



Spinal cord stimulator for the treatment of ischemic pain-Burger's Disease and Raynaud's disease: A report of 2 cases and literature review

İskemik ağrı-Burger hastalığı ve Raynaud hastalığı tedavisinde spinal kord stimulatörü uygulaması: 2 olgu sunumu ve literatür taraması

Esra ERTİLAV,¹ Osman Nuri AYDIN²

Summary

Ischemic pain is the main symptom of a group of diseases that result in inadequate blood flow to the extremities and ischemia. In this symptomatology, two major disease are distinguished: critical vascular disease and Raynaud's phenomenon. Critical vascular disease background of atherosclerosis caused by diabetes mellitus or hypertension. Raynaud phenomenon is divided into primary and secondary form. The primary form is due to vasospasm and there is no underlying cause. Secondary form is associated with underlying connective tissue or rheumatic diseases, peripheral vascular diseases such as thromboangitis obliterans (Burger's disease). Clinical findings in Raynaud's disease are vasomotor changes with cold exposure such as bruising, coldness, painful paresthesias, ulcers due to chronic ischemia. Clinic presentation in critical ischemic disease is intermittent claudication for earlier stage and resting pain, gangrene, necrosis and trophic changes were added in advanced stages. The treatment of the Raynaud's disease in early stage is medical and conservative. In case of advanced stage ischemic vascular disease, medical treatment resistant pain, insufficient response to endovascular treatment, inoperable cases, interventions such as sympathectomy and spinal cord stimulation (SCS) can be applicable. SCS reduces vascular resistance through vasodilator mediators and increases blood flow. SCS also suppresses sympathetic vasoconstriction, increases tissue vascularity, reduces tissue damage, provides ulcer healing and pain reduction. In this report we demonstrated that persistent Raynaud's disease and advanced stage Burger's disease were successfully treated with SCS.

Keywords: Burger's disease; ischemic pain; Raynaud's disease; spinal cord stimulator.

Özet

İskemik ağrı, ekstremitelere yetersiz kan akımıyla sonuçlanan bir grup hastalığın ana semptomudur. Bu semptomatolojide iki ana hastalık ayırt edilir: kritik vasküler hastalık ve Raynaud fenomeni. Kritik vasküler hastalık diabetes mellitus veya hipertansiyonun neden olduğu aterosklerozun zemininde gelişmektedir. Raynaud fenomeni primer ve sekonder forma ayrılır. Primer form vazospazmdan kaynaklıdır ve altında yatan bir neden yoktur. İkincil form, altında yatan bağ dokusu veya romatizmal hastalıklar, tromboangit obliterans (Burger hastalığı) gibi periferik vasküler hastalıklar ile ilişkilidir. Raynaud hastalığında klinik bulgular, soğuğa maruz kalma ile morarma, soğukluk, ağrılı parestezi gibi vasomotor değişiklikler ve kronik iskemiden kaynaklanan ülserlerdir. Kritik iskemik hastalıkta klinik prezentasyon, erken evre için intermitten kladikasyon ve ileri evrelerde istirahat ağrısı, kangren, nekroz ve trofik değişiklikler de eklenir. Raynaud hastalığının erken evrede tedavisi medikal ve konservatiftir. İleri evre iskemik vasküler hastalık, tıbbi tedaviye dirençli ağrı, endovasküler tedaviye yetersiz yanıt, inoperabl vakalar gibi durumlarda sempatektomi ve spinal kord stimülasyonu (SKS) gibi girişimler uygulanabilir. SKS vazodilatör mediatörlerle vasküler rezistansı azaltır ve kan akımını artırır. SKS ayrıca sempatik vazokonstriksiyonu baskılar, doku kanlanmasını artırır, doku hasarını azaltır, ülser iyileşmesini sağlar ve ağrıyı azaltır. Bu olgu bildirimlerinde dirençli Raynaud hastalığının ve ileri evre Burger hastalığının SKS ile başarılı bir şekilde tedavi edildiğini gösterdik.

Anahtar sözcükler: Burger hastalığı; iskemik ağrı; Raynaud hastalığı; spinal kord stimulatörü.

