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Case Study

Spinal Modulation by Dexamethasone Sodium Phosphate, Cyclophosphamide and Miconazole Iontophoresis in asymptomatic SARS-COV2 patient with Extensive Myelitis

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Abstract

A very rare neurological complication of SARS-CoV-2 infection includes transverse myelitis. I assume a post-infectious etiology in terms of secondary immunogenic overreaction. Iontophoresis is the process of the permeation of ionic (charged) drugs into the body under the influence of electrical current. Besides increasing therapeutic efficiency by, by passing first pass metabolism there are less risks of systemic absorption and undesirable side effects. The study was conducted in a SARS-CoV-2 patient with transverse myelitis, by transdermal application of dexamethasone sodium phosphate, cyclophosphamide and miconazole by iontophoresis at corresponding vertebral levels to look for the neurological outcome who had been unresponsive to intravenous methylprednisolone. With Dexamethasone sodium phosphate and cyclophosphamide iontophoresis there was modulation of the activity of posterior grey column, fasiculus gracilis and corticospinal tracts, and with miconazole iontophoresis I was able to ameliorate the dyesthesias, fasiculations and muscle atrophy probably due to neuromodulation at substantia gelatinosa and lamina IX and remyelination effect. There were no systemic or localized side effects and no adverse effects occurred during the treatment period.

Keywords: Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2); Guillain-Barré Syndrome (GBS); Cerebro Spinal Fluid (CSF); Transverse Myelitis (TM); Reverse Transcriptase Polymerase Chain Reaction (RT-PCR); Interleukin (IL); Thoracic (T); Lumbar (L); Sacral (S); Intravenous (IV); Magnetic Resonance Imaging (MRI); Once Daily (OD); Neuromyelitis Optica (NMO); Anti Nuclear Antibody (ANA); AntiNeutrophil Cytoplasmic Antibodies (ANCA); Angiotensin Converting Enzyme (ACE); Veneral Disease Reference Laboratory (VDRL); Digital Subtraction Angiography (DSA); Herpes Simplex Virus (HSV); Epstein Barr Virus (EBV); Varicella Zoster Virus (VZV); CytoMegalo Virus (CMV); Human Immuno Deficiency Virus (HIV); Lipopolysaccharide (LPS); Regulated on Activation Normal T Cell Expressed (RANTES); Transforming Growth Factor Beta-β1 (TGF-β1); Nitric Oxide (NO); Macrophage Inflammatory Protein (MIP); Dexamethasone Sodium Phosphate (DEX-SP); Transforming Growth Factor B-Activated Kinase (TRAF); Jun N- Terminal Protein Kinase (JNK); InterLeukin Associated Kinase (IRAK); Pro-inflammatory T Helper (Th); Cytokine Interferon-γ (IFN_{γ}); Oligodendrocyte Progenitor Cells (OPCs); Cytochrome P450 Monooxygenase (CYP)

After the recognition of COVID-19 disease, caused by the SARS-CoV-2, several reports refer to neurological symptoms in such patients [1,2], including Guillain-Barré Syndrome (GBS) [3-9]. A very rare neurological complication of SARS-CoV-2 infection includes transverse myelitis. Till date, a total of ten cases of transverse myelitis from acute SARS-CoV-2 infection have been reported (Sarma and Bilello, 2020; Zhao., *et al*. 2020; Chow., *et al*. 2020; Chakraborty., *et al*. 2020; Valiuddin., *et al*. 2020; AlKetbi., *et al*. 2020; Durrani., *et al*. 2020; Munz., *et al*. 2020; Zachariadis., *et al*. 2020; Abdelhady., *et al*. 2020) [53] In 30-60% of idiopathic TM cases, there is an antecedent respiratory, gastrointestinal, or systemic illness [13]. I assume a post-infectious etiology in terms of secondary immunogen-

ic overreaction. The association between COVID-19 and GBS has recently been described both as parainfectious [3,7] and as post-infective event [4,5,9], similar to other infections and coronavirus [11,12], suggesting a mechanism of molecular mimicry or part of systemic inflammatory cascade triggered by the virus.

Transverse myelitis has been attributed to infectious, parainfectious, systemic autoimmune diseases, paraneoplastic, and ischemic diseases (Joshi., *et al*. 2020; Kincaid and Lipton, 2020; Lycklama., *et al*. 2020; Borchers and Gershwin, 2020).

The diagnosis of trans-verse myelitis involves characteristic clinical presentation of bilateral signs and symptoms with a clearly defined sensory level, in addition to evidence on neuroimaging, CSF and serologic studies (Proposed diag-nostic criteria and nosology of acute transverse myelitis, 2002). This case report points towards COVID-19 as a possible cause of acute transverse myelitis [53].

