SCIENCE SET
OPEN ACCESS PUBLISHERS

Case Report

Science Set Journal of Medical and Clinical Case Studies

Tramadol Plus Pregabalin Combined with Cilostazol as Treatment for Severe Pain in A Filipino Patient with Critical Limb Ischemia secondary to Microscopic Polyangitis a Case Report

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Submitted: 13 February 2025 **Accepted:** 17 February 2025 **Published:** 27 February 2025

Citation: *Gonzales, R. E., & Ingco, P. A. C. (2025). Tramadol Plus Pregabalin Combined with Cilostazol as Treatment for Severe Pain in A Filipino Patient with Critical Limb Ischemia secondary to Microscopic Polyangitis a Case Report. Sci Set J of Med Cli Case Stu, 4(1), 01-07.*

Abstract

Critical limb ischemia is a resting limb pain secondary to poor vascular flow. It has a wide range of differential diagnosis with several proposed medical or surgical treatment strategies. Despite the multiple approach developed, pain management has been individualized due to the challenge encountered in its control. This study describes the successful use of Tramadol in conjunction with Paracetamol, Pregabalin and Cilostazol as pain regimen in a medically treated patient presenting with severe lower limb pain from a non-healing wound secondary to critical limb ischemia.

We report a case of a 28-year old female, non-hypertensive and non-diabetic with a 19 months history of progressive right lower extremity neuropathic and nociceptive pain with associated weakness. Multiple work-up and treatments were done where initial assessment was polyarteritis nodosa r/o Takayasu Arteritis. Patient was treated with the combination of Pregabalin Prednisone, Azathioprine, Aspirin, Colchicine, Ketoanalogues + Amino Acids, Sodium Bicarbonate, Tramadol+ Paracetamol. Despite treatment there was progression of pain hence admission where she was put on multidisciplinary care. In patient work-up was done and patient was eventually assessed to have Critical limb ischemia secondary to Microscopic polyangiitis; Chronic kidney disease Stage 3B sec to glomerulonephritis. Pain was progressive in nature and was controlled using PCA Tramadol with the following settings: Concentration of 10mg/90mL, Basal rate of 7.5mg/hour, Bolus rate of 5mg/demand. Lock out interval of 30 minutes. Adjunctive pain medications included Paracetamol, Pregabalin and Cilostazol. As the patient responded with her immunosuppressants and cardiovascular medications, pain medications were then subsequently titrated down and was eventually shifted back orally to Pregabalin 75mg OD and Tramadol + Paracetamol 37.5/325mg/tab 1 tab every 6 hours, with rescue doses of Tramadol + Paracetamol 18.75 +185mg 1 tablet every 4 hours as needed for pain >/= 4/10.

This case report demonstrates adequacy of Tramadol in conjunction with Pregabalin, Paracetamol and Cilostazol in the treatment of ischemic pain in a patient with critical limb ischemia secondary to microscopic polyangiitis.

Introduction

Critical limb ischemia is defined by the American Heart Associated as more than or equal to 2 weeks of ischemic resting pain with associated nonhealing wound or ulcers and gangrene in a single or both lower extremity ascribed to a an objectively proven arterial occlusive disease [1]. Patients have variable outcomes and treatment has been challenging as non-operative or operative management have been available as options of treatment. Among these patients, 20-30% would require limb amputation, a quarter will have ongoing symptoms and 8.9% will die within 1 year of diagnosis [2].

Optimal pharmacologic treatment is not yet fixed but management have focused on increasing survival, maintenance of limb integrity, prevention of amputation and pain control [2, 6]. Treatment with strong recommendations which was based on high quality evidences have been outlined and involves interdisciplinary care and have been focused on the initiation of

the following: combination of antithrombotic therapy with an antiplatelet agent, statins, antihypertensives, smoking cessation, glycemic control, vasoactive agents such as cilostazol. Other recommendations include surgical or endovascular revascularization [1, 3, 8].

In conjunction with the medical or surgical management is the critical role of palliative treatment in the improvement function and quality of life especially in patients with no options for revascularization. This includes control of pain associated activity limitation which encompass the combination of supervised exercise program, proper leg positioning, use of topical analgesics, gabapapentinoids, opioids, regional anesthesia, hyperbaric oxygen therapy and spinal cord stimulation [4].