¹Department of Neurology-Algology, Adnan Menderes University Faculty of Medicine, Aydın, Turkey

²Department of Anesthesiology-Algology, Adnan Menderes University Faculty of Medicine, Aydın, Turkey

Submitted: 08.10.2019 Accepted after revision: 12.03.2020 Available online date: 23.07.2020

Correspondence: Dr. Esra Ertılav. Adnan Menderes Üniversitesi Tıp Fakültesi, Nöroloji-Algoloji Bilim Dalı, Aydın, Turkey.

Phone: +90 - 530 - 140 89 50 **e-mail:** eertilav@gmail.com

© 2020 Turkish Society of Algology

Introduction

Critical vascular disease is common in patients older than 55 years due to arterial vascular disease developing at the backdrop of atherosclerosis.^[1]

Raynaud's phenomenon is examined under primary and secondary form,^[2] and its primary form (Raynaud's disease) is idiopathic vasospastic disorder that occurs without apparent cause and with good prognosis.^[3] The secondary form (Raynaud's syndrome) seen with connective tissue and rheumatic disease (scleroderma, sjogren's disease, rheumatoid arthritis, systemic lupus erythematosus, polymyositis), peripheral vascular disease (thromboangitis obliterans-Buerger's disease),^[4] malignancy or chemotherapy (such as cisplatin, bleomycin).^[5] Pathophysiology of Raynaud's disease is still unclear, increased physiological vasoconstriction in the cold with increased sensitivity to α_2 -agonists and serotonin are accused. Vasoconstrictive endothelin-1, calcitonin gene related peptide (CGRP) and cyclooxygenase play a modulating role.^[6]

Clinical symptoms in critical vascular disease begin with intermittent claudication, in advanced stages resting pain, gangrene, necrosis and trophic changes were added follow. Raynaud phenomenon presented with pain, paleness, bruising and unhealing ulcers due to chronic ischemia.

In early stages Raynaud's disease, treatment is pharmacological and conservative. Therapeutic approaches in conservative and pharmacological treatment resistant conditions include sympathetic nerve block, surgical sympathectomy, spinal cord stimulation and recurrent amputations. Treatment in Buerger's disease is performed as smoking cessation, medical treatment, and bypass surgery in eligible patients. SCS is a good treatment option in patients with advanced stage disease where surgery is not appropriate, who does not respond to medical treatment and sympathetic blocks.

SCS has been used since 1967 to treat various chronic pain syndromes such as failed back surgery syndrome, degenerative low back or leg pain, spinal stenosis, nerve root avulsion, complex regional pain syndrome, postherpetic neuralgia, neuropathic perineal pain, interstitial cystitis, urinary incontinence, refractory angina and peripheral vascular diseases.^[7-9]

Patients with chronic limb ischemia who are not suitable for endovascular intervention or surgery may be candidates for SCS treatment. In addition, patients who have undergone revascularization and cannot achieve pain control even after appropriate medical treatment may benefit from treatment with SCS.

The mechanism of action of SCS is unclear and several theories have been proposed. The electrodes in the epidural space stimulate myelin-free c fibers and myelinated A δ fibers in the dorsal root ganglia. This leads to activation of cell signaling molecules such as extracellular signal regulated kinase (ERK) and protein kinase B (AKT). Activation of ERK and AKT transient potential vanilloid receptor 1 (TRPV1) and depolarization of nerve terminals result in the release of vasodilators such as CGRP, which have potent microvascular vasodilatory effects. The release of CGRP causes the release of endothelial nitric oxide (NO) and stimulates smooth muscle cell relaxation. These effects decrease vascular resistance and increase blood flow. In addition, SCS suppresses sympathetic vasoconstriction through inhibition of sympathetic nicotine transmission at the ganglion and postganglion level. Pain control or suppression of nociceptive transmission is achieved by the release of opioid peptides such as met-enkephalin.^[9,10]

In this 2 cases report, we will emphasize the successful application of SCS in ischemic pain with persistent Raynaud's disease and advanced Buerger's disease.