A person in his late 40s with no underlying commorbidity had presented with a sudden onset headache, bilateral lower limb weakness and urinary incontinence. On RT- PCR the patient had been covid positive. His IL) Interleukin 6 levels were (12 pg/mL, normal < 5·9), also associated with Covid-19 disease [10]. IL-6 is one of the primary cytokine involved in infection induced cytokinine storm. Patient had been managed as a case of myelopathy with a spinal shock and had received IV Methylprednisolone for 3 days and then the patient was transitioned to oral prednisone 60 mg OD taper, for four months. His MRI dorsal spine showed diffused intramedullary/ edema involving the conus and mid lower dorsal cord. His CSF analysis showed moderate CSF pleocytosis with neutrophilic predominance. CSF protein content was mildly raised, with normal sugar levels. LDH levels in the CSF were markedly raised. CBC was within normal limits. Anti NMO antibodies and oligoclonal bands were negative in both CSF and serum. Anticardiolipin and phospholipid antibodies were negative too. Vasculitic profile including ANA, ANCA, ACE levels were within normal limits. VDRL and viral markers were non reactive. His DSA and spinal angiogram was normal. Microbiologic testing on CSF and serum was negative (HSV1-2, EBV, VZV, CMV, HIV, Mycoplasma Pneumoniae, Borrelia).

Before starting with transdermal dorsal vertebral iontophoresis, 5 months after the sequale the patients neurological examination revealed diminished sensation, in the dermatome T8- T12, with the loss of all superficial, deep and combined cortical sensations except deep touch sensation till T12 dermatome, with a Medical Research Council (MRC) scale grading of muscle power as 3/5 in the abdominal muscles, 2/5 in the quadrates lamborum and 0/5 in the lower limbs. The patient had a flaccidity in his lower limbs. The patient was complaining of dysthesias and persistent fasiculations in his lower limbs. There was no bladder or bowel control. The abdominal reflex was present, B/l knee reflexes were absent and ankle reflex was present. The plantars were extensors in nature.

Dexamethasone sodium phosphate (4mg) and cyclophosphamide (250mg) transdermal iontophoresis on corresponding vertebral segments (T9-T12) and T12-L2 was initially initiated for first three weeks followed by iontophoresis by miconazole nitrate gel 2% and polyethylene glycol for next three weeks to look for the outcome. On day 3 of the iontophoresis the plantars were down going, On day 4 pelvic control started developing. On Day 5 knee extensors and ankle dorsiflexors were grade 1, On day 10 the patient gained Knee and ankle joint proprioception and the patient responded to deep pressure sense at L5-S1, S1-S2, S3- S4 dermatome. On Day 15 pelvic control of Grade 3 was achieved. On Day 22 we started with the transdermal iontophoresis of Micanazole nitrate gel 2% to look for the outcome. On day 28th Pelvic Control of Grade 4 was achieved and by day 35th, the patient had a full relief from dyesthesias and fibrillations. His long toe flexors and dorsiflexors, knee extensors, hip extensors were grade 1 and there was a slight increase in muscle tone.

Discussion

Dexamethasone helps to reduce inflammation and calms down an overactive immune system. The exact mechanism of action is not clear but some of the possible mechanisms include antiedema effect, stabilization of blood brain barrier, reduction of proinflammotory cytokines and apoptosis of T cells [54]. Dexamethasone sodium phosphate (Dex-P) delivered via iontophoresis is commonly used in physiotherapy to treat tendinopathies; bursitis, shin splints, rheumatoid arthritis and delayed muscle soreness [14-36]. Dexamethasone acts as a stimulator of glucocorticoid receptors signaling pathway, which reduces the production of cytokines and decreases neutrophil tissue invasion and damage. In addition, dexamethasone inhibits the phospholipase A2 enzyme that plays a role in the biosynthesis of leukotrienes, prostaglandins, thromboxane A2, and prostacyclin [37]. It has been found that abnormal neuroinflammation ignited by overproduction of chemokines and cytokines via microglial cells can induce the occurrence and de-

velopment of neurodegenerative disorders. It has been found that dexamethasone sodium phosphate inhibited the neuroinflammatory response and migration in LPS Lipopolysaccharide-activated BV-2 microglia by inhibiting the secretion of RANTES, as regulated on activation, normal T cell expressed and secreted transforming growth factor beta-β1 TGF-β1, and NO nitric oxide and increasing the production of MIP-1α macrophage inflammatory protein-1α and interleukin 10 IL-10, besides inhibition of TRAF6/TAK-1/JNK tumor necrosis factor receptor-associated factor 6/ Transforming growth factor B- activated kinase 1/ Jun N- terminal protein Kinase signaling pathways mediated by IRAK-1 and IRAK-4 (InterLeukin Associated Kinase 1 and 4) [38].

