

Nonarteritic anterior ischemic optic neuropathy treated with intravenous prostaglandin E1 and steroids

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BACKGROUND: Acute nonarteritic anterior ischemic optic neuropathy (NAION) is considered to be acute ischemia of the posterior ciliary arteries. Prostaglandin E1 (PGE1), a powerful microcirculation vasodilator, has been shown to improve ocular blood flow.

DESIGN: A nonrandomized, comparative trial.

METHODS: Eight consecutive cases of NAION were treated with intravenous steroids and PGE1. Seven control cases of NAION were

treated with acetylsalicylic acid and oral steroids. Fisher's exact test was used for statistical analysis.

RESULTS: The visual acuity improved in seven cases of NAION treated with PGE1 and was unchanged in one. Of the seven control cases, four had no change in vision and three lost further visual acuity on follow-up visits.

CONCLUSIONS: Intravenous PGE1 and steroids should be considered in cases of NAION to immediately restore blood flow to the optic nerve and improve visual acuity.

Key Words: *Macular star; Nadroparin; Neuroretinitis; Nonarteritic anterