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Case Report

FIXED DOSE COMBINATION OF MECOBALAMIN AND PREGABALIN IN THE TREATMENT OF OROFACIAL NEUROPATHIC PAIN

Manuel Dwiyanto Hardjo Lugito

Oral Medicine Department, Faculty of Dentistry, Universitas Prof Dr Moestopo (Beragama), Jakarta, Indonesia

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KEYWORDS

Mecobalamin, Pregabalin, Orofacial Neuropathic Pain

ABSTRACT

Introduction: orofacial neuropathic pain is extraordinary disease in character with its complicated management. Mecobalamin has been used to provide regeneration of traumatized nerves. Pregabalin with its analgesic activities relieves the clinical signs of neuropathic pain. The aim of this case report is to explain fixed dose combination of Mecobalamin and Pregabalin as the treatment of neuropathic pain caused by inferior alveolar nerve and facial nerve neuropathy.
Case: First case was an inferior alveolar nerve neuropathy experienced by 63 years old female with complaints of persistent pain and numbness around the left chin and left lower lip the day following the procedure of surgery for the treatment of dentoalveolar abscess on left second premolar of mandibula. Second case was facial nerve neuropathy experienced by 54 years old female had persistent pain and numbness of the anterior two-thirds of the tongue after total thyroidectomy and 1,100 MBq (30 mCi) activity of Radioactive iodine (RAI) therapy, followed with two 131I whole body scans.
Case Management: Mecobalamin 500 µg and Pregabalin 75 mg twice daily for 5 weeks were given with tolerable side effects and improvement symptoms.
Discussion: Pregabalin combined with Mecobalamin can reduce orofacial neuropathic pain. Pregabalin possess analgesic property and reduce neuropathy-related pain symptoms while Mecobalamin facilitates myelinogenesis and nerve regeneration.
Conclusion: Fixed Dose Combination of Mecobalamin and Pregabalin has the potential analgesic effect, reduced neuropathic orofacial pain at a below than determined dosage in case of inferior alveolar and facial nerve neuropathic pain.

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Corresponding Author:
Manuel Dwiyanto Hardjo Lugito
Oral Medicine Department, Faculty of Dentistry
Universitas Prof Dr Moestopo (Beragama), Jakarta, Indonesia
e-mail address: manuel_lu@dsn.moestopo.ac.id

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INTRODUCTION

Orofacial neuropathic pain is a general term adopted to represent several clinical syndromes, which may be spontaneous or provoked by local damage or systemic disease affecting the somatosensory system. Symptomatically these painful syndromes may be in episodes or prolonged and are often complicated to differentiate from dental disorders. [1,2] Long term and advanced severity of pain causes associated mental illness, lethargy, distress, sleep disorders, and alleviation general physical functional.[3,4]

Prevalence of orofacial pain ranges from 10% to 15% in the adult population.[5] Local damage to the trigeminal nerve only infrequently led to a painful neuropathy. The prevalence of non-odontogenic pain, of which a majority is probable to eligible for a Post Traumatic Trigeminal Neuralgia diagnosis, range from 3 to 5% of patients undergoing root canal treatment.[6] The aetiology of facial paraesthesia is almost known in 83% of cases and less than 50% is related to dental procedure or condition with inferior alveolar and mental nerves are the most afflicted nerves. Specifically rate of 0.96% cases of sensory disruption related with mandibular premolars.[7]

Radioactive iodine (RAI) therapy has become the standard type of adjuvant therapy for differentiated thyroid cancer, focused at the ablation of residual thyroid tissue after total thyroidectomy, followed with thyroid hormone therapy.[8] Iodide I-131 (131I), used in RAI therapy, is a radio isotopic agent used for the treatment of hyperthyroidism and thyroid carcinomas which absorb iodine.[9,10] A wide range of salivary gland discomfort and swelling in the region of parotid, submandibular, and thyroid bed have been described after RAI therapy. The prevalence of these side effects is usually temporary but may lasting as varying from 2% to 67% in multiple studies(9)[10] while salivary glands inflammation occurs in 7 to 86% of patients.[3]

The overall treatment of neuropathic pain is complicated in consequence of the inadequacies of the current therapeutic preferences. There is inadequate valid data on the fixed dose combination (FDC) of pregabalin and mecobalamin in immediate release or as a sustained release formulation.[4] Pregabalin (PGB) is a newer generation gabapentinoid and selected as one of the first-line drugs for the therapy of neuropathic pain. Pregabalin is potent for persistent numbness, central and peripheral neuropathic pain and that it obtains rapid pain reduction. Methylcobalamin is a crucial constituent in the synthesis of the myelin sheath and in the preservation of nerve function. Vitamin B12 is important in regeneration and maintaining the myelin sheath. Methylcobalamin has a crucial function in the of myelin sheath and aids to recover the function of the nerve in neuropathy.[4,11] The objective of the present case reports was to carry out treatment of inferior alveolar nerve and facial nerve neuropathy of the FDC of sustained-release pregabalin and immediate release methylcobalamin (PGM-SR) in healing neuropathic pain in daily practice.

CASE

Case 1

A 63-year-old female patient underwent extraction of left mandibular first premolar with subsequent development of numbness around the left chin and lower lip the day following the surgery and extraction of 34. The patient's body mass index is obese with no systemic disease was found. Intraoral examination revealed 18, 27, 34 were missing, 44, 45, 47 were radixes. Figure 1 showed radiographic examination consisted of well demarcated radiolucency at the root of a nonvital tooth. The size of the lesion extended laterally superiorly and inferiorly from the apex Results of haematology examination included haemoglobin, haematocrit, erythrocyte, thrombocyte, leukocytes, MCV, MCH, and MCHC were normal.

Figure 1. Radiolucency of mandibular bone of left first premolar. The lesion extended laterally, superiorly, and inferiorly from the apex (Case 1).

Several medications including non-steroidal anti-inflammatory, analgesic, and antibiotic therapy were not able to provided her any pain and numbness relief. After a week of persistent pain and unpleasant numbness, the patient was finally referred to the oral medicine clinic. The score of pain assessed using a 10-point visual analogue scale (VAS) was 5. There is no previous scale to rate numbness, but it was assessed by the patient on an 11-point scale, from 0 (no numbness) to 10 (truly no sensation). The patient rated her numbness as 0/10 at best and 6/10 at worst. At the first visit, her score of numbness was 2/10. No facial muscle weakness was evident. The working diagnosis was an inferior alveolar nerve neuropathy

Treatment with Mecobalamin 500 µg and Pregabalin 75 mg twice daily for 5 weeks were given. Two weeks after 1st visit, patient only reported mild drowsiness and less complain with improvement symptoms with VAS score was 3. Slight tenderness to light touch and hyperalgesia to pinprick was noted in the area supplied by the mental nerve on the left side. Three weeks after 2nd visit, she felt pain once in the last 2 weeks without any numbness on her left chin. Extraction of 44 and 45 was performed after her complain of numbness was eliminated.

Case 2

Facial nerve neuropathy experienced by 54 years old female with persistent pain and numbness of the anterior two-thirds of the tongue a week after therapy of differentiated thyroid carcinoma including total thyroidectomy and Radioactive iodine (^{131}I) therapy, followed with two ^{131}I whole body scans 2 years ago. No previous pain and numbness in oral cavity before being treated for differentiated thyroid carcinoma. Treatment with Thiamine, Pyridoxine, Cyanocobalamin, and Acetaminophen gave no pain alleviation. Treatment with Amitriptyline 25 mg twice daily provided partial pain alleviation; while also being associated with unpleasant drowsiness, prompting her to cease its use. She remained frustrated and continued to ask for better pain control.

Physical examinations showed normal blood pressure, overweight, no taste disturbance and normal salivary flow rate. Numbness did not deteriorate or ease rapidly. Results of haematology examination included haemoglobin, haematocrit, erythrocyte, thrombocyte, leukocytes, MCV, MCH, and MCHC were normal. TSH levels was 0.04 mU/L (normal 0.35 to 4.94 mU/L). The result of intraoral examinations showed no abnormalities. The score of pain using a visual analogue scale (VAS) was 4 and numbness was 4/10. Her routine medication are Levothyroxine 100 mcg and Carvedilol 6.25 mg.

Figure 2. Normal mucosa and tongue (Case 2)

TREATMENT

Mecobalamin 500 µg and Pregabalin 75 mg twice daily for 5 weeks were given. One week after 1st visit, she reported improvement of her pain with VAS score was 2 and only mild drowsiness with no tenderness to light touch was noted in the area supplied by the mental nerve. Two weeks after 2nd visit, she rarely felt pain without any numbness on her left chin. Until now, she still receives mecobalamin 500 µgm once daily to maintain her nervous system.

DISCUSSION

The mental nerve and its branches innervate sensory of cutan of the chin and lower lip, the mucous membranes on the buccal of the lower lip.[12] Mental foramina in mandible can be located inferior to the first premolar, second premolar or first molar, or between the first and second premolar or the second premolar and the first molar. The average position of mental foramina is 25.8 mm laterally from the midline and about 13 mm superior to the inferior border of the mandibular body.[13]

As in panoramic result of the first case (figure 1) showed radiolucency of periodontium and mandibular bone of left first premolar. Partial nerve injury of mental nerve was suspected due to dental extraction process and concurrently abscess compression[14] as happened in the first case. Inflammation, infection, pressure of abscess of 34 and surgery led to nerve damage, and established a cascade of events from the peripheral to the central nervous system. Traumatic injury to a distal end of the nerve fibre of peripheral nerve conduces Wallerian degeneration while Schwann cells, which should aids to provide trophic support of nerve fibers, start to initiate the degeneration and lose their myelin or encapsulation in the case of unmyelinated nerves.[15,16]

In the second case, ionizing radiation (^{131}I) discharges high-energy gamma radiation[17] and influences adjacent non-malignant cells by release cytokines and inflammatory mediators.[18] The inflammatory response can lead fibrosis, atrophy, and ulceration of the tissues, including nerves,[19] ischemia, oxidative stress[20] and therefore nerve damage may develop.[19] Oxidative stress might influence the thyroid by degrade ordinary T3 to set reverse T3 and impedes the activity of T3 as the powerful neurotrophic substance. The abnormal function of thyroid may be related with the release of inhibitions for sensitive trigeminal sensation. [21]

Pregabalin is selected as the first-line drugs for the therapy of neuropathic pain, persistent numbness.[6,11] Pregabalin is an antagonist of voltage gated Ca2+ channels and capable to regulate different potassium channels. Pregabalin alleviate the neuronal excitability and inhibiting the release of different neurotransmitters. Pregabalin mediated anti-inflammatory actions involving reduced release of pro-inflammatory cytokines utilize as an intermediary in its anti-nociceptive actions in peripheral neuropathic pain.[22]

Mecobalamin is a crucial constituent in the synthesis of the myelin sheath, the recovery and protection of nerve function.[6,11]Mecobalamin is a synthetic and active form of vitamin B12 and acts as an important cofactor in activities of B(12)-dependent methyltransferases. Mecobalamin is capable to substitute endogenous vitamin B_{12}, increase vitamin B_{12} levels, important for neural metabolism, DNA and RNA production.[23,24] Methylcobalamin is methylated vitamin B-12 and contains a methyl group in its structure. Methylcobalamin is also converted into Mecobalamin in the body. Stimulation of vitamin B_{12} might release endogenous opioids or actuate the opioid receptors such as GABA, which reduce Ca^{2+} mediated discharge of neurotransmitters and enhance conductance through K+ channels and causes hyperpolarization of the postsynaptic membrane of the dorsal horn neurons, leading to alleviated pain conduction.[25]

The controversy of potential analgesic effects of vitamin B_{12} may increase availability and effectiveness of noradrenaline and 5-hydroxytryptamine in the descending inhibitory nociceptive system.[26] Vitamin B_{12} also acts as a scavenger of the reactive oxygen species owing to its anti-necrotic and anti-apoptotic effects on neurons.[27]

Mecobalamin has been used in combination with other drugs to manage peripheral neuropathy.[24] Total 12 weeks of fixed combinations of methylcobalamin, folic acid, biotin, benfotiamine, and pyridoxine generated a significant reduction within 4 weeks.[27] The fixed dose combination of 75 or 150 mg pregabalin combined with 1500 mcg methylcobalamin, gave a good reduction in average pain score and good to excellent efficacy and tolerability.[4] Methylcobalamin 750 µg and Pregabalin 75 mg for 4 weeks is well tolerated and efficacious in treating the neuropathic pain.[28,29]

Combination the first-line neuropathic pain therapy with mecobalamin is preferable than without supplementation therapy.[30] Neurosurgical interventions, other medication (tacrolimus, capsaicin)[6] are other alternative treatment while erythropoietin and stem cell therapy are future treatment for neuroprotection and neural regeneration.[16] Pregabalin combined with Mecobalamin can reduce orofacial neuropathic pain. Pregabalin possess analgesic property and reduce neuropathy-related pain symptoms while Mecobalamin facilitates myelinogenesis and nerve regeneration.

CONSLUSION

Fixed Dose Combination of Mecobalamin and Pregabalin has the potential analgesic effect, reduced neuropathic orofacial pain at a below than determined dosage in case of inferior alveolar and facial nerve neuropathic pain.

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