REVIEW

Advance in Functional Restoration of Injured Nerve with Low Level Laser and its Utilization in the Dental and Maxillofacial Region

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Abstract The inferior alveolar nerve and facial nerve are the two most important nerves in the dental and maxillofacial region. The injury to them is one of the major postoperative complications after alveolar surgery and orthognathic surgery. However, recovering the nerve function after injury takes a long time and the recovery effect tends to be unsatisfactory. In recent years, an intensively investigated technique, low level laser which has been applying in assisting the recovery of nerve function, has been gradually proved to be effective in clinically treating postoperative nerve injury. In this article we review in terms of the mechanisms involved in low level laser-assisted functional restoration of nerve injury and its clinical application in the recovery of nerve function in the dental and maxillofacial area as well.

THE inferior alveolar nerve and facial nerve are the most important nerves in the maxillofacial region. Because of their superficial anatomic location, structure and distribution, they are the most vulnerable to injury in maxillofacial trauma and maxillofacial surgery. Moreover, usually it is difficult and takes a long time for the recovery of nerve function after injury, which brings great discomfort and pain to patients.

In recent years, with the rapid development of stomatology laser medicine, low level laser (LLL) applied in the restoration of nerve function has become a hot topic. There is no clear definition of LLL, but LLL

is generally defined by most scholars as a particular category of laser light having a wavelength between 600-1100 nm, an output power less than 500 mW, and an energy density less than 50 J/cm². Many kinds of LLLs, such as gallium arsenide laser with wavelength of 904 nm, output power of 70 Wpk, energy density of 10 J/cm², gallium aluminum arsenide carbon dioxide laser with wavelength of 830 nm, output power of 100 mW, energy density of 4 J/cm², and carbon dioxide laser with wavelength of 650 nm, output power of 25 mW, energy density of 25 J/cm², etc., have been applied to treatment of the dental and maxillofacial diseases such as root canal cleaning and sterilization, therapying peri-implantitis and temporomandibular joint disease, alleviating deep periodontal pocket, and curing oral aphtha ulcer, especially promoting the recovery of nerve function. In this paper, we summarize

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the underlying molecular and histological mechanisms of LLL participating in functional restoration of injured nerve and its clinical application in the recovery of nerve function of the maxillofacial area, aiming to provide insight into this technique.

Mechanism by which LLL promotes the recovery of nerve function

Molecular biology

Neurotrophins are a class of secreted proteins produced by nerve-innervated tissues and astrocytes and essential for the growth and survival of neurons. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), as members of the neurotrophin family, are main regulators of neuronal survival, growth, differentiation,^[1] and regeneration.^[2, 3] Whenever nerves are damaged, they can prevent neurons from dying, improve pathological state of neurons, and accelerate nerve repair.^[2, 3]

The accumulated evidence has proved that the vital role of NGF in promoting the development, maintenance and regeneration of sensory and sympathetic nerves.^[4] Gravvanis *et al.*^[5] have confirmed that NGF, as an independent factor, can accelerate hyperplasia of peripheral nerve, and promote repair of injured nerve and recovery of muscle motor potential after nerve injury. Interestingly, in an *in vitro* study with Schwann cells irradiated by a LLL (gallium-aluminum-arsenide, GaAlAs, wavelength 810 nm, output power 50 mW, energy density 1 J/cm² and 4 J/cm²), real time PCR showed NGF expression was significantly increased on day 20 after irradiation.^[6] Schwann cells are the glial cells that surround the axon of neurons in the peripheral nervous system, and function in expression and secretion of various neurotrophic factors,^[7, 8] which suggest LLL may improve and restore function of injured nerve through inducing NGF expression in Schwann cells.^[9, 10]