For pain control, opioids have been the mainstay treatment and is titrated according to the patients level of comfort while preventing the development of untoward side effects. Critical limb ischemia pain may be induced in different situation such as position change, wound debridement or dressing changes hence a fast acting and short lived medication such as Fentanyl has been a good option [5]. Gabapentinoids are used as an adjunct to opioids to control the inflammation induced neuropathic pain. Gabapentin has been shown to result in notable decrease in baseline pain score and night pain among patients with critical limb ischemia [5, 6]. Cilostazol has been used to treat intermittent claudication caused by narrowing of arteries by facilitating vasodilation and inhibiting phosphodiesterase III and platelet aggregation. Its use has been shown to decrease symptomatic intermittent claudication and improvement in ambulation with optimal therapeutic effect reached until 12 weeks of intake [7].

Other adjunctive vascular analgesia are also recommended to hasten pain control which include paracetamol, non-steroidal anti-inflammatory drug (NSAIDS), epidurals or local anesthetic catheters. However, in the management pathway created by BSUH Acute pain service, NSAIDS are advised to be avoided.

The combination of drugs used to treat critical limb ischemia has been difficult due to the individualized pattern of prescription to these patients. There is no recommended specific cocktail of pain medications as a standard of care, however several approaches have been outlined to guide clinicians in their management options [8].

This case report highlights the use of Tramadol in combination with Paracetamol, Pregabalin and Cilostazol for the treatment of Neuropathic and Nociceptive pain secondary to critical limb ischemia associated with Microscopic Polyangiitis.

Objectives

1. To present a case of Microscopic polyangiitis presenting as right lower extremity pain and weakness.
2. To present the pain medications used in the treatment of a patient with critical limb ischemia secondary to a vasculitis.

Significance

Critical Limb Ischemia is a cause of significant chronic pain and distress which may lead to consequential disability when left undiagnosed or inadequately treated. Several guidelines and pathways have been proposed on how to help patients in a multi-specialty level however there is no specific recommended treatment. Pain control has been difficult most especially to patients who chose pure palliative approach. This case report presents the use of Tramadol in combination with Paracetamol, Pregabalin and Cilostazol in the management of a patient with leg pain secondary to critical limb ischemia.

Case History

This is a case of a 28 year old G0P0 patient who presented with 19 months history of right lower extremity discomfort. She has no known co-morbidities and works as a call center agent. She does not smoke, drink alcohol or use illicit drugs. Patient has a family history of hypertension on the maternal side and a sister who suffered stroke in the young. Patient has also been trying to conceive for the past 4 years but to no avail.

Her disease course started 19 months prior to admission when she initially noted to have numbness with pins and needle like sensation on the right hip to the right foot NRS 4-5/10. The discomfort was described as continuous aggravated by ambulation and partially relieved by rest.

The symptoms progressed to difficulty in ambulation described with easy fatigability of the affected extremity with associated changes in balance described as falling to the right. At that time, patient had minimal difficulty doing activities of daily living but was still able to work from home. No medications taken, no consult done 6 months prior to admission, symptoms progressed to on and off bluish discoloration of the right foot with associated difficulty performing basic activities of daily living. Patient went for consult where creatinine was noted to be elevated at 1.9. Cranial MRI was also done which revealed acute cerebellar infarct. Patient and was eventually diagnosed to have multiple sclerosis and discharged with Methylprednisolone 16mg OD for 2 months, Pregabalin 50mg OD and Ketoanalogue TID.

Interim, noted improvement of weakness with decreased frequency of numbness and paresthesia. No other symptoms noted. 3 months prior to admission, patient noted appearance of wound on right foot after getting a massage. Still with numbness and paresthesia on right foot with pain increasing to NRS 6-7/10. Patient followed up with her Neurologist and was advised to discontinue steroids and initiate low dose Aspirin 2 months prior to admission, there was still progression of symptoms. Consult with Rheumatologist was done where she was given the initial diagnosis of Polyarteritis Nodosa. Patient was prescribed with tapering dose of Prednisone 10mg for 1 week, then 20mg for another week, and then 10mg thereafter.