Case Reports

Case 1 – A 55-year-old male patient who had followed up Cardiovascular Surgery clinic for 15 years with Buerger's disease. His thumb of left foot was amputated 10 years ago. He referred to our outpatient clinic due to painful necrotic ulcers on the thumb of right foot. On physical examination, distal peripheral pulses of the lower limbs were weak. The thumb of left foot had been amputated (Fig. 1). There were necrotic ulcers on the thumb of right foot and second finger. The right lower limb was hyperemic and the left lower extremity was cyanotic. The patient's pain occurs supine position and while he had resting, and he could sleep only by sitting. His pain was 9/10 according to visual analog scale (VAS) and according to Fontaine classification he was



Figure 1. Clinical findings of patient: The thumb of left foot had been amputated. There were necrotic ulcers on the thumb of right foot and second finger. The right lower limb was hyperemic and the left lower extremity was cyanotic.



Figure 2. MRG angiography: Angiography showed a severe obliterating arteriopathy of the right tibialis posterior and peroneal artery circulation on the right and collateral contrast material filling.

accepted as stage 4. Angiography showed a severe obliterating arteriopathy of the right tibialis posterior and peroneal artery circulation (Fig. 2). Spinal cord stimulator was implanted in the patient to provide permanent pain relief (Fig. 3, 4).

In early follow-up (second week); VAS score was 4, walking time was 15 minutes (pre-operative: 5 minutes), walking distance: 100 m (pre-operative: 60 m), sleep quality: 4 hours (pre-operative: 2 hours)

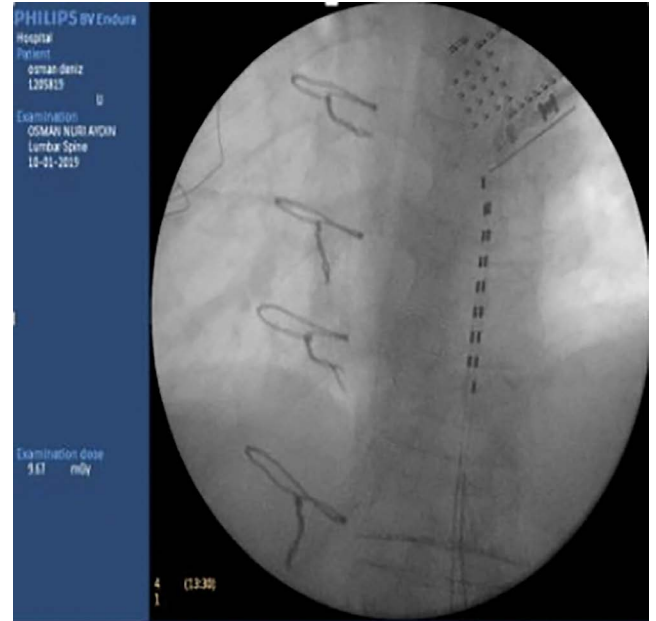


Figure 3. Posterior anterior (PA) images of fluoroscopy after SCS implantation: Positioning of 2 electrodes over the dorsal horn column at T8-9 dorsal vertebra level.



Figure 4. Lateral images of fluoroscopy after SCS implantation: Positioning of 2 electrodes the dorsal horn column at T8-9 dorsal vertebra level.

recorded. Due to infected ulcerative wounds, the patient was also followed by the wound care unit.

Case 2- A 35-year-old female patient who was followed with Raynaud's disease in Cardiovascular Surgery clinic for 2 years was admitted to our outpatient clinic with complaints of coldness, pallor, pain, and numbness in both of her hands. On examination, cyanotic discoloration, multiple ulcers and dystrophic changes of the nails were detected. She had se-

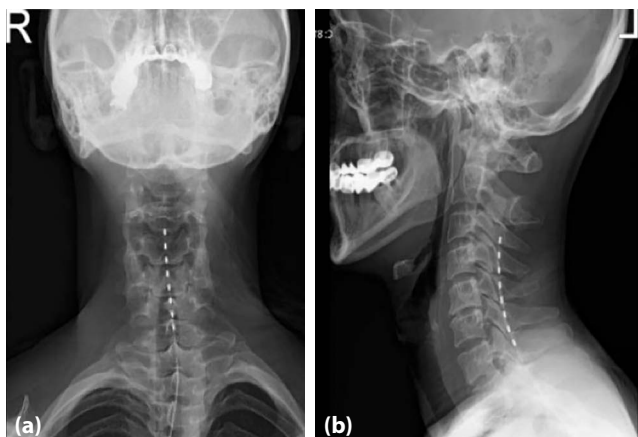


Figure 5. (a) Right SCS electrode on the X-ray image at PA position. **(b)** Right SCS electrode on the X-ray image at lateral position.