In patients with severe acute immune-mediated longitudinally extensive transverse myelitis who fail to respond to corticosteroids and plasma exchange, cyclophosphamide induction should be considered [39]. This agent and regimen provides a robust immunosuppressive response and can be induced rapidly. Cyclophosphamide has been shown to decrease the secretion of the pro-inflammatory T helper (Th) 1 cytokine interferon-γ (IFNγ) and interleukin (IL)-12 and to increase the secretion of the anti-inflammatory Th2 cytokines IL-4 and IL-10 in cerebrospinal fluid (CSF) and peripheral blood. Methotrexate which is also a immunosuppressant and chemotherapy agent has been administered through iontophoresis by using hydrogel patches [40]. It was found that the transport was influenced by physicochemical properties of the system (cross-linking density of the hydrogel and copolymerisation), duration of electrical currents and the condition of the skin. Besides this the iontophoretic application of cyclophosphamide has been used to treat breast cancer and mastitis [41]. Further in a study Cyclophosphamide administration in association with osmotic blood-brain barrier opening did not cause significant neural toxicity [42].

Based on the defined role of dexamethasone and cyclophosphamide as chemical neuromodulators, neuromodulation by way of iontophoresis in asymptomatic SARS-COV 2 with extensive myelitis was considered to look for outcome. The other considerations which were kept in view were rate of iontophoretic delivery and the chemical property of Cyclophosphamide as it is inert until activated by enzymes in the liver. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. In the present study, the levels of the plasma concentration of the drug reached, which might have passed into systemic circulation through dermal capillary network to liver to undergo activation remains unclear. Complete blood count including Liver Function, Kidney Function Tests were carried out on weekly basis to rule out any toxicity due to cyclophosphamide iontophoresis, and the parameters were normal.

Studies designed to evaluate the depth of penetration of the drugs (DEX, prednisolone, salicylate, and lidocaine) into local tissue following iontophoresis have demonstrated that a depot is formed in the area of the epidermis [43-46]. Deeper penetration of the drug apparently occurs not from iontophoretic current, but from passive diffusion. Passive diffusion is a slower, mass transfer process compared with iontophoresis. Thus, for equivalent iontophoretic dosages, it is time, not current magnitude, that dictates the ultimate local depth of penetration. In living tissue, however, other factors such as local blood flow will determine the ultimate depth of local penetration. A study conducted [47] to determine the time course of dexamethasone sodium phosphate (Dex-P) during iontophoresis to underlying tissues using microdialysis there was no difference in Dex-total between current intensities (P = .99), but a greater amount of Dex-total was recovered superficially at 1 mm compared to the 4-mm depth (P<.0001). 17 I In our study we used 40mA plain faradic current delivered for 10 minutes to reach a therapeutic effect. The dexamethasone was delivered through cathode and cyclophosphamide through anode. Metallic electrodes secured with lint pads which were instilled with drugs were used for iontophoresis. Cyclophosphamide 250 mg was diluted with 20 ml saline. Through our study we were able to modulate the activity of posterior grey column, fasciculus gracilis and corticospinal tracts which was apparent as the patient gained joint proprioception of the knee and ankle and responded to the deep pressure sense at L5-S1, S1-S2,S3-S4 dermatome, down going plantars and attaining a pelvic control of Grade 3 in quadrapod position. It has been found that the antifungal miconazole and the steroid clobetasol stimulates mouse and human oligodendrocyte progenitor cells (OPCs) into generating myelin-producing cells in culture. [48,49]. They found that miconazole and eight other related drugs all blocked an enzyme called CYP51. Blocking CYP51 encouraged stem cells to form new oligodendrocytes. These are the cells that create the myelin coatings around nerve cells.

CYP51 is part of the molecular pathway that produces cholesterol. The researchers discovered that blocking two other enzymes in that pathway also promoted oligodendrocyte production. The utilization of chemical penetration enhancers in conjunction with iontophoresis is regarded as the most effective method to enhance the passage of molecules across the skin barrier 50. In our study

we used polyvinyl alcohol [51,52] to enhance the permeability of Miconazole. Transdermal iontophoretic application of miconazole nitrate for three weeks was able to ameliorate dyesthesias, fasiculations and muscle atrophy probably due to neuromodulation at substantia gelatinosa and lamina IX and remyelination effect.

Conclusion

Dexamethasone Sodium Phosphate, Cyclophosphamide and Miconazole Iontophoresis on subsequent transdermal spinal levels can be considered in patients with myelitis, for modulation, during acute stages.

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