1.5 months PTA, still with pain NRS 6-7/10 and tenderness on right foot with occasional numbness, paresthesia and weakness. No associated fever, chills, myalgia or arthralgia. Patient continued taking maintenance medication which would provide temporary relief. Sought consult back to Rheumatologist where diagnosis was revised to Takayasu Arteritis. Patient was advised to do arterial duplex scan and was advised to add the following medications: 1. Pregabalin 50mg OD 2. Prednisone 20mg OD 3. Azathioprine 50mg OD 4. Aspirin 80mg OD 5. Colchicine 0.5mg OD 6. Ketoanalogues + Amino Acids 1-tab OD 7. Sodium Bicarbonate 650mg 1-tab OD 8. Dolcet Mini 37.5/325mg 1-tab PRN for the pain.

Interim noted progression of right lower extremity pain to NRS 8/10, hence advised admission.

Physical examination showed stable vital signs, (+) hyperpigmented patches on antecubital area and on the chest, (+) approximately 3x2 cm dry wound on dorsal aspect of the right foot and on the lateral side of the foot with no purulent discharge, (+) tender, cold to touch. Absent pulses R PA and PTA, +1 pulses on L DPA ans PTA, no edema
Neurologic exam showed motor strength of bilateral upper extremity and left lower extremity of 5/5, Right hip flexion and extension 4+/5, R knee extension and flexion 3/5, R Dorsiflexion and plantarflexion 3/5 with no sensory deficits

Work up was done throughout admission and showed the following trends and results:

1. 1. Arterial duplex scan of the upper extremity showed
a. Bilateral upper extremity arterial disease, thrombotic with:
i. Chronic total occlusion of the mid brachial artery with evidence of collateralization
ii. Chronic total occlusion of the bilateral ulnar arteries with evidence of collateralization.
2. Arterial duplex scan of the lower extremity showed
a. Right lower extremity arterial disease, thrombotic with:
i. Total occlusion of the right mid to distal anterior tibial and dorsalis pedis arteries with evidence of collateralization.
ii. Total occlusion of the left distal posterior tibial artery with evidence of collateralization in its distal segment
3. Venous compression tests showed normal results.
4. Complete blood count initially showed elevated white blood cells but eventually decreased to normal value prior to discharge.
5. Creatinine levels showed increasing trends with highest reaching 2.8mg/dL and was eventually maintained at 1.6mg/dL prior to discharge.
6. Urinalysis showed persistent proteinuria ranging from +1 to +3 and elevated random urine protein creatinine ratio.
7. Acute phase reactants including ESR and C-reactive protein are both 2x elevated the upper normal limit.
8. Rheumatologic work up showed negative anti-nuclear antibody but positive for the presence of lupus anticoagulant

Table 1: Other significant laboratory results done during in patient management

Test	
Lipid Profile	Total Cholesterol 214 mg/dL Triglycerides 106 mg/dL HDL 95 mg/dL LDL 108mg/dL
Whole abdominal ultrasound	Right kidney 10.8 x 5.1cm with cortical thickness 1.0 cm Left kidney 10.2 x 5.4 with cortical thickness of 0.9 cm Bilateral renal parenchymal disease
Computed tomography of the whole abdomen	Gallbladder polyps and/or slude balls Bilateral Renal Parenchymal Disease Significant urinary retention of 33% Unremarkable study of the visualized pancreas, liver, spleen and uterus.
Duplex Scan Renal Arteries	No evidence of renal artery stenosis, bilateral. No evidence of renal parenchymal disease, bilateral. Normal kidney size, bilateral. Patent renal veins, bilateral.
Carotid/ Arterial Duplex	Carotid artery disease with: a. Less than 50% stenosis (approximately 16 to 49%) in the left internal carotid artery. b. Less than 50% stenosis in the left common carotid artery Kinked bilateral internal carotid arteries. Normal antegrade flow in the bilateral vertebral arteries.

Initial Impression at the time of admission was Chronic Limb threatening ischemia to consider Takayasu Arteritis; CKD Stage 3B sec to Vasculitis Patient was initially seen in the Emergency Room awake, comfortable. No fever, chills, nausea or vomiting. No chest pain, palpitations, abdominal pain, dyspnea. No dysuria, no BM changes. Significant complain as severe pain on wound of right foot with associated paresthesia. Vital signs were stable and physical examination of the lower extremity showed tender and cold to touch dry wound on dorsal aspect of the right foot and on the lateral side of the foot. She was started on Clindamycin 600mg IV every 8 hours, Enoxaparin 0.6mL SQ Q12, Colchicine 0.5mg OD, increase in Azathioprine to 20mg 2 tabs after breakfast. Pain was controlled using Pregabalin 75 mg at bedtime.

