

# Laser therapy in the management of neuropathic pain: preliminary experience on 43 patients

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## ABSTRACT

The aim of this case series is to report on the effect of MiS, a new laser therapy device which uses two synchronized emissions with 905 nm and 808 nm wavelengths, pulsed and continuous, respectively, with high peak power, in the management of neuropathic pain. A total of 43 patients (mean age: 53 years, from 23 to 85 years) presenting neuropathic pain associated to different anatomical areas, such as cervical zone, spine, foot/ankle, hand/wrist, shoulder, elbow, hip and knee were treated with laser therapy by MiS. Pain (VAS score) and functionality (therapist evaluation) were evaluated at the end of treatment. The severity of pain decreased over time and was lower at the end of treatment. MiS laser therapy demonstrated to be safe and effective in patients affected by neuropathic pain and represents a valuable tool for the management of these patients.

## INTRODUCTION

Pain is described as a complex, subjective experience, involving the transduction of harmful environmental stimuli together with the cognitive and emotional processing by the brain [1,2]. Neuropathic pain is a form of

chronic pain resulting from any kind of damage to the central or peripheral nervous system without nociception [3,5]. Neuropathic pain is a painful condition that may comprise different types of pathologies: such as postherpetic neuralgia, painful diabetic polyneuropathy, post-surgery neuropathic pain, multiple sclerosis, spinal cord injury, stroke and cancer. Patients with neuropathic pain often have spontaneous pain, allodynia, and hyperalgesia.

The estimation of the incidence and prevalence of neuropathic pain is difficult because of the lack of simple diagnostic criteria for large epidemiological surveys in the general population [6]. A portion of these patients is specifically affected by peripheral neuropathy and seek medical treatment to alleviate the pain and improve the function associated to conditions that are localised at several body levels: spine, being lumbar-sciatic pain a very common problem, cervical area, elbow, wrist and hand, knee, ankle and foot, hip. For instance, sciatica is a form of radicular pain, and is described as a disease of the peripheral nervous system. It is a very common condition and the main cause of absences from work, with great economic impact on society [7]. The trend in terms of life expectations getting

longer suggests that more and more people will be experiencing this type of pain in their life. Chronic neuropathic pain is characterised by complexity of neuropathic symptoms, poor outcomes and difficult treatment decisions.

On the biological side, nerve inflammation plays an important role in the development and progression of neuropathic pain. For instance, recent studies have indicated that hypoxia-inducible factor 1a (HIF-1a) is crucial in inflammation [8], while other previous studies have identified the relationship between proinflammatory cytokines, and neuropathic pain development [9-12].

Therapeutic options are in many cases related to conservative treatment, consisting of modifying the pain-precipitating activity, biomechanical correction with physiotherapy or the use of antidepressants, analgesics and/or steroids [13,14]. Specifically, painkillers are the main drugs to treat pain, although these have shown only 30% effectiveness in patients with neuropathic pain [15-17]. Unfortunately, these drugs have undesirable side effects and, currently, there is a worldwide trend in opioid reduction for acute and chronic pain management [18-20]. Physical methods are an interesting alternative to the pharmacological treatment because of the absence of side effects.

Recent studies have reported the use of laser therapy in patients with peripheral somatosensory neuropathy and neuropathic pain [21,22]. Specifically, clinical studies on the effects of laser therapy on injured nerves reported an increase in nerve function [21]. Moreover, laser therapy demonstrated to be effective for promoting axonal growth in injured nerves in animal models [23-26].

Positive effects of MLS<sup>®</sup> therapy in promoting repair processes of peripheral nerves, acting on the recovery of the lesioned function and the muscle mass and inducing faster myelination of the regenerated nerve fibers, have been reported by Gigo-Benato et al. [27].

*In vitro* studies were carried out to characterize the effect of MLS<sup>®</sup> pulse and have shown that MLS<sup>®</sup> treatment induces an increase of NLRP 10, a protein with anti-inflammatory action.

