines regarding the frequency and duration of administration of the intravenous pulses.³ Corticosteroid pulse therapy has the benefit of achieving the expected therapeutic response due to the very high doses used. In addition, there is elimination of the side effects that are known to occur due to prolonged corticosteroid therapy.⁴

Indications⁵

1. Pemphigus Vulgaris
2. Lichen Planus
3. Systemic Sclerosis
4. Systemic Lupus Erythematosus

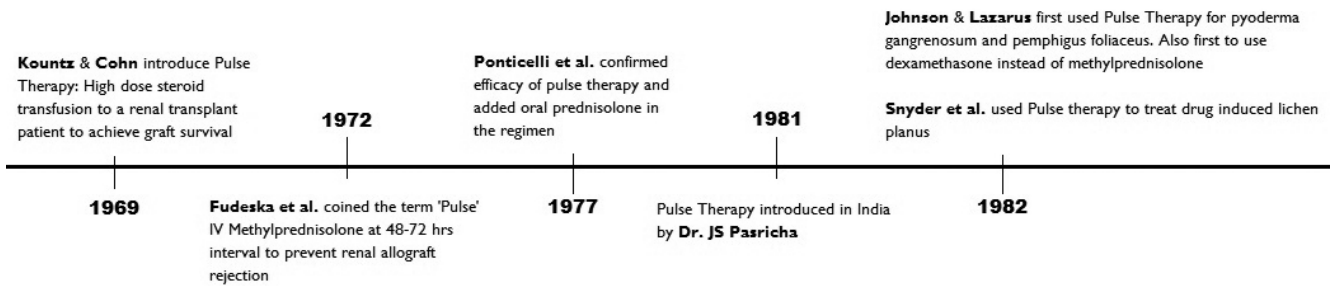


Figure 1: Timeline showing milestones in Pulse Therapy

5. Dermatomyositis
6. Pyoderma Gangrenosum
7. Toxic Epidermal Necrolysis
8. Steven Johnson's Syndrome
9. Sarcoidosis
10. Systemic Vasculitis

Contraindications

1. Systemic infections, including fungal sepsis and uncontrolled hypertension
2. Pregnant, lactating and unmarried patients.⁶
3. Known hypersensitivity to the individual steroid preparation.³

Corticosteroid Regimen⁵

1. Dexamethasone cyclophosphamide pulse therapy (DCP)
2. Dexamethasone azathioprene 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 (DCP) THERAPY

DCP therapy is the intermittent administration of high doses of intravenous corticosteroids and cyclophosphamide. Three daily doses of dexamethasone (100mg) or methylprednisolone (500-1000mg) and a single dose of cyclophosphamide (500mg) is given monthly.⁷ It was introduced by Dr. JS Pasricha in 1981 at The All India Institute of Medical Sciences (AIIMS), New Delhi, India.⁸

Dexamethasone Cyclophosphamide Pulse therapy is divided into 4 phases^{5,9}

Phase I consists of Dexamethasone 100 mg in 5% Dextrose as a slow IV infusion over 2 hours for three consecutive days along with cyclophosphamide 500 mg infusion on one of the days. This constitutes one DCP.

Such DCPs are repeated every 28 days till no new lesions appear between pulses. Cyclophosphamide 50 mg / day is given orally. During this phase the patient may continue to develop recurrences of clinical lesions in between the DCPs and can therefore be given conventional doses of oral corticosteroids to achieve quicker clinical recovery.

The patient is considered to enter phase II, once the skin and mucosal lesions subside. In phase II, the DCP schedule is given for a fixed duration of 9 months. In phase III, only oral cyclophosphamide 50mg/day is given for a year. In phase IV, all the drugs are stopped and the patients are kept under regular follow up.⁵

DCP therapy in children

In children above the age of 12 years, DCP therapy can be employed without any modification. However, for children below 12 years of age, the doses have to be reduced by half.¹⁰

DCP therapy in systemic diseases

In case of diabetic patients, 10 units of soluble insulin is added for every 500ml bottle of 5% dextrose and the patient's regular treatment for diabetes is continued. Similarly, the respective medication should be given to patients having associated diseases such as hypertension and tuberculosis. In case of any infection, the pulse may be delayed by a week or two until the infection subsides.¹⁰