Multispecialty care was involved which included Cardiology, Nephrology, Rheumatology and Neurology service for co-management ON the same of admission, patient complained of right foot pain with a numerical rating scale (NRS) of 9 out of 10 hence was given Tramadol+ Paracetamol 37.5/325mg, 1 tablet every 8 hours and Cilostazol 100mg 2x a day. However, this only provided minimal and partial relief hence on the third day, patient was referred to pain management with the assessment of Vascular Pain with Neuropathic Component secondary to critical limb ischemia. Pain medications were revised to the following:

1. Paracetamol 1g/IV every 8 hours
2. Pregabalin 75 mg/ capsule, 1 capsule every 12 hours
3. Patient controlled Analgesia (PCA) Tramadol with the concentration of 10mg/ml, basal rate at 10mg/hour, 5mg per demand and 30 minutes lock out

4. Cilostazol 100mg/capsule, 1 capsule 2x a day was maintained

9 hours post hooking to PCA Tramadol, patient noted significant improvement of pain to NRS 3 out of 10. Lower extremity movement and room ambulation was more tolerated with minimal assist. PCA tramadol was gradually titrated until basal rate of 7mg/hour, bolus rate of 5mg/demand and 30 minutes lockout. Pregabalin was decreased to 75mg once a day and cilostazol maintained to 2x a day.

Kidney biopsy was eventually done and revealed a final diagnosis of Microscopic Polyangiitis. During the admission, patient had several rounds of antibiotic treatment. Antiplatelets, anticoagulants, statins, steroids and immunosuppressants were also given and were titrated according to patients response.

Patients intermittent claudication eventually improved until on the 14th hospital day, her PCA tramadol was gradually down titrated until Basal dose of 0mg/hour, bolus dose of 5mg/demand and lock out rate of 30 minutes was reached. Pain medications were shifted to oral Tramadol + Paracetamol 37.5/325mg 1 tablet every 6 hours, Rescue doses of Tramadol + Paracetamol 18.75 +162.5mg every 4 hours as needed for pain score more than or equal to 4/10, Cilostazol 500mg 2x a day and Pregabalin 75mg once a day. Patient was eventually discharged requiring rescue doses of 2-3 capsules a day.