NLPR 10 inhibits the activity of caspase 1 and PYCARD protein complex, which promote the maturation of the inflammatory cytokines interleukin-1  $\beta$  (IL-1 $\beta$ ) and interleukin 18 (IL-18). Therefore, ultimately, NLPR 10 inhibits the production of pro-inflammatory interleukins IL-1 $\beta$  and IL-18, reducing inflammation [28]. The decrease in inflammation leads to a normalization of vascular function and thus to a decrease of the edema. Obviously, the decrease in inflammation and edema results in a decrease of pain symptoms, that are frequently present in patients.

MiS is a medical device for laser therapy which combines the synchronized pulse of traditional MLS<sup>®</sup> therapy with the high peak power typical of high intensity laser therapy. These specific characteristics allow MiS to act on pain and its causes, leading to significant and persistent improvement of pain symptomatology and concomitant recovery of functionality.

This case series collects the case reports of two physiotherapy centers that have treated 43 patients for peripheral neuropathy using MiS, a new laser therapy, reporting changes in pain and in function, and safety associated to the use of the device.

## MATERIALS AND METHODS

This is a case series collecting patients from routine practice in two Italian physiotherapy centers: Fisiolab (Vicenza- Italy) and Rehabilitation Center (Padova- Italy). Forty-three patients of both sexes affected by several conditions related to peripheral neuropathies have been included in the series.

During the treatment, patients and therapists wore safety glasses to prevent eye damage.

Diagnosis and instrumental evaluation (i.e. X-Ray, Ultrasounds, CT, MRI), when available, were recorded.

Additionally, patients were evaluated by the specialist performing the treatment before therapy start.

The patients that were included in this series received MiS (ASA Srl, Italy) treatment focused on the peripheral neuropathy as stand-alone treatment or as a part of their treatment programme.

MiS is a class IV NIR laser with two synchronised sources, one consists in 6 pulsed 905 nm laser diodes, the second is a continuous/frequency-modulate 808 nm laser diode. Maximum average power is 6W $\pm$  20%, while maximum peak power is 1kW. MiS has 2 interchangeable handpieces (with diameters of 2 and 5 cm).

The total number of sessions and the time of each session were adjusted based on each patient response to the treatment and ranged from 2 to 13 sessions, with a duration ranging from 6 to 20 minutes (according to body location). The used frequency was 30 Hz for all the body areas, while intensity was adapted to the anatomical site as follows: 80% for shoulder and hip, 70% for spine, 60% for elbow, wrist/hand, knee, ankle/foot and 50% for head and cervical area. Dosage was adjusted based on size of the area to be treated, patient and pathology characteristics and condition stage.

Trigger points, when present, were treated in all patients with the following parameters: Frequency: 10 Hz, time: 23 s, Intensity: 25%. In the trigger point phase, the hand piece was perpendicular to the treated points.

Pain evaluation was performed before and after each laser session using a Visual Analogue Scale (VAS) scale. It is a scale comprising 10 grades, with 10 representing 'unbearable pain' and 0 representing 'no pain'. It is a pain scale commonly used in the medical field, and it was shown to be a reliable and valid measure of pain [29,30]. Safety has been specifically assessed and the therapists recorded any side effect and/or rebound effect happened during

the treatment. Functional evaluation and global assessment were reported by the specialist for each patient.

## RESULTS

Demographic and clinical characteristics of all patients at baseline were recorded. Patients demographic characteristics are reported in Table I.

For 34 patients, peripheral neuropathy treatment was the focus of the overall therapy cycle, while 9 patients received other MiS treatments beside the peripheral neuropathy protocol (i.e. specific for edema, muscle pain and contracture) in their therapeutic path.

VAS pre and post treatment, along with change in VAS expressed as a percentage of the initial value are reported in Table II, divided by treated anatomic areas. As expected when dealing with neuropathic pain, average pain at baseline was moderate to severe (mean was >7 for all groups). Overall, VAS pre-treatment mean was 7,8 and VAS post-treatment mean was 1,6, corresponding to a decrease in pain of 79,5%. Pain completely disappeared in patients treated for elbow, hip and shoulder problems. Considering all the groups, improvement was at least 60% respect to baseline, meaning that initial pain score was reduced of above 60% at the end of the treatment cycle.

It has to be noted that some patients were not seeking medical treatment for pain, but for symptoms related to nerve irritation, as for example paraesthesia, dysesthesia, hyporeflexia, etc. In these cases, the treatment with MiS

**Table I** - Demographics

<b>Sex</b>	M=55,8% F=44,2%
<b>Active (sport activity)</b>	YES=46,5% NO = 44,2% NA=9,3%
<b>Age</b>	Mean= 53 yrs (23 to 85)

**Table II** - VAS pre and post treatment divided by anatomical distribution of the treated areas

Area	Patient #	VAS Pre (mean)	VAS post (mean)	$\delta$ VAS%
Spine	17	8,8	2,2	75%
Cervical area	3	8,3	3	63,9%
Elbow	4	9	0	100%
Knee	4	8	1,5	81,3%
Ankle/foot	3	7	2	71,4%
Hip (mainly pudendal nerve)	9	7	0	100%
Shoulder	1	9	0	100%
Wrist/Hand	2	7,5	2,5	66,7%
<b>TOTAL</b>	<b>43</b>	<b>7,8</b>	<b>1,6</b>	<b>79,5%</b>

gave excellent results and the therapists have reported strong improvements in sensitivity and dysesthesia reduction.

In general, looking at VAS value trend, it was possible to appreciate pain decrease during time, rather than intra-session. Some patients, reported fluctuation in VAS score between the sessions during the treatment cycle. This could be related to a prompt increase of physically demanding activities by the patients after perceiving benefit from the initial laser therapy sessions.

In general, laser treatment provided a positive impact on pain and function on the majority of the patients, only for 2 of them no significant improvement after the laser therapy cycle was reported.

## DISCUSSION

Neuropathic pain can substantially impair quality of life as it often associates with other problems, such as loss of function, anxiety, depression, disturbed sleep and impaired cognition and physical therapies have been

suggested as potential alternative for treatment [6]. The results of this case series show that patients treated with MiS for peripheral neuropathy had an improvement in terms of pain symptoms measured with VAS, even when starting from high VAS values, typical of neuropathic pain. The improvement was gradual and was normally seen after some sessions rather than at the end of each laser treatment, suggesting that MiS is able to induce biological responses whose effects depend on the evolution of the underlying biological processes over time, which could be interesting to address in future basic and clinical studies. MiS inherits the wavelengths (808 nm and 905 nm), the characteristic synchronized modulation of continuous and pulsed emissions, and the scientific evidence of the action mechanisms from MLS<sup>®</sup> laser therapy. Experimental and clinical research demonstrated that MLS<sup>®</sup> pulse exerts a positive effect in the treatment of many musculoskeletal diseases [31-34]. This effect is related to anti-inflammatory, anti-edema and

tissue healing actions [28,35]. Besides relying on MLS<sup>®</sup> pulse features, MiS is characterised by a very high peak power in the order of kW. The modulation in short pulses allows to control the peak power avoiding damaging thermal effects.

In the literature, Kobiela Ketz et al [36] suggested that the reduction of hypersensitivity mediated by laser treatment in a model of neuropathic pain induced by spinal nerve injury could be exerted by modulating macrophages and microglia components. Preliminary *in vivo* investigation related to laser therapy use in neuropathic pain relief highlighted therapeutic effects that might be used for clinical application in neuropathic cases [37]. In the specific field of neuropathic pain, preclinical experiments carried out on animal models demonstrated that the treatment with MiS promotes the recovery of the myelin sheath in nerve fibres that have been damaged in the lesion area, as confirmed by histological and immunohistochemical evaluations [38]. These data support the concept that laser therapy by MiS could be a suitable tool in the management of neuropathic pain.

No rebound effect has been observed, thus confirming the safety of the device in this cases series, which included individuals with different characteristics, pathologies and stage of conditions.

Patients gave a positive feedback on the treatment feeling, especially when the 5 cm handpiece was used on large areas, as its shape allowed a sort of massage over the patient's skin, making the treatment well accepted and contributing to build compliance to session attendance.

## CONCLUSION

This case series reports on the use of MiS in the management of 43 cases of neuropathic pain localised in different anatomical areas. Based on the results reported, the new MiS laser therapy demonstrated to be safe and effective in patients affected by neuropathic pain. Therefore, laser therapy by MiS may represent a valuable and well-accepted tool for the management of peripheral neuropathies.

