Diode Laser 810 nm as a potential treatment to improve visual function in Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

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Received: 20 Jan 2011
Accepted: 11 Feb 2011
Published: 27 Feb 2011
Irn J Med Hypotheses ideas, 2011, 5:3


Abstract
Nonarteritic anterior ischemic optic neuropathy (NAION) is one of the most widespread visually disabling diseases in the middle-aged and elderly population. The optic nerve damage appears to result from a perfusion insufficiency in the short posterior ciliary arteries leading to infarction of the retrolaminar portion of the optic disc. Induced Heat shock protein (Hsp) is known to have neuroprotective effects against ischemic injury of the central nervous system in mammals. Transpupillary thermotherapy (TTT) application to the optic nerve head induces Hsp70 expression. We hypothesize that Transpupillary thermotherapy (TTT) could be a novel method for improving and preserving the function of the optic nerve fibers in the eye with NAION. An 810-nm diode laser beam is focused to the center of the optic nerve head to induce Hsp. Controlled prospective and randomized clinical trial is necessary to confirm conclusively the effectiveness of this method.

Keywords
Diode Laser 810 nm, Nonarteritic Anterior Ischemic Optic Neuropathy, Transpupillary Thermotherapy, Heat shock protein

Introduction
Nonarteritic anterior ischemic optic neuropathy (NAION) is one of the most widespread visually disabling diseases in the middle-aged and elderly population, although no age is immune (1). The optic nerve damage in nonarteritic anterior ischemic optic neuropathy appears to result from a perfusion insufficiency in the short posterior ciliary arteries leading to infarction of the retrolaminar portion of the optic disc. The underlying mechanisms are still unclear (2).
The natural course of changes in visual acuity in eyes with NAION was documented by Hayreh et al. In the eyes seen within 2 weeks of onset of visual loss, during a follow-up of 6 months, when visual acuity was 20/70, it improved in 41%, deteriorated in 19%, and remained stable in 40% (1).

Current best practice on treating general health risk factors to lessen the chance of future cardiovascular events (e.g. control of blood pressure, obesity, diabetes and cessation of smoking) should be considered because no new therapy would be a substitution for this purpose (1,2).

Multiple medical and surgical treatment options, including optic nerve sheath decompression, hyperbaric oxygen, neuroprotective agents, systemic corticosteroid therapy, levodopa, and Intravitreal triamcinolone have been investigated, but no proven effective treatment is currently available (2-4).

Heat shock protein (Hsp) is present in almost all living cells (5). It is rapidly induced by a variety of environmental stresses, and its role is to protect cells against stress (6,7). Induced Hsp is known to have neuroprotective effects against ischemic injury of the central nervous system in mammals (8-10).

Heat shock proteins are thought to play a vital role in normal cellular function. In response to environmental stresses such as heat, anoxia, and exposure to cytokines, cells newly synthesize large quantities of heat shock proteins. Because of their protective capacity, the increased expression of heat shock proteins helps cells to survive stressful conditions and also promotes recovery from stress (11-13). The accumulation of heat shock proteins in various cells of the nervous system during acute toxic metabolic states and in a variety of degenerative, inflammatory, and neoplastic neurologic diseases implicates their role for neuronal survival (14-17).

The members of hsp70 family are known to be rapidly induced by hyperthermic, light, or ischemic injury in rat and rabbit retinas (18-20). In addition, recent observations revealed increased immunostaining of hsp60 and hsp27 in the retina and optic nerve head of eyes with glaucoma (21). These findings suggest that these heat shock proteins may be components of a natural defense mechanism in the retina, optic nerve head, or both.

Transpupillary thermotherapy (TTT) is currently being applied to retinal diseases such as subfoveal occult choroidal neovessels in age-related macular degeneration (AMD) (22,23). An experimental study showed heat shock protein (Hsp70) hyperexpression in chorioretinal layers after TTT (24).

Kim et al., study confirm that TTT application to the rat's optic nerve head induces Hsp70 expression, and demonstrates that the optimal laser setting for Hsp70 induction without tissue damage is 100 mW for 60 seconds (25).

**The Hypotheses**

In light of these results, we hypothesize that transpupillary thermotherapy (TTT) could be a novel method for improving and preserving the function of the optic nerve fibers in the patient with NAION.

**Evaluation of Hypotheses**

We suggest an experimental case series after initial animal studies to find a safe and suitable power and exposure time, to investigate the effect of TTT, on visual outcome, in NAION.