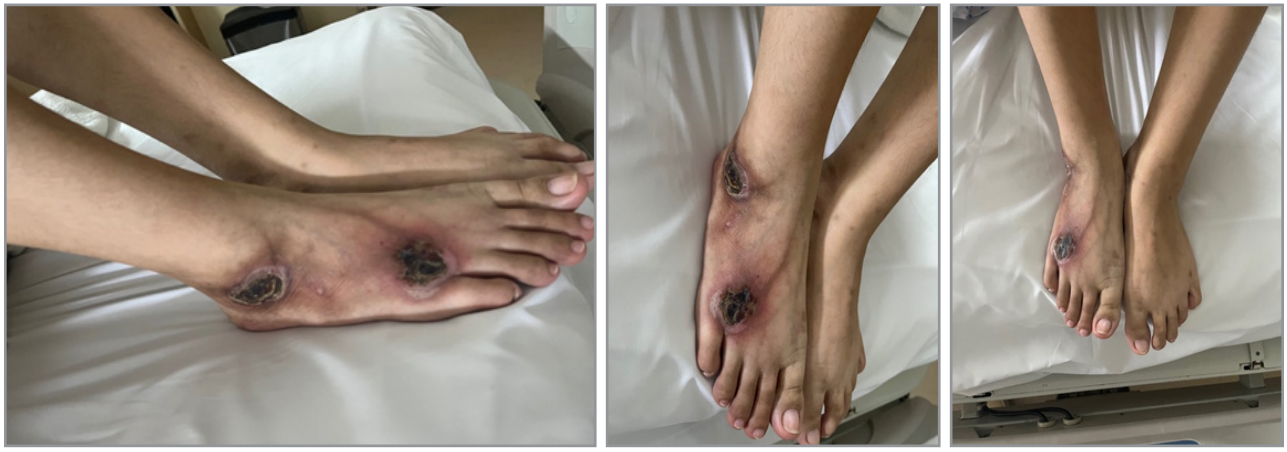

Figure 1: Initial Presentation of the patient's right foot on admission

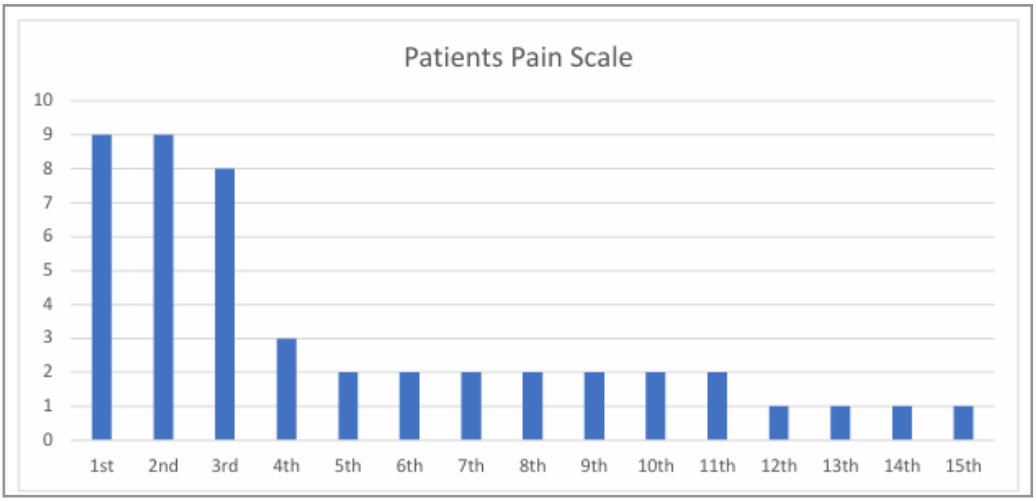

Table 1: Pain scores during hospital stay. The bar graph shows the day by day average pain score of the patient. X- Axis represents the hospital day while Y-Axis represents the numerical rating scale ranging from 0 (No Pain) to 10 (Worst Possible Pain).

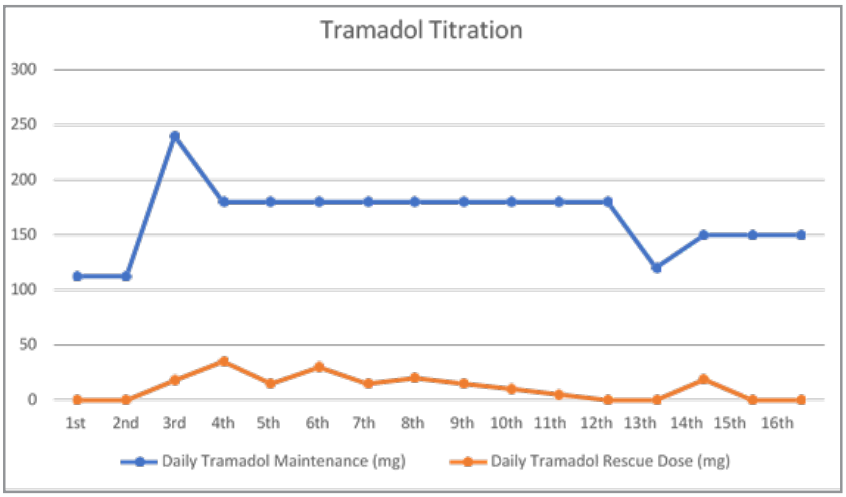

Table 2: Tramadol dose given during the hospital stay. The line graph shows the day by day titration of Tramadol required to decrease the patients pain score to NRS </=4/10. X- Axis represents the hospital day while Y-Axis represents the amount of medication administered