## REFERENCES

1. Julius D, Basbaum AI (2001) Molecular mechanisms of nociception. *Nature* 413:203–210
2. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. (2010) Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clinic proceedings*. *Mayo Clin* 85(3):3–14
3. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353(9168):1959–64.
4. Zimmermann M. Pathobiology of neuropathic pain. *Eur J Pharmacol*. 2001;429(1-3):23–37
5. Dickenson A, Suzuki R (2005) Targets in pain and analgesia. In: Hunt SP, Koltzenburg M (eds) *The neurobiology of pain*. Oxford University Press, New York
6. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, Freeman R, Truini A, Attal N, Finnerup NB, Eccleston C, Kalso E, Bennett DL, Dworkin RH, Raja SN. Neuropathic pain *Nat Rev Dis Primers*. 2017 Feb 16; 3
7. Stafford MA, Peng P, Hill DA. Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. *Br J Anaesth* 2007;99:461-473.
8. Hsieh, Yueh-Ling & Chou, Li-Wei & Chang, Pei-Lin & Yang, Chen-Chia & Kao, Mu-Jung & Hong, Chang-Zern. (2012). Low-level laser therapy alleviates neuropathic pain and promotes function recovery in rats with chronic constriction injury: Possible involvements in hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ). *The Journal of comparative neurology*. 520. 2903-16.
9. Sommer C, Kress M. 2004. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neurosci Lett* 361:184–187.
10. Sommer C, Schäfers M. 2004. Mechanisms of neuropathic pain: the role of cytokines. *Drug Disc Today Dis Mech* 1:441–448.
11. Li F, Fang L, Huang S, Yang Z, Nandi J, Thomas S, Chen C, Camporesi E. 2011. Hyperbaric oxygenation therapy alleviates chronic constrictive injury-induced neuropathic pain and reduces tumor necrosis factor- $\alpha$  production. *Anesth Analg* 113:626–633.
12. Liou JT, Liu FC, Mao CC, Lai YS, Day YJ. 2011. Inflammation confers dual effects on nociceptive processing in chronic neuropathic pain model. *Anesthesiology* 114:660–672.
13. Edwards PH, Wright ML, Hartman JF. A practical approach for the differential diagnosis of chronic leg pain in the athlete. *Am J Sports Med* 2005; 33:1241-1249.
14. Touliopolous S, Hershman EB. Lower leg pain diagnosis and treatment of compartment syndromes and other pain syndromes of the leg. *Sports Med* 1999;27:193-204
15. Serpell MG (2002) Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. *Pain* 99(3):557–566
16. Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, Hueppe M et al (2003) Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, doubleblind, placebo-controlled study. *Pain* 106(1-2):151–158
17. Schestatsky P, Llado-Carbo E, Casanova-Molla J, Alvarez-Blanco S, Valls-Sole J (2008) Small fibre function in patients with meralgia paresthetica. *Pain* 139(2):342–348
18. White PF, Kehlet H: Improving pain management: are we jumping from the frying pan into the fire? *Anesth Analg*. 2007; 105(1): 10–2.
19. White PF: Multimodal analgesia: its role in preventing postoperative pain. *Curr Opin Investig Drugs*. 2008; 9(1): 76–82.
20. White PF: What are the advantages of non-opioid analgesic techniques in the management of acute and chronic pain? *Expert Opin Pharmacother*. 2017; 18(4): 329–33.
21. Fallah A, Mirzaei A, Gutknecht N, et al.: Clinical effectiveness of low-level laser treatment on peripheral somatosensory neuropathy. *Lasers Med Sci*. 2017; 32(3): 721–8.