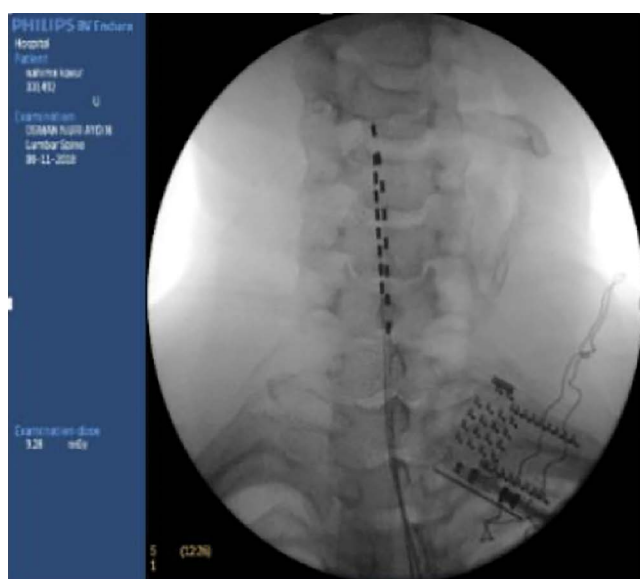


Figure 6. Right and left SCS electrodes on flouroscopy images at PA position.

vere allodynia and hyperalgesia. Radial pulses were normally palpated. The patient followed up as Raynaud's disease with normal arterial angiography. She was recommended to quit smoking. The patient who did not respond to the medical treatment received 2 times diagnostic stellate ganglion blockage, 2 times neurolytic stellate ganglion blockage and 2 times stellate ganglion radiofrequency thermocoagulation. Despite the interventional procedures, ulcerative lesions and pain control could not be achieved in the upper extremity. Cervical SCS was applied to the patient with the aim of permanent pain relief and ulser healing (Fig. 5).

At the 6 months follow-up, the VAS score was 4 (pre-operative: 9). Allodynia and hyperalgesia of the patient regressed. Digital ulcers showed a significant regression. Pallor and cyanosis in the extremities

decreased significantly. During the 1-year follow-up, the patient presented with similar complaints in the left upper extremity and one more lead was implated on the left side (Fig. 6).

Discussion

Peripheral vascular diseases and Raynaud's phenomenon are common diseases and if not treated with a multidisciplinary approach, they cause serious problems such as disability due to limb loss and chronic pain affecting quality of life. Early treatment of Raynaud's disease is conservative, while Raynaud's syndrome is aimed at the treatment of the underlying disease and early stage peripheral vascular disease treated with pharmacologically. In advanced stage and conservative/medical treatment resistant cases, interventional and surgical treatment options are preferred for pain relief, ulcer healing, and reduction of amputation rates.

Patients with chronic limb ischemia that are not suitable for endovascular intervention or bypass surgery and those who cannot achieve pain control despite these procedures may be candidates for sympathectomy and SCS. Sympathectomy can be performed thermally, chemically or surgically. Sympathectomy primarily has a vasodilatory effect on the collateral circulation resulting from a reduced sympathetic tone.

Improved oxygenation of the tissues leads to less tissue damage, which results in decreased pain and increased healing of the ulcers. Pain reduction also occurs due to the interruption of sympathetic nociceptive interaction.

