Laser Regeneration of Spine Discs Cartilage: Mechanism, In-Vivo Study and Clinical Applications

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Abstract Laser Reconstruction of the spine discs (LRD) is a novel minimally invasive approach for the treatment of spine diseases. This approach belongs to the laser therapy, but it differs from low intensity laser therapy because LRD uses local and moderate heterogeneous laser heating that mostly does not effect directly on the cells; LRD procedure modifies the extra cellular matrix to provide better surroundings for the cells. Our main finding is that laser irradiation can activate the growth of hyaline cartilage. The predictability of the result, the locality and safety of laser effect allowed to use the technology for spine problems. LRD can be performed in an outpatient setting requiring only 30 min to complete without the need for general anesthesia. The new type of Erbium doped glass fiber laser (1.56 μm in wavelength) has been tested first on animals and then in a clinical trial. The mechanism of laser-induced tissue regeneration include: (1) formation of nanopores enchasing water permeability through end plates and annulus fibrosus of the disc that provide feeding for biological cells, and (2) activation of cell due to mechanical oscillations resulting from the periodically thermo expansion of nucleus pulposus under modulated laser irradiation. The clinical trials have shown positive results for 90% from 240 laser treated patients.

Keywords: Laser induced biostimulation, laser reconstruction, spine disc healing, spine treatment, near infrared laser therapy.

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Introduction: The Problem

Discogenic degenerative spine diseases are still a serious problem as they are a major cause of back pain that deteriorates the quality of life of patients and leads to disability [1]. To avoid the negative effects of surgery minimally invasive methods have been increasingly adopted during the last years [2] due to benefits, such as minimum injury, no need for general anesthesia and significant shortening of rehabilitation time. This trend includes puncture techniques conducting various physical stimuli [3–5], to the disc tissues. However, despite the clinical use of intradiscal therapy, its medical background and long-term efficacy sometimes seem doubtful [6–8].

In 2000 we introduced a novel approach to the treatment of spine disc degeneration based on the thermo mechanical effect of modulated laser irradiation without strong heating of the tissues [9–14]. The LRD procedure involves puncture of the disc, laser irradiation of the nucleus pulposus (NP) to facilitate the reparative processes in the tissue. This paper is aimed to present the results of animal study, clinical data and discussion of possible mechanisms of laser-induced activation of the generation of hyaline cartilage in spine discs.

In-Vivo Animal Studies

The effect of laser radiation on the generation of hyaline cartilage in spine disc has been demonstrated first for rabbits [9, 10]. Annulus fibrosus (AF) and NP of the intervertebral discs of rabbits have been irradiated *in vivo* using an 1.56 μm fiber laser with various pulse duration and repetition rate (from 0.3 to 2 Hz). Conventional histological technique and atomic force microscopy (AFM) have been used for examination of the new growing tissue. It has been demonstrated that laser radiation of spine discs induces metaplasia of fibrous cartilage into hyaline type cartilage (Fig. 1).

In 2 months after laser irradiation, the most pronounced signs of regeneration are seen in the inner layers of AF and in the NP. Neogenic tissue has features both of fibrous and hyaline cartilage types: the shape and ultra structure of chondrocytes are close to the cells of hyaline cartilage, but the structure of intercellular matrix possesses the random (disorderly) distribution of thin collagen fibrils like hyaline cartilage, as well as more thick and more aligned collagen fibrils like in the fibrous cartilage. This cartilaginous tissue is called as fibrous-hyaline cartilage. Apparently, its origin is poorly differentiated chondroblasts activated as a result of laser radiation. Alongside with that, there are the regions of typical hyaline type cartilage with homogeneous matrix structure and lacunas surrounded chondrocytes.

For AFM examination, samples of new tissues arisen in the intervertebral discs as a result of laser radiation were kept in 70% proof alcohol, and then cut into sections of about 300 μm in thickness perpendicular to the irradiated surface. The surface of the cartilage samples was imaged with a commercial multimode microscope NanoScope IIIa with phase extender (Digital Instruments, Santa Barbara, CA) operated in tapping