Exclusion criteria include: (1) Confirmed giant cell arteritis; (2) History of any ocular surgeries; (3) Optic neuropathy due to acute bleeding (4) Advanced diabetic retinopathy; (5) Uncontrolled glaucoma; (6) Any ocular disorders that cause visual acuity reduction rather than NAION.

For functional assessments, best corrected visual acuity (BCVA) is determined using standard Snellen acuity chart. The visual acuities were converted to log MAR (log of the minimum angle of resolution) values. An improvement ≥0.3 logMAR units between the pre- and post treatment visual acuities is considered to be an improvement of visual acuity, while a decrease of >0.3logMAR units is considered to be a worsening. The technicians should be instructed to obtain the BCVA at each patient visit. The technicians are not always aware of the treatment status.

Visual fields are tested with Humphrey automated static perimetry, program 24-2, using a size III stimulus. The mean deviation score is recorded for the initial and the 6 month visits. We define improvement in visual field as a difference in mean deviation of +3.0 dB or more between the 6-month and the initial visual field tests. Worsened visual field is defined as a difference in mean deviation of -3.0 dB or fewer between the 6-month and the initial visual field tests (26). The visual acuity and visual field testing are performed before and 6 months after treatment.

All patients are underwent OCT measurements at the initial examination and after 6 months. The mean value of 360° average RNFL thickness obtain from three good-quality images (signal strength≥6) are considered.

An 810-nm diode laser with a TTT adaptor installed on a slit lamp is used in a continuous mode. A Goldmann contact lens is used, with methylcellulose as a coupling agent and 0.5% topical proparacaine for topical anesthesia. A laser beam is focused to the center of the optic nerve head to induce Hsp.

Primate model of NAION is induced by injecting Rose Bengal (RB) dye intravenously in a dose of 2.5 mg/kg. RB was intravascularly photoactivated in the optic disc with a neodymium-Yttrium aluminum garnet (Nd: YAG), frequency- doubled diode laser (532 nm) with a 1.06-mm spot size, at 200 mW, for times ranging from 7 to 10 seconds (27).
Discussion

From the animal models it has been found that Hsp70 overexpression in these experiments increases the survival rates of retinal ganglion cells (RGCs) (28, 29). The induction of Hsp72 in the mammalian central nervous system by hyperthermia has been associated with neuronal tolerance against ischemic insults and neuroprotective effects against light-induced injury in the rat retina (30, 31).

Transpupillary thermotherapy (TTT) slowly increases tissue temperatures to as much as approximately 10°C above baseline levels (32, 33). A tissue temperature increase of approximately 8° to 10°C theoretically should be safe for the overlying neurosensory retina, and yet it may still be sufficient to induce favorable local tissue changes [33]. In comparison, standard threshold retinal laser photocoagulation causes a temperature increase of 20° to 40°C at the level of the retina and RPE and, predictably, results in full-thickness damage to the retina and other histopathologic alterations that extend deep into the choroid (34).

The laser parameter to eyes with NAION has significant limitations. There is highly likely that such pathologic features would influence the effects of the local temperature increase induced by TTT. Fluid, for example, probably helps to minimize any excessive heat-damaging effects of TTT to the neurosensory retina (35).

In conclusion, controlled prospective and randomized clinical trial is necessary to confirm conclusively the effectiveness of this method after application of TTT in experimental induced NAION animal model to find suitable power and exposure time.

Acknowledgements

We gratefully acknowledge Rosha & Khashayar Ghaffariyeh for their kind cooperation.
None of the authors have any financial or proprietary interest in any material or method mentioned. There is no financial relationship with these centers.

Overview Box

First Question: What do we already know about the subject?
Nonarteritic anterior ischemic optic neuropathy (NAION) is one of the most widespread visually disabling diseases. Induced Heat shock protein (Hsp) is known to have neuroprotective effects against ischemic injury of the central nervous system in mammals. Transpupillary thermotherapy (TTT) application to the rat's optic nerve head induces Hsp70 expression.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?
We hypothesize that Transpupillary thermotherapy (TTT) could be a novel method for improving and preserving the function of the optic nerve fibers in the eye of patient with NAION.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?
An 810-nm diode laser is used in a continuous mode. A laser beam is focused to the center of the optic nerve head in experimental induced NAION animal model to find suitable power and exposure time then apply in human cases.

References