BDNF as a modulatory factor of pain neurons, which is involved in pain generating, is released by nociceptors. The released BDNF together with glutamate and neuropeptide substance P is fast anterogradely transported to presynaptic terminals to activate spinal dorsal horn secondary neurons to feel pain at last.^[11] The increasing levels of BDNF in dorsal root ganglion neurons and spinal dorsal horn, which serves as a modulator at the first synapse of the pain transmission pathway in the spinal dorsal horn, can promote

neuropathic pain to happen through BDNF/TrkB signal pathway.^[12-14] Oliveira Martins *et al.* applied LLL therapy (gallium-arsenide, GaAs, wavelength 904 nm, output power 70 Wpk, a spot area of 0.1 cm², frequency 9500 Hz, energy density 6 J/cm²) to treating inferior alveolar nerve injury of experimental rats, and the result showed the LLL could increase pain threshold of the rats and improve nociceptive behavior. Meanwhile, western blot demonstrated that laser irradiation could increase NGF level in the injured inferior alveolar nerve by 53%, and could decrease BDNF level induced by nerve injury by 40% and lower total pain threshold as well.^[15]

Those results indicated that LLL may be a useful modality in controlling and reversing pain sensitivity and accelerating neural tissue regeneration by influencing NGF and BDNF expression.

Histocytology

Neurological damage, as it is known, may contribute to varying degrees of histocytological and morphological changes of neurons, ultimately resulting in neurological dysfunction. Similarly, the functional recovery of neurons after injury is associated with a histocytological and morphological return of injured tissues to normal. Several studies have provided evidence of morphological basis for functional recovery of injured peripheral nerve after application of LLL. They found that LLL ultimately make the functional recovery of peripheral nerve come true specifically through increasing axon number and density, augmenting sheath thickness and nerve fiber diameter of the broken end of injured nerve.^[16, 17] Buchaim *et al.*^[18] employed LLL (wavelength 830 nm, pulsed, optical power 30 mW, 0.2586 W/cm², 6.2 J/cm², beam area of 0.116 cm²) to irradiate the head, middle and tail of the seam respectively of a rat model undergoing buccal branch anastomosis of the facial nerve, three times a week over 5 weeks, morphological analysis performed 35 and 120 days after operation with optical and electron microscope showed the axon number and density of the broken end of injured nerve was greater *versus* the simple suture group, and the diameter of nerve fibers and the thickness of nerve sheath of the laser group were augmented as well. Meanwhile, the injured facial nerve irradiated by LLL has a higher frequency of whisker movement, which indicated that LLL could improve recovery of motor function of facial nerve. Moreover, LLL excels at accelerating revascularization of dam-

aged nerve. GaAlAs+GaAlInP diode laser (780 nm, 2 J, 100 mW, 40 seconds used on the day of surgery and 4 J, 200 mW, 40 seconds on the subsequent days) was used to irradiate the skin area of injured nerve of sciatic nerve anastomosis rat models, histological examination showed the number of new vessels of the LLL treated region were more compared to the non-laser rats on the third day after surgery, and the tendency became more and more distinct with the time gone by.^[19]

Besides promoting the healing of injured nerves, LLL irradiation can be directly applied to welding nerves, in which it shows advantages of time-saving, being easy to learn, and more quick restoration of postoperative neurological function in comparison with conventionally used method. For example, in a rabbit model, a diode laser (wavelength 810 ± 1 nm, pulsed, optical power 0.5 W, 15.9 W/cm^2 , 8.0 J/cm^2) used to weld the buccal branch of the facial nerve which was sharply transected, compared with the simple suture group, histopathological analysis of the laser-welding area, showed LLL has an obvious advantage in increasing axon number and density and augmenting sheath thickness and nerve fiber diameter.^[16, 20-23] Although at 4 weeks the laser-welding area presented a robust inflammatory reaction, at 16 weeks it disappeared completely, which demonstrated laser welding with a biological solder had no a deleterious effect on the nerve axons or fascicles.^[20]