Adverse Effects

Corticosteroids have known side effects of causing opportunistic infections, diabetes mellitus, hypertension, osteonecrosis etc.^{5,6} The adverse effects of DCP therapy are made up by the constituent drugs i.e. dexamethasone and cyclophosphamide such as:¹¹

1. Generalized weakness
2. Weight gain
3. Myalgia
4. Arthralgia
5. Dysgeusia

6. Hiccups
7. Arrhythmia
8. Insomnia
9. Headache
10. Gastrointestinal effects such as anorexia, nausea, vomiting, diarrhoea and dyspepsia
11. Fever, Chills, Rigor, Sweating, Pedal edema and thrombophlebitis
12. Secondary pyogenic infections of skin lesions and oral candidiasis
13. Gonadal toxicity of cyclophosphamide may manifest as amenorrhea, with or without ovarian failure, infertility and azoospermia. A high incidence of amenorrhea and oligomenorrhea has also been observed
14. Generalized pigmentation of the skin and nails
15. Hair loss
16. Changes in leukocyte counts, platelet counts, hemoglobin, blood glucose, electrolyte levels and liver function tests

Modifications:

- I. A few changes were made in the DCP therapy protocol by Rao et al. The modifications included:¹²
 1. Substitution of cyclophosphamide with either azathioprine or methotrexate in a few patients.
 2. Intercurrent infections were treated by conventional steroid therapy. The first pulse was initiated only after the control of secondary infection, reduction in number of existing lesions and cessation of appearance of new lesions.
 3. Urinary complications of cyclophosphamide was avoided by adding an additional pack of 500ml 5% dextrose when cyclophosphamide 500 mg was added to the drip on the second day of DCP
 4. Administration of supportive drugs: Oral calcium 500 mg daily, during the first three phases and Inj. vitamin D3 lakh units once a month during the first two phases.¹²
- A good response was seen in patients who took treatment regularly and it was concluded that the modifications to the original DCP therapy protocol were effective.¹²
- 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.¹³

The modifications shortened the duration of phase I to 3-4 months in most of the patients.¹³

DEXAMETHASONE AZATHIOPRENE PULSE (DAP) THERAPY

In unmarried patients or those married patients who have not completed their family, cyclophosphamide is replaced with 50mg azathioprine as cyclophosphamide is known to cause oligo / azoospermia and amenorrhoea.¹²

Side effects from azathioprine are bone marrow suppression including leukopenia, thrombocytopenia, anaemia, increased susceptibility to infections (especially varicella and herpes simplex viruses), hepatotoxicity, alopecia, GI toxicity, pancreatitis. In addition, lymphoproliferative diseases and infection rates may be elevated.¹⁴

DEXAMETHASONE-METHOTREXATE PULSE (DMP) THERAPY

Cyclophosphamide is replaced by 7.5 mg of methotrexate (three doses of 2.5 mg at 12 hourly intervals) weekly given orally, during the first three phases of pulse therapy along with Dexamethasone pulses in first two phases. DMP is instituted in patients who are unable to complete Phase I even after 12 pulses (1 year) of DCP or DAP therapy.¹²

COMPARISON BETWEEN DCP, DAP, DMP

A non-comparative study of DCP, DAP and DMP therapies in pemphigus patients concluded that amongst the three, DCP was the best regimen with quickest onset of remission and continuance of remission. In DAP therapy, daily dose of 50 mg azathioprine was found to be counterproductive. DMP, however did not fulfil the promise of a practical treatment option in recalcitrant pemphigus.¹⁵

METHYL PREDNISOLONE PULSE THERAPY (MPPT)

Methylprednisolone is an intermediate acting, potent anti-inflammatory agent. Methylprednisolone is administered at a dose of 20-30 mg/kg per pulse; upto a maximum dose of 1 g.¹⁶

MPPT has been used in the treatment of lupus nephritis,

nonrenal lupus, rapidly progressive glomerulonephritis, minimal change nephrotic syndrome, rheumatoid arthritis, multiple sclerosis, polymyositis and polyarteritis nodosa.¹⁷