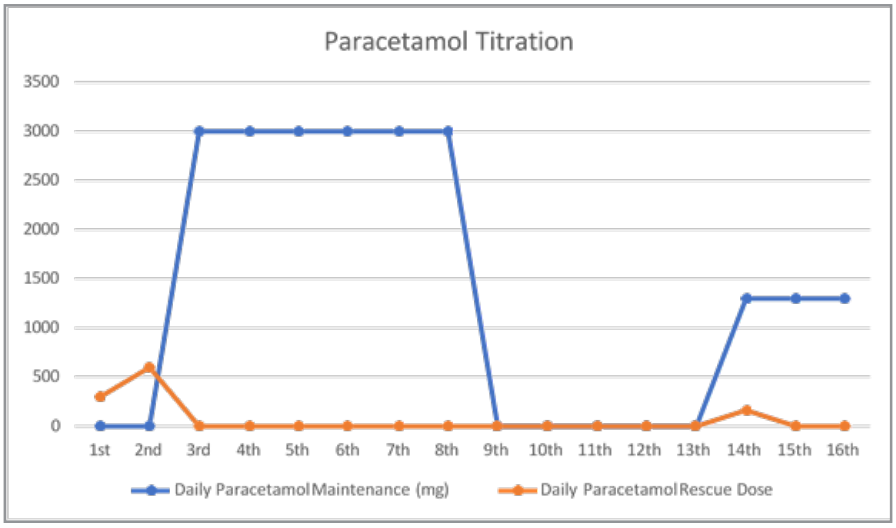

Table 3: Paracetamol dose given during the hospital stay. X- Axis represents the hospital day while Y-Axis represents the amount of medication administered.

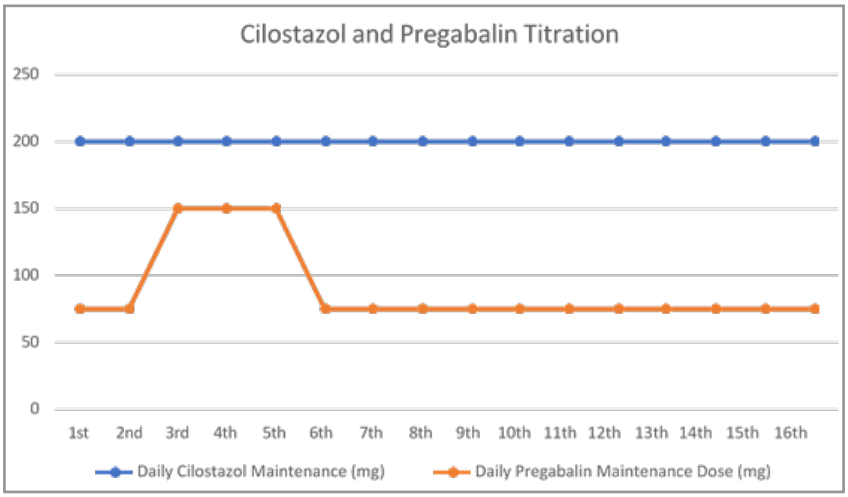

Table 4: Co-analgesic adjuncts given during the hospital stay. X- Axis represents the hospital day while Y- Axis represents the amount of medication administered.

Discussion

We presented a case of a 28-year-old female with critical limb ischemia secondary to tibial and dorsalis pedis artery occlusion. Her symptoms initially presented as intermittent claudication which lasted for one year prior to the initial consultation. Upon initial investigation, our patient was suspected to have vasculitis and was initially treated with the combination of antiplatelet, anticoagulant, steroids, calcium channel blocker, statin and pain medications as the patient refused invasive procedures.

Critical limb ischemia (CLI) or ischemic limb pain has several pathophysiologic causes which include atherosclerosis, vasculitis, thromboembolic disease, arterial embolic disease, in situ thrombosis, cyclic adventitial disease, throboangiitis obliterans or trauma. Our patient presented with a rare type of necrotizing vasculitis due to small and medium sized vessels with several organs involved. Aside from vasculitis, she reported easy fatigability, muscular and joint pains, increasing creatinine levels with increasing trends in random urine protein creatinine ratio. The patients medications were slowly titrated until after kidney biopsy, her final diagnosis was eventually signed out as microscopic polyangiitis (MPA).

Microscopic polyangiitis is a rare type of vasculitis which causes the small blood vessels to be inflamed. It is a type of autoimmune disease which involves several organ systems including rapidly progressing glomerulonephritis, pulmonary capillaritis, musculoskeletal, peripheral and central nervous system involvement [9].