Randomized controlled trials that show no beneficial effects on sympathectomy pain relief are present,^[12-14] also there are studies showing that ulcer healing, pain relief and decrease in major amputation rates.^[15-17] Although the effects of sympathectomy are not consistent, it is applied in selected cases because there are studies reporting positive results on ulcer healing, pain regression and amputation prevention. In addition, in a study, the effectiveness of bipolar radiofrequency in critic limb ischemia of thermocoagulation was demonstrated with longer analgesia time.^[18] We applied recurrent thermal and chemical sympathetic ganglion block in our patient who was followed with medical treatment resistant

Raynaud's disease. In our case, we used SCS successfully for permanent pain control and ulcer healing.

The patients who are not suitable for endovascular interventions are followed by medical treatment consisting of analgesic, vasodilator and anticoagulant drugs, while SCS is an effective alternative treatment for reducing refractory ischemic pain by improving microcirculatory blood flow in these patients.^[19–25] SCS provides pain reduction according to the gate control theory and modulating neurotransmitters released from the dorsal horn.^[26] The vasodilatory mechanism may be ascribed to the suppression of sympathetic vasoconstriction and the activation of vasodilatory molecules, thereby causing endothelial nitric oxide (NO) release and stimulating smooth muscle relaxation.^[27,28]

Although its effects and efficacy are well known, there are a limited number of studies on the use of SCS in peripheral arterial disease.^[21,29–33] Current knowledge supports the use of this treatment in ischemic limb disease. There are not enough clinical studies related to use of SCS with Raynaud's disease and Burger's disease.

In a retrospective study of patients treated with SCS in Burger's disease, the positive effect of SCS on limb survival and development of new ulcers were discussed.^[34] There are also case reports of successful treatment of SCS in Burger's disease and Raynaud's disease.^[35–38]

In the follow-up of treatment in critical ischemic disease, many examinations showing perfusion have been identified. In addition to ankle brachial index (ABI) and transcutaneous oxygen tension (TcPO₂), at previous studies MR angiography perfusion (MRAP), technetium-99m-labeled Methoxyisobutyl isonitrile (99mTc-MIBI) -single-photon emission computed tomography (SPECT), and Thallium-201 (201Tl) – SPECT were used to show microvascular perfusion insufficiency in critical ischemic disease.^[39–43] And also, a recent study showed that lower-limb 201Tl scintigraphy revealed that microcirculation intensity increased in the lower extremities of patients in the SCS treatment group after SCS implantation relative to that before SCS implantation.^[44] Thus, the efficacy of SCS and its positive effects on microvascular cir-

ulation were objectively tested by noninvasive advanced imaging techniques.

In this case report, we hope that the current data will be supported by future studies by emphasizing the positive effects of SCS on critical ischemic disease for pain relief, ulcer healing and amputation delay when used in selected patients with Raynaud's disease and Burger's disease.

Conclusion

Interventional methods are preferred in the treatment of advanced vascular disease and inoperable patients for revascularization to prevent amputation, pain relief and ulcers. SCS provides pain management in selected cases with ischemic vascular disease that is resistant to conservative and minimally invasive pain treatment and is effective in reducing the amputation rate and ulcer healing.

Patient Consent: *The patients had consented for submission of the case report for submission to the journal.*

Funding: *No funding was received for this research.*

Conflict-of-interest issues regarding the authorship or article: *None declared.*

Peer-review: *Externally peer-reviewed.*

References

1. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. Cochrane Database Syst Rev 2005;3:CD004001.
2. Block JA, Sequeira W. Raynaud's phenomenon. Lancet. 2001;357:2042 – 2048.
3. Wigley FM. Clinical practice. Raynaud's Phenomenon. N Engl J Med. 2002; 47: 1001–1008.
4. Mills JL Sr. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. Semin Vasc Surg. 2003; 16: 179–189.
5. Ting J, Fukshandsky M, Burton A. Treatment of refractory ischemic pain from chemotherapy-induced Raynaud's syndrome with spinal cord stimulation. Pain Practice. 2007; 7(2): 143–146.
6. Cooke JP, Marshall JM. Mechanisms of Raynaud's disease. Vasc Med. 2005; 10: 293–307.
7. Özdemir İ, Akbaş M, Yeğin A, DAĞISTAN G, Erkan DÖ. Spinal kord stimülasyonu uygulanan 62 hastanın retrospektif değerlendirilmesi. Ağrı Dergisi. 2017; 29(1): 25-32.
8. Wolff A, Vanduyhoven E, van Kleef M, Huygen F, Pope JE, Mekhail N. 21. Phantom pain. Pain Pract. 2011; 11(4): 403-13.
9. Deer TR, Raso LJ. Spinal cord stimulation for refractory angina pectoris and peripheral vascular disease. Pain Physi-