Clinical application of LLL

LLL used to improve recovery of inferior alveolar nerve

The inferior alveolar nerve perforates the lower margin of lateral pterygoid muscle, passes through the mandibular nerve groove accompanied by the inferior alveolar artery and vein, then enters the mandibular canal from the mandibular foramen, which finally manages the bilateral mandibular teeth, periodontal membrane and alveolar bone. The inferior alveolar nerve injury is one of the most common postoperative complications for the removal of impacted mandibular wisdom teeth and sagittal split ramus osteotomy on account of its anatomic location and structure.^[24] Its main clinical manifestations are sensory abnormalities and obtuseness mainly involving the lip, gingiva and chin.^[25] LLL has been proved to be effective in recovering function of inferior alveolar nerve after injured. For example,

in a study of 20 patients receiving mandibular sagittal split osteotomy who were randomly divided into two groups, neurosensory recovery of those who underwent LLL and light-emitted diode radiation (810 nm, 5 J/cm^2 and 632 nm, 2 J/cm^2) on 1 day and 2, 3, 7, 14 and 28 days after surgery, in the following four regions: the entrance of the mandibular foramen, along the osteotomy line, the lips, and chin region, was compared with the non-laser group. The results showed that visual analog scale score increased by 25% at 2 weeks, 21% at 2 months, and 24% at 6 months after surgery, brush stroke value was raised by 21.5% at 2 months and 15.1% at 6 months, and 2-point discrimination significantly decreased by 15.3% at 2 weeks and 16.2% at 2 months. Contact detection was greater after 6 months than the non-laser group although there was no significant intergroup difference, and pinprick test value returned to normal at 45 days, which was faster than the control group. The above results indicated that LLL may facilitate restore function of inferior alveolar nerve.^[26] Similarly, in another two randomized clinical trial studies, LLL can effectively improve neurosensory disorders of mandibular nerve damaged during sagittal split osteotomy.^[27, 28]

What is more, LLL could achieve a better healing of affected nerve. Guarini *et al.*^[29] followed up 41 patients of inferior alveolar nerve injury after sagittal split ramus osteotomy treated by LLL, and found 85% patients of the laser group obtained clinical improvement at 2 years postsurgery, which was greater than that of the placebo group (70% to 75%). It is generally recognized that most of patients achieve full functional recovery within six months after nerve impairment. If the impairment continues for more than one year, patients will remain with a permanent impairment of nerve function.^[30] Therefore, we advise that to treat the neurosensory impairment of the inferior alveolar nerve due to surgical damage, LLL should start as soon as possible, and continue for as long as completely healed.^[31] The earlier LLL starts, the better the results are.

LLL used to treat peripheral facial palsy

Bell's palsy as a type of peripheral facial palsy, manifested as partial or complete facial palsy, mostly can be attributed to virus infection induced facial nerve edema or inflammation.^[32] No definite treatment guideline has been recommended. Corticosteroids, antiviral drugs, facial muscle exercises as well as electri-

cal stimulation are the most frequently supplied medicines for Bell's palsy.^[33-35] Over the years LLL has been applied clinically to treat Bell's palsy and appears to have good results. For example, a three-year-old boy with a sudden onset of facial asymmetry with unknown cause received a gallium aluminum arsenide semiconductor diode laser treatment (70 mW; 17.5 J/cm², 780 nm in the initial 4 sessions and 10 J/cm², 660 nm for other 7 sessions) which was applied by direct contact with the facial area in a continuous emission mode for totally 11 sessions, without oral medication or other methods. After 3 weeks of treatment, facial nerve function of the boy was completely recovered.^[36] In another clinical study including 46 patients with Bell's palsy administrated with LLLT (GaAlAs infrared laser, 830 nm, 100 mW, 10 J/cm²) over a period of 6 weeks, facial disability index score which is the most frequently used index for assessment of severity and progression of Bell's palsy, was significantly better than that of the control group.^[37] A randomized double blind placebo-controlled trial involving 48 Bell's palsy patients also indicated that LLL treatment *versus* facial massage and exercises alone can improve both facial disability index and House-Brackmann scale score.^[38]

In conclusion, LLL could promote the regeneration and recovery of injured nerve and improve the symptoms of patients after nerve injury, and maybe LLL could reliably and effectively serve as an auxiliary tool to promote the functional recovery of injured nerve in orthodontics and alveolar operations. However, the underlying mechanisms by which LLL promotes nerve repair are needed to be clarified.

Conflict of Interest Statement

The authors declare no conflict of interests.

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