The 2022 American College of Rheumatology and European Alliance of Association for rheumatology has validated the classification for patients with MPA. The diagnosis is considered among patients with small or medium vessel vasculitis while excluding alternate diagnosis mimicking vasculitis. The criteria has a scoring system which is calculated based on the clinical, laboratory, imaging and biopsy results. A score of more than or equal to 5 is needed for the classification of microscopic polyangiitis [10].

Primary medical approach of treatment in these patients include induction therapy which is comprised of glucocorticoids in combination with an immunosuppressant of either rituximab or cyclophosphamide. This is followed by a maintenance therapy of either rituximab, azathioprine, methotrexate or mycophenolate after remission have been obtained [11]. In conjunction with the medical management is the palliative care that has to be offered due to the great discomfort the disease can present especially among patients at the latter part of the disease course.

Our study have focused on the palliation of pain in the background of a patient with critical limb ischemia secondary to MPA. Although our patient presented with a vascular type of disease, it is probable that several mechanism of pain is involved in her condition which include somatic, vascular and neuropathic

types of pain. In CLI, arterial capacity to produce vasomotion and vasodilation are compromised secondary to multiple mechanism. First there is an arterial stenosis which lowers the ankle brachial index resulting to the constant pain at rest. Second, the compromised vasodilation and enhanced vasoconstriction results to the ineffective blood flow during ambulation and exercise hence causing intermittent claudication Neuropathic pain is due to several pathologic mechanisms which is related to distal axonopathy affecting the nerve fibers of all sizes [12-14].

Ideal treatment for ischemic limb pain is achieved through reperfusion therapy. In addition, interventional pain procedures such as spinal cord stimulation and lumbar sympathectomy have been explored. Most of the data available include cases of patient who underwent such invasive protocols. There are limited case reports on patients managed palliatively wherein invasive procedure is not an option. In times when palliative approach is chosen, pain control becomes taxing both to the patient and the clinicians. In these situation, the multidisciplinary team involved in the care of these patients should always consider the quality of life as the most important aspect of treatment [8].

Several guidelines have been published regarding the choices of medications in alleviating the pain in these types of patients, which include the choice of rapid onset opioids as the cornerstone of treatment in combination with gabapentinoids, topical analgesics, cilostazol, anti-depressants and regional anesthesia. There is no standard pharmacologic treatment that has been recommended in the management of pain secondary to a medically managed critical limb ischemia [8]. Even so, it was emphasized in the study made by Pickmans et al., that opioids should not be used as a single treatment agent and it is preferably mixed with an adjunctive pharmacologic and non-pharmacologic therapies [4]. When using opioids as the primary analgesic of choice, it should be slowly titrated according to the patients need to control the baseline and breakthrough pain [5]. Gabapentin should also be considered early as in requires longer titration strategies.

In our patient, initial control of right lower extremity pain was done using slow titration of Tramadol using PCA. Tramadol was combined with the early initiation of adjunctive analgesics including paracetamol, pregabalin and cilostazol. It can be seen in table 1 that the patients symptom significantly improved from the first day when pain service initiated the combination of pain medications. Table 2, 3 and 4 outlines the gradual titration and decreasing pain medication requirement of the patient. Together with the other immunosuppressive and vascular medications initiated, pain medications was eventually titrated back to the admission dose prior to discharge.

There are limited data and case reports published regarding the combination of pain medications used among patients with critical limb ischemia. Among the published cases, the common opioid used among admitted patients are the short acting pure agonist such as fentanyl and morphine. In our patient,

the choice of pain control was with the use of a weak opioid with other non-opioid adjuncts. The dose of all her pain medications were eventually titrated down when immunosuppressants, statins and blood thinners were titrated according to the patients need and requirement. This case report emphasize the importance of considering Tramadol as the initial opioid of choice among patients with vasculitis.

To the best of our knowledge, this is first case report regarding the use of a Tramadol, a weak opioid for pain control in a patient with MPA suffering CLI

Conclusion

In conclusion, pain control in patients with critical limb ischemia has been difficult as it is individualized according to the treatment pathway the patient belongs to. Careful titration of pain medication is important as to prevent untoward outcomes. Our study have demonstrated the effectiveness of using Tramadol in combination with Pregabalin, Paracetamol and Cilostazol in the control of pain in a Filipino patient with critical limb ischemia.

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