22. de Andrade AL, Bossini PS, Parizotto NA: Use of low level laser therapy to control neuropathic pain: A systematic review. *J Photochem Photobiol B*. 2016; 164: 36–42.
23. Costantini D, Delogu G, Lo Bosco L, Tomasello C, Sarra M. The treatment of cranio-facial pain by electroacupuncture and laser irradiation. *Ann Ital Chir* 1997;68:505-9.
24. Pinheiro AL, Cavalcanti ET, Pinheiro TI, Alves MJ, Miranda ER, De Quevedo AS, et al. Low-level laser therapy is an important tool to treat disorders of the maxillofacial region. *J Clin Laser Med Surg* 1998;16:223-6.
25. Shaver SL, Robinson NG, Wright BD, Kratz GE, Johnston MS. A multimodal approach to management of suspected neuropathic pain in a prairie falcon (*Falco mexicanus*). *J Avian Med Surg* 2009;23:209-13
26. Iijima K, Shimoyama N, Shimoyama M, Yamamoto T, Shimizu T, Mizuguchi T. Effect of repeated irradiation of low-power He-Ne laser in pain relief from postherpetic neuralgia. *Clin J Pain* 1989;5:271-4.
27. Gigo-Benato D, Geuna S, de Castro Rodrigues A, Tos P, Fornaro M, Boux E, Battiston B, Giacobini-Robecchi MG. Low-power laser biostimulation enhances nerve repair after end-to-side neurotomy: a double-blind randomized study in the rat median nerve model. *Lasers Med Sci*. 2004;19(1):57-65.
28. Monici M, Cialdai F, Ranaldi F, Paoli P, Boscaro F, Moneti G, Caselli A. Effect of IR laser on myoblasts: a proteomic study. *Molecular Biosystems*. 9:1147-1161,2013
29. Revill SI, Robinson JO, Rosen M, Hogg MI. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; 31:1191–1198
30. Ohta K, Bousquet PJ, Akiyama K, Adachi M, Ichinose M, Ebisawa M, et al. Visual analogue scale as a predictor of GINA-defined asthma control. The SACRA study in Japan. *J Asthma* 2013;50(5):514-21.
31. Alayat MS, Elsoudany AM, Ali ME. Efficacy of Multiwave Locked System Laser on Pain and Function in Patients with Chronic Neck Pain: A Randomized Placebo-Controlled Trial. *Photomed Laser Surg*. 2017 Aug;35(8):450-5
32. Gworys K, Gasztych J, Puzder A, Gworys P, Kujawa J. Influence of Various Laser Therapy Methods on Knee Joint Pain and Function in Patients with Knee Osteoarthritis. *Ortop Traumatol Rehabil*. 2012;14 (3): 269-77
33. Rayegani SM, Bahrani MH, Samadi B, Sedighpour L, Mokhtarirad MR, Eliaspoor D. Comparison of the effects of low energy laser and ultrasound in treatment of shoulder myofascial pain syndrome: a randomized single blinded clinical trial. *Eur J Phys Rehabil Med*; 2011, 47:391-90
34. Vignali L, Caruso G, Gervasi S, Cialdai F. MLS® Laser Therapy in the treatment of patients affected by Tendinopathies. *Energy for Health*; 2017, 16:10-15
35. Monici M, Cialdai F, Romano G, Corsetto PA, Rizzo AM, Caselli A, Ranaldi F. (2012) effect of IR laser on myoblasts: prospects of application for counteracting microgravity-induced muscle atrophy. *Microgravity science and technology*; 25(1):35-42;
36. Kobiela Ketz A, Byrnes KR, Grunberg NE, Kasper CE, Osborne L, Pryor B, Tosini NL, Wu X, Anders JJ. Characterization of macrophage/microglial activation and effect of photobiomodulation in the spinal nerve injury model of neuropathic pain. *Pain Med*; 2017, 18(5):932–946.
37. Masoumpoor M1, Jameie SB, Janzadeh A, Nasirinezhad F, Soleimani M, Kerdary M. Effects of 660 nm Low Level Laser Therapy on Neuropathic Pain Relief Following Chronic Constriction Injury in Rat Sciatic Nerve. *Arch Neurosci*. 2014 July; 1(2): 76–81.
38. Micheli L, Cialdai F, Pacini A, Branca JJV, Morbidelli L, Ciccone V, Lucarini E, Ghelardini C, Monici M, Di Cesare Mannelli L. Effect of NIR laser therapy by MLS-MIS source against neuropathic pain in rats: in vivo and ex vivo analysis. *Sci Rep*. 2019 Jun 26;9(1):9297.