The Ischemic Optic Neuropathy Decompression Trial

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ONARTERITIC ANTERIOR ISCHEMIC OPTIC neuropathy (NAION) is the most common cause of acute optic nerve disease in the elderly and often results in severe visual loss. The average annual incidence has been estimated at 2.3 to 10.2 per 100 000 persons aged 50 years and older with about 1500 to 6000 new cases seen each year in the United States. Although the visual acuity in patients with NAION remains better than 20/60 in approximately 50% of affected patients, the visual field is invariably abnormal, and more than one-third of patients have vision worse than 20/200 in the affected eye. Second eye involvement occurs in approximately 15% to 20% of patients with NAION within 5 years and often results in a dramatic reduction in patient independence and quality of life.

No therapy for acute NAION or prevention of fellow eye involvement has yet proved to be effective. In 1989, it was first suggested that optic nerve decompression surgery (ONDS) might improve vision, particularly in patients with a progressive form of NAION. The surgery involves making 2 or more slits or a window in the optic nerve sheath, allowing cerebrospinal fluid to escape, purportedly reducing the pressure surrounding the optic nerve. Subsequent publications reported a beneficial effect of ONDS, even in the nonprogressive form of NAION, while others were in disagreement about the efficacy. None of these reports were based on a randomized controlled trial, sample sizes were small, uniform visual testing procedures were not used, and progressive disease was not well defined. As surgery was being performed more frequently, it became imperative to test the procedure in a randomized clinical trial before use of the procedure became even more widespread.

The Ischemic Optic Neuropathy Decompression Trial (IONDT) was a randomized, single-masked, controlled trial conducted at 25 US clinical centers, sponsored by the National Eye Institute. The objective of the IONDT was to assess the safety and efficacy of ONDS compared with observation alone in patients with NAION. Secondary objectives were to describe the demographic and clinical characteristics and the natural history of a large prospectively followed-up cohort of patients with NAION seen within 2 weeks of onset.

Eligibility criteria for randomization to either ONDS or observation included a diagnosis of acute unilateral NAION in a patient aged 50 years or older and a visual acuity of 20/64 or worse and better than no light perception. Patients who were eligible except for having a visual acuity better than 20/64 were followed weekly and subsequently randomized only if their visual acuity fell to 20/64 or worse within 30 days (“late-entry group”). Standardized histories and examinations were obtained at 3, 6, 12, 18, and 24 months and annually thereafter by certified study personnel, and masked personnel performed outcome measures. Surgery was performed by experienced, certified study surgeons according to an explicit study protocol. A surgical quality-assurance committee developed and implemented a quality-assurance program, which included administration of surgical technique questionnaires, masked review of operative notes, and approval of a masked videotape of an ONDS performed by each study surgeon.

Recruitment for the IONDT began in October 1992. On the recommendation of its data and safety monitoring committee, recruitment was stopped in October 1994.

The preliminary results bearing on the primary outcome measure were reported in 1995 in the Journal of the American Medical Association and were based on data from 244 patients with NAION and visual acuity of 20/64 or worse, representing 125 patients randomized to observation and 119 to surgery. As regards visual improvement at 6 months (defined as an improvement of 3 lines or more), patients assigned to surgery did no better than patients who were observed without intervention; 32.6% of the surgery group improved compared with 42.7% of the observed group. Furthermore, patients who underwent surgery had a significantly greater risk of losing 3 or more lines of vision at 6 months; 23.9% in the surgery group worsened compared with 12.4% in the cohort who did not have surgery. No difference in treatment effect was observed between patients with progressive NAION and all others. The conclusion of this first publication from the IONDT was that ONDS for NAION is not effective, may be harmful, and should be abandoned. This caveat was reinforced by a January 3, 1995, flier from the National Eye Institute.
Several subsequent publications from the IONDT have provided information on the clinical characteristics of patients with NAION and the natural history of the disorder. Of 1680 patients evaluated for the IONDT, 420 were either randomized or included as natural history patients eligible for inclusion except for visual acuity. The baseline characteristics of these patients provided the first description of NAION from a large prospective study population that used a standard definition of NAION and only included patients evaluated within 2 weeks of the onset of symptoms. Sixty-two percent of the patients were men and 95% were white. The mean age at onset was 66 years. Hypertension was self-reported by 47% of patients and diabetes mellitus by 24%. Forty-two percent of patients recalled that their visual symptoms were first noted within 2 hours of awakening. Initial visual acuities in the study eye ranged from 20/20 or better to light perception, with 49% of the patients seeing better than 20/64 and 34% seeing 20/200 or worse. The nonrandomized patients (visual acuity better than 20/64) were younger and had a lower prevalence of hypertension and diabetes mellitus.