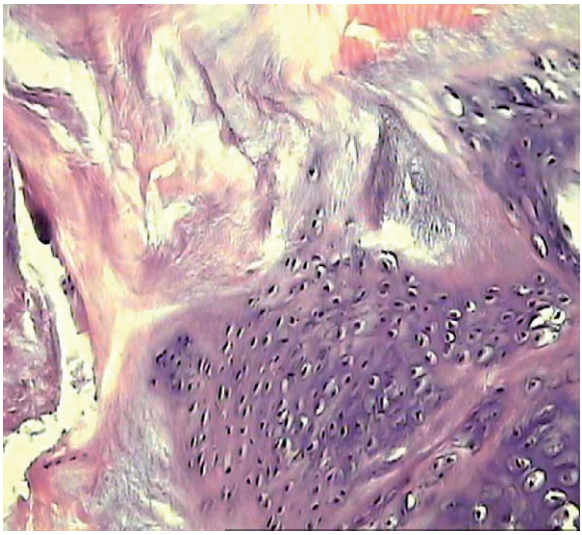

Fig. 1 Histological microphotograph of the new tissue growing in a rabbit spine disc in a month after laser treatment (×200)

mode at about 300 kHz. AFM has shown that nondestructive laser irradiation provokes formation of new nano-pores in cartilaginous matrix (Fig. 2).

In vivo studies performed on rabbits showed, that the therapeutic effect is due to spatial-temporal irregularities of temperature and mechanical stress in the tissue caused by local heating from modulated laser irradiation. Non-ablative laser treatment induces the formation of hyaline and fibrous-hyaline cartilage within the NP and the AF. Laser procedure doesn't cause any destruction of the discs, does not lead to the tissue necrosis, injury of adjacent spinal nerves and vessels.

Mechanism of Laser-Induced Regeneration of Cartilage

Mechanisms of laser-induced regeneration of hyaline type cartilage in the intervertebral discs are still under investigation [13, 14]. Possible mechanisms include:

(1) Non-destructive laser radiation leads to the formation of nano-pores in cartilage matrix (Fig. 2). Nano-pores promote water permeability and increase the feeding of biological cells.
(2) Space and temporary modulated laser beam induces non-homogeneous and pulse repetitive thermal expansion and stress in the irradiated zone of cartilage. Mechanical effect due to controllable thermal expansion of the tissue and micro and nano-bubbles formation in the course of the moderate (up to 45–50°C) heating of the NP activate biological cells (chondrocytes) and promote cartilage regeneration. The temperature dynamics during LRD is shown on the Fig. 3.

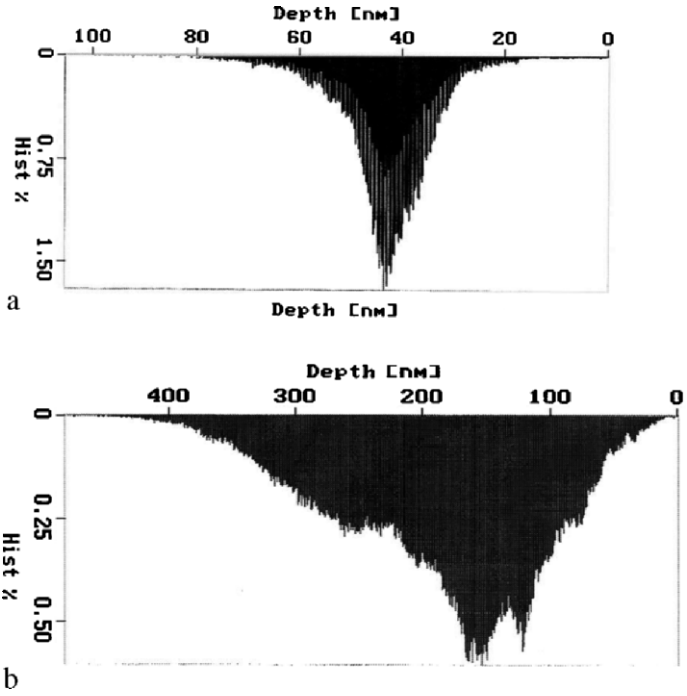

Fig. 2 Size distribution of nanopores in cartilage (**a**) before and (**b**) after laser treatment

It is known that dynamic mechanical oscillations may activate tissue regeneration. There are specific amplitudes and frequencies of mechanical oscillations which have positive effect on chondrocytes proliferation [13, 15]. Temperature and amplitude of the thermo mechanical oscillations relating to temperature oscillations shown on the Fig. 3 diminish rapidly with the distance from the laser spot centrum. This character of oscillations in the laser treated disc provides a possibility to control the locality of laser-induced regeneration.

Laser-induced heterogeneous heating and mechanical oscillations in the NP result in the formation of temporal micro bubbles shown on the Fig. 4. The formation and movement of these small gas micro bubbles provoke a creation of new pores (of sub-microns in size), which (together with mechanical oscillations) promote regeneration processes in the spine disc [13].

It is important that mechanical properties of the disc tissue do not change for the worse as a result of laser treatment, because the size of micro-bubbles arising under LRD is much less than characteristic dimensions of cavitation bubbles forming under ultrasound treatment of the tissues. Also the submicron-pores arising under laser treatment in the AF and in the end plates of the discs are much smaller than large pores and cracks which may diminish mechanical properties of the tissue and lead to disc degeneration.