- cian. 2006; 9(4): 347-52.
10. Pedrini L, Magnoni F. Spinal cord stimulation for lower limb ischemic pain treatment. *Interact Cardiovasc Thorac Surg.* 2007; 6(4): 495-500.
 11. Brümmer U, Condini V, Cappelli P, et al. A. Spinal cord stimulation in hemodialysis patients with critical lower-limb ischemia. *Am J Kidney Dis.* 2006; 47(5): 842-7.
 12. Cross FW, Cotton LT. Chemical lumbar sympathectomy for ischemic rest pain. A randomized, prospective controlled clinical trial. *Am J Surg.* 1985; 150: 341-345.
 13. Barnes RW, Baker WH, Shanik G. et al. Value of concomitant sympathectomy in aortoiliac reconstruction. Results of a prospective, randomized study. *Arch Surg.* 1977; 112: 1325-1330.
 14. Fyfe T, Quin RO. Phenol sympathectomy in the treatment of intermittent claudication: a controlled clinical trial. *Br J Surg.* 1975; 62: 68-71.
 15. Repealer van Driel O, Van Bockel J, Van Schilfgarde R. Lumbar sympathectomy for severe lower limb ischaemia: results and analysis of factors influencing outcome. *J Cardiovasc Surg.* 1998; 29:310-314.
 16. Keane FB. Phenol lumbar sympathectomy for severe arterial occlusive disease in the elderly. *Br J Surg.* 1977; 64: 519-521.
 17. Mashiah A, Soroker D, Pasik S, Mashiah T. Phenol lumbar sympathetic block in diabetic lower limb ischemia. *J Cardiovasc Risk.* 1995; 2: 467-469.
 18. Destegül D, Işık G, Özbek H, Ünlügenç H, İlginel M. Radio-frequency thermocoagulation for the treatment of lower extremity ischemic pain: Comparison of monopolar and bipolar modes. *AGRI-The Journal of The Turkish Society of Algology.* 2017; 29(2): 64-70.
 19. Eldabe S, Thomson S, Duarte R, et al. The effectiveness and cost-effectiveness of spinal cord stimulation for refractory angina (RASCAL study): a pilot randomized controlled trial. *Neuromodulation.* 2016; 19: 60-70.
 20. Tsigaridas N, Naka K, Tsapogas P, Pelechas E, Damigos D. Spinal cord stimulation in refractory angina. A systematic review of randomized controlled trials. *Acta Cardiol.* 2015; 70: 233-243.
 21. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database Syst Rev.* 2013;2:CD004001.
 22. Tshomba Y, Psacharopulo D, Frezza S, Marone EM, Astore D, Chiesa R. Predictors of improved quality of life and claudication in patients undergoing spinal cord stimulation for critical lower limb ischemia. *Ann Vasc Surg.* 2014; 28: 628-632.
 23. Broggi G, Servello D, Franzini A, et al. Spinal cord stimulation for treatment of peripheral vascular disease. *Appl Neurophysiol.* 1987; 50: 439-441.
 24. Augustinsson LE, Linderroth B, Mannheimer C, Eliasson T. Spinal cord stimulation in cardiovascular disease. *Neurosurg Clin N Am.* 1995; 6: 157-165.
 25. Ghajar AW, Miles JB. The differential effect of the level of spinal cord stimulation on patients with advanced peripheral vascular disease in the lower limbs. *Br J Neurosurg.* 1998; 12: 402-408.
 26. Guan Y. Spinal cord stimulation: neurophysiological and neurochemical mechanisms of action. *Curr Pain Headache Rep.* 2012; 16: 217-225.
 27. Tanaka S, Komori N, Barron KW, Chandler MJ, Linderroth B, Foreman RD. Mechanisms of sustained cutaneous vasodilation induced by spinal cord stimulation. *Auton Neurosci.* 2004; 114: 55-60.
 28. Wu M, Linderroth B, Foreman RD. Putative mechanisms behind effects of spinal cord stimulation on vascular diseases: a review of experimental studies. *Auton Neurosci.* 2008;138:9-23.