Of the original randomized patient cohort, 174 continued to participate in the IONDT for at least 24 months. Mean visual acuity was statistically significantly improved from baseline value at all study visits and for both treatment groups, although visual acuity declined gradually in both groups after the 3-month visit. There were no significant differences between careful follow-up and ONDS in mean change in vision from the baseline and any follow-up time point. The 24-month data confirmed that there was no benefit of ONDS compared with observation in patients with NAION.

Of the 418 patients ultimately enrolled in the IONDT as either randomized or observational patients, previous NAION or other optic neuropathy was present in the fellow eye of 21.1% of patients at baseline. New NAION in the fellow eye occurred in 14.7% of patients at risk during a median follow-up of 5.1 years. Randomized patients experienced a higher incidence (17.4%) than nonrandomized patients (10.4%). A history of diabetes mellitus and baseline visual acuity of 20/200 or worse in the study eye, but not age, sex, aspirin use, or smoking, were significantly associated with new NAION in the fellow eye. Final fellow eye visual acuity was significantly worse in those patients with new fellow eye NAION whose baseline study eye visual acuity was 20/200 or worse. The IONDT provided evidence that the incidence of fellow eye NAION is lower than had been previously reported.

Regarding visual field analyses, the IONDT provided an opportunity to validate a computerized expert system evaluating visual fields in a prospective clinical trial. Following establishment of criteria for the type and severity of visual field defects by an expert panel, a rule-based computerized expert system interpreted the Humphrey visual fields from baseline and 6-month visits. The pattern of defects at baseline for patients randomized to surgery did not differ from that of patients randomized to observation without intervention. The most common visual field defect at baseline was superior and inferior arcuate defects with a central scotoma for randomized eyes (19.2%) and superior and inferior arcuate defects for nonrandomized eyes (30.6%). The visual field patterns at 6 months were not different from those at baseline. For randomized study eyes, the superior altitudinal defects and inferior altitudinal defects improved, while among the nonrandomized study eyes, only the inferior altitudinal defects improved. No treatment effect was noted.

The IONDT also provided an opportunity for publications regarding the epidemiology of participation in large, multicenter trials and the designs and methods associated with such studies. Additionally, a surgical randomized controlled trial such as the IONDT presented special difficulties in quality assurance and uniform surgical quality control. The mechanisms for surgical quality assurance developed for the IONDT greatly increased the credibility of the IONDT results and provided a methodological framework that may be applied to future multicenter surgical studies.

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The pathophysiology of NAION remains a mystery, and worse, there is no treatment established to be effective. Thus, it can be understood why there was so much hope when a 1989 publication in the Archives reported that 12 of 14 patients with progressive NAION enjoyed visual improvement after optic nerve sheath decompression. Patients with a progressive course compose only a small fraction of NAION cases, and it was only the progressing patients for which optic nerve sheath fenestration was suggested to be helpful. Nevertheless, this qualification failed to deter ophthalmologists from performing the procedure in both progressive and nonprogressive cases of NAION. Fortunately, several investigators decided to determine whether the procedure was truly efficacious, initiating the Ischemic Optic Neuropathy Decompression Trial (IONDT), which was funded by the National Eye Institute. The IONDT studied patients with clinically diagnosed new-onset NAION, randomizing them between optic nerve sheath fenestration or follow-up alone.

More than a decade after publication of the results of the IONDT, it is appropriate to consider to what extent the results of the IONDT have influenced the management of patients with NAION. At first glance, it would seem that the IONDT conclusively showed that optic nerve sheath fenestration does not improve visual acuity in patients with NAION and may also be harmful. However, a closer analysis uncovers some ambiguity. First, the IONDT did not definitively answer whether fenestration helped the group of patients for which the therapy was originally described: namely, those with progressive NAION. The 1989 article describing optic nerve sheath fenestration for progressive NAION had specifically demonstrated that it was ineffective for nonprogressive NAION. The IONDT was underpowered to specifically assess progressive NAION, and the negative findings seen in both progressing and nonprogressing cases has made it unlikely that a more adequately powered study can be performed in the future. Of the 237 randomized patients in the IONDT, only 16 patients in the surgery group and 11 patients in the follow-up group could be considered progressive by 1 clinical criterion, namely, worsening of 3 or more lines of visual acuity before randomization. In comparison, if one were to design a new study to have an 80% probability of detecting (at \( P=.05 \)) a 50% greater improvement of 3 lines or more beyond that found in the IONDT careful follow-up group, 66 patients per group would be required. Thus, the question of whether or not optic nerve sheath fenestration might have a benefit for patients with progressive NAION has not been answered to a reasonable degree of medical certainty.

Second, including a surgical arm in an investigation of this kind adds special difficulties. This is especially true when there are many centers and surgeons involved in the investigation. Optic nerve sheath fenestration is not a new procedure, having been increasingly employed in the treatment of patients with intracranial hypertension, but it is a low-volume procedure and surgeons may