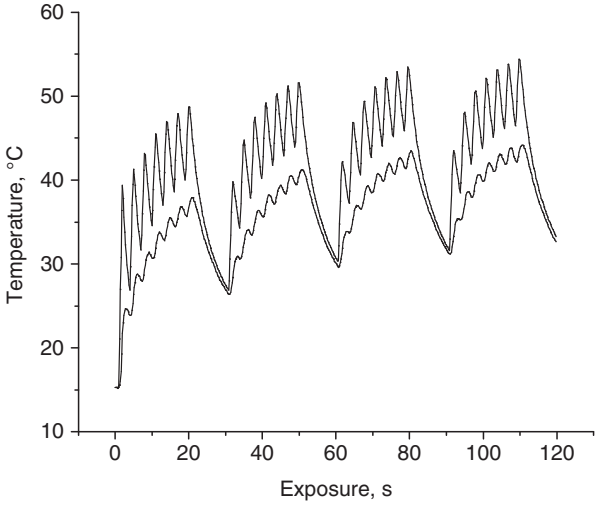

Fig. 3 Temperature in a rabbit NP in the course of laser irradiation at the centre of laser spot (*upper curve*) and 1 mm apart from the centre (*lower curve*). Laser power is 1 W; exposure time is 20 s for each set of irradiation; each set consists of seven laser pulses; duration of a laser pulse is 2 s; interval between pulses is 1 s; interval between neighboring sets is 10 s

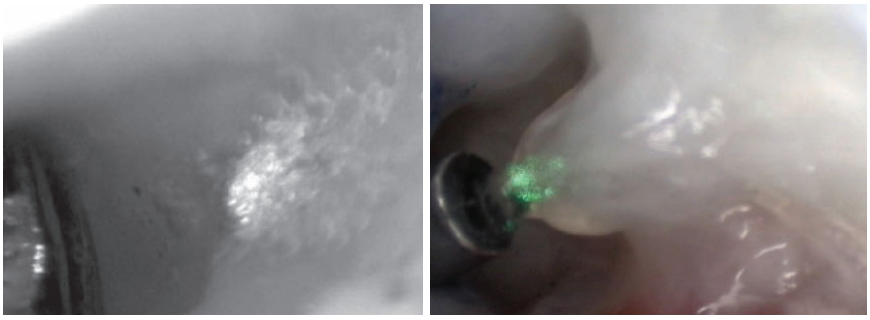

Fig. 4 Endoscopic images of a rabbit NP during laser irradiation: (**a**) Laser power is of 1.5 W, exposure time of 15 s. Micro cavitation (micro bubbles of few micrometers in size are seen). (**b**) Laser power is of 2.5 W, exposure time of 30 s Macro caviation. Periodic thermal expansion produced mechanical oscillations. The diameter of the optical fiber (on the left) is of 1 mm

Other possible mechanisms (more active motion of the disc liquid media and of ions contained in them, increasing of Ca concentration near the cells; possible activation of stem and committed cells that become a source of cartilage tissue regeneration) discussed in [13] require future studies.

Clinical Trials of LRD

Indications for percutaneous LRD were chronic pain in neck and back or chronic vertigo as a sign of vertebro-basilar insufficiency that could not be controlled by complex conservative therapy. Necessary conditions for LRD therapy were clear signs of degeneration of intervertebral discs on MRI scans (dark discs), including the appearance of a hyperintensive zone [16], and induction of highly to moderately concordant pain syndrome during CT-discographic challenge and presence of fissures in the AF [17]. Contraindications for LRD therapy were absence of signs of degeneration of intervertebral discs at MRI and CT-discography, significant protrusion or extrusion of intervertebral discs associated with apparent compression of nervous structures, significantly reduced height of intervertebral discs, local and general infections, blood coagulation disorders and uncontrolled coagulopathy, obvious psychological component in the pain syndrome, including extreme intolerance to discography.

Since 2001 the laser reconstruction of intervertebral discs have been performed at the Spine and Orthopedic Medical Center in Moscow for 240 patients with chronic symptoms of low back or neck pain who failed to improve with non-operative care. LRD was given in the out-patient setting under local anesthesia. Cervical discs were punctured with the use of anterior-lateral approach. The needle diameter was 18G while that of the laser light guide 0.6 mm. LRD therapy was conducted through the needle introduced into the disc under X-ray guidance to irradiate several zones in the disc. In cervical spine, the central zone of the NP and two zones of the transition layer of the AF were irradiated. In lumbar spine, two central zones of the NP and two zones of the transition layer of the AF were irradiated. An Er-glass fiber laser (wavelength 1.56 μm) was used for irradiation. Every zone was irradiated by three series of pulses (each series lasted for 30 s with intervals of 20 s between them; pulse duration – 2 s, interval between pulses – 1 s).