 29. Klomp HM, Steyerberg EW, Habbema JD, van Urk H, ESES Study Group. What is the evidence on efficacy of spinal cord stimulation in (subgroups of) patients with critical limb ischemia? *Ann Vasc Surg.* 2009; 23: 355-363.
 30. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess.* 2009; 13: 1-154.
 31. Amann W, Berg P, Gersbach P, Gamain J, Raphael JH, Ubbink DT. Spinal cord stimulation in the treatment of non-reconstructable stable critical leg ischaemia: results of the European Peripheral Vascular Disease Outcome Study (SCS - EPOS). *Eur J Vasc Endovasc Surg.* 2003; 26: 280-286.
 32. Augustinsson LE, Carlsson CA, Holm J, Jivegard L. Epidural electrical stimulation in severe limb ischemia. Pain relief, increased blood flow and a possible limb-saving effect. *Ann Surg.* 1985;202:104-110.
 33. Broseta J, Barbera J, de Vera JA, et al. Spinal cord stimulation in peripheral arterial disease. A cooperative study. *J Neurosurg.* 1986; 64: 71-80.
 34. Donas KP, Schulte S, Ktenidis K, Horsch S. The role of epidural spinal cord stimulation in the treatment of Buerger's disease. *Journal of vascular surgery* 2005; 41(5): 830-836.
 35. Ryu SW, Jeon HJ, Cho SS, et al. Treatment of digit ulcers in a patient with Buerger's disease by using cervical spinal cord stimulation-a case report. *Korean journal of anesthesiology.* 2013;65(2):67.
 36. Pace AV, Saratzis N, Karokis D, Dalainas D, Kitas GD. Spinal cord stimulation in Buerger's disease. *Annals of the rheumatic diseases.* 2002; 61(12): 1114-1114.
 37. Sibell DM, Colantonio AJ, Stacey BR. Successful use of spinal cord stimulation in the treatment of severe Raynaud's disease of the hands. *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 2005; 102(1): 225-227.
 38. Benyamin R, Kramer J, Vallejo R. A case of spinal cord stimulation in Raynaud's Phenomenon: can subthreshold sensory stimulation have an effect? *Pain Physician.* 2007; 10(3): 473-478.
 39. Duet M, Virally M, Bailliart O et al. Whole-body (201)Tl scintigraphy can detect exercise lower limb perfusion abnormalities in asymptomatic diabetic patients with normal Doppler pressure indices. *Nucl Med Commun.* 2001; 22: 949-954.
 40. Cosson E, Paycha F, Tellier P et al. Lower-limb vasculariza-

- tion in diabetic patients. Assessment by thallium-201 scanning coupled with exercise myocardial scintigraphy. *Diabetes Care*. 2001; 24: 870–874.
41. Kusmirek J, Dabrowski J, Bienkiewicz M, Szuminski R, Plachcinska A. Radionuclide assessment of lower limb perfusion using 99mTc-MIBI in early stages of atherosclerosis. *Nucl Med Rev Cent East Eur*. 2006; 9: 18–23.
 42. Liu JT, Chang CS, Su CH, Li CS. Insights into microcirculation underlying critical limb ischemia by single-photon emission computed tomography. *Medicine* 2015; 94: e1075.
 43. Wright KL, Seiberlich N, Jesberger JA, et al. Simultaneous magnetic resonance angiography and perfusion (MRAP) measurement: initial application in lower extremity skeletal muscle. *J Magn Reson Imaging* 2013; 38: 1237–1244.
 44. Liu JT, Su CH, Chen SY, Liew SJ, Chang CS. Spinal Cord Stimulation improves the microvascular perfusion insufficiency caused by critical limb ischemia. *Neuromodulation: Technology at the Neural Interface* 2018; 21(5): 489-494.