CYCLOPHOSPHAMIDE PULSE THERAPY

Pulse intravenous cyclophosphamide therapy is given at a dose of 500 to 1000 mg/m² over 1 hour. The half-life of cyclophosphamide in intravenous doses of 6 to 80 mg/kg is 4 to 6.45 hours.¹⁸ Table 1 illustrates the adverse effects of cyclophosphamide.¹³

Frequent	Rare
Nausea, Vomiting	Hyperpigmentation
Alopecia	Fibrosis of the bladder and lungs
Amenorrhea, Oligospermia, Azoospermia	Altered hepatic function
Leukopenia, Thrombocytopenia	Mucous ulcers
Hemorrhagic cystitis	Myocarditis
	Malignant neoplasm of the skin and bladder
	Non-Hodgkin's lymphoma

Table-1: Adverse effects of cyclophosphamide

ORAL MINI PULSE CORTICOSTEROID THERAPY

High doses of drugs are given intravenously to patients on corticosteroid pulse therapy. Hence, they have to be kept under observation in a hospital set-up. This can be prevented in patients with oral lesions without skin involvement by the oral mini pulse therapy (OMP). It has the advantage of pulsing and allows for oral administration with lesser dosages. This ensures a better patient compliance with lower risk of short and long-term side effects associated with corticosteroid therapy.¹⁹

The OMP regimen was introduced mainly to treat fast spreading or extensive vitiligo for achieving similar therapeutic results as pulse therapy with minimum side effects. Now it is being tried for treatment of lichen planus especially refractory cases. A dose of 10 mg oral betamethasone is given either once weekly or split in 2 equal doses on 2 consecutive days a week.¹⁹

TOPICAL CORTICOSTEROID PULSE THERAPY

It is the intermittent use of superpotent corticosteroids.

Three consecutive applications of topical clobetasol propionate (0.05%) at 12 hour intervals for a week is used for treating psoriasis.¹⁰

PULSE THERAPY IN ORAL LESIONS

Pulse therapy is employed to treat oral manifestations of autoimmune disorders as well as individual oral mucosal lesions without skin involvement. A success rate of 88% is observed with Dexamethasone Cyclophosphamide Pulse therapy in pemphigus vulgaris patients.²⁰ There are many reports of improvement in pemphigus patients by DCP therapy and it was found to be effective in inducing and maintaining remission of the disease.^{11,21,22} The rate of complete remission was 92.8%, resistance was 1.4%, and mortality was 0% with pulse therapy using 1000mg intravenous methylprednisolone for 4 days plus 500 mg intravenous cyclophosphamide for 1 day in patients suffering from pemphigus vulgaris having skin and mucosal lesions.²³

Initially, there was a lot of concern about the administration of large doses of corticosteroids, but today it is given as a routine infusion in a day care or OPD setting. Patients are free to go home a few hours after completion of the infusion. Need for infusion is eliminated in patients with oral lesions without skin involvement. The introduction of oral mini pulse therapy is beneficial for such patients. 5 mg betamethasone is given in the morning after breakfast for two consecutive days every week for a period of three weeks. After reduction in the burning sensation, dose of betamethasone is to be tapered by 0.5 mg every week. The therapy can be stopped after complete remission of the lesions. This has been very effective in the treatment of resistant cases of oral lichen planus.¹⁹

Treatment of moderate to severe oral lichen planus using oral mini pulse therapy comprising oral consumption of 5 mg betamethasone on two consecutive days per week is effective.²⁴ An excellent to good response was seen within three months in lichen planus patients who were treated with the oral mini pulse therapy.²⁵ A patient suffering from generalised and bullous lichen planus was treated with the standard oral mini pulse therapy. In addition, betamethasone dipropionate 0.01% gel was given twice a day for topical application on the oral and genital lesions.²⁶ Hence, oral mini pulse therapy has been proven to be a safe and effective therapeutic alternative for the treatment of lichen planus.

CONCLUSION

Pulse therapy appears to be successful in the treatment

of many autoimmune disorders. It was found to be a novel path breaking therapy for pemphigus vulgaris. It has found its applications in the treatment of oral mucosal lesions as well. Considering the fatal nature and grave prognosis of the diseases where pulse therapy is used, the benefit definitely scores over the risk. However, long-term follow-up is necessary to compare the incidence of malignancy in patients receiving pulse doses of immunosuppressive agents with that in patients receiving continuous oral treatment.

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