All patients obtained LRD demonstrated improvement. Substantial relief of back pain was obtained in 90% of patients treated who returned to their daily activities with many participating in recreational sports [12–14]. As our clinical observations show, discogenic pain syndrome was controlled or alleviated immediately after the procedure in the majority of patients. This can be due to dereception of pathological nerves, changes in the cartilage mechanical properties and relaxation of strain leading to disc decompression. In many patients pain syndrome alleviation was a gradual process lasting for 3–4 months during which new cartilage tissue was growing. In such cases maximal clinical improvement was observed in 6–8 months and was followed by stabilization of patients' condition, which lasted through the whole follow-up period.

Postoperative MRI examination of the patients has shown: (a) The locality of laser effect: New well hydrated tissue is growing in the laser treatment zones only. (b) The increasing of water contents in the disc (the increasing of T2 signal) was observed for 80% patients after LRD. (c) Decreasing in the protrusion size for some patients after LRD.

The method of laser treatment of spinal diseases was registered with the Federal Service of Supervision in the health and social development sector of the Russian Federation (registration certificate FS-2006/025).

LRD therapy allows to halt disc destruction and prevent the development of disc fibrosis and spinal segment instability. Thus the spine will be in a better shape and there will be no causes for pain syndrome to develop. LRD therapy is different from other puncture methods of treatment, as it is non-destructive. In experimental conditions temperature was measured in all disc zones, in the posterior longitudinal ligament and spinal canal. The temperature change of the most bulk of the disc tissue during LRD is less than 2°C. Only small area (of about 1 mm^3 in the volume) near the laser fiber tip is heated to the 45–50°C. At this heating temperature disc tissue is not destroyed and the procedure is thermally safe but still laser heating of different zones is not uniform, which creates a significant temperature gradient resulting in a significant mechanical effect that modifies the fields of mechanical strains in disc tissue. The safety of the procedure is also ensured by the control system allowing to adjust delivered laser power and stop the irradiation if there appear gaps or big gas bubbles (when microgravity is transformed into cavitation that can lead to disc injury).

The mode of action of non-destructive laser irradiation on intervertebral disc tissue is multifaceted. It was shown experimentally that it can induce the formation of fibrous-hyaline and hyaline cartilage in the disc [13, 14]. Additionally to a high number of proliferating chondrocytes, including multiple multicellular cell clones indicative of regeneration activity induction by LRD, this type of tissue was found at histological examination of two biopsy specimens taken during later surgery for disc hernia recurrence in several years after previous microdiscectomy in combination with LRD. In these two cases, the disc cavity was filled with well structured fibrous-hyaline cartilage and there were no defects in the AF.

Arcuo Medical Inc. has manufactured the equipment for Laser reconstruction of spine discs. The specification of the equipment: Erbium-glass fiber laser, Wavelength 1.56 μm, Average power 0.3–3 W, Beam modulation: pulse duration from 10 ms to 2 s, Pulse repetition rate 0.3–10 Hz, Exposure time 10–30 s, A number of pulse series 3–5, Pause between pulse series 10–30 s. The equipment includes a feedback control system which provides efficacy and safety of laser procedure.

The advantages of LRD compared to other techniques of low-invasive physical treatment of spine disc diseases are:

1. LRD is directed to the reason of the disease due to activation of tissue regeneration.
2. We do not heat AF. The locality, the efficacy and safety of LRD can be controlled by the stress distribution and dynamics using space and temporal modulation of laser radiation.
3. The positive dynamics of the results. The stability of the improvement of life and pain relief.

Open Questions and Future Work Are Necessary to Study

1. Mechanisms of tissue regeneration need future investigation
2. The origin of chondrocytes producing hyaline type cartilage (stem cells, or rapid diffusion of chondrocytes from hyaline plates?)

3. The reasons of different dynamics of pain relief (including denervation of pathologic nerves in the AF, stress relaxation, growth of the new tissue decrease spine instability)
4. Long term stability (more than 5 years) of the positive results

Conclusions

Laser reconstruction of spine discs is a novel minimally invasive approach for the treatment of intervertebral disc diseases. The new type of Erbium doped glass fiber laser (1.56 μm) has been tested first on animals and then in a clinical trial. The histological studies showed that laser treatment stimulated growth of hyaline cartilage in the spine discs. Since 2001 LRD procedure has been performed for 240 patients in Moscow. Most of the patients demonstrated significant improvement, returned to the work and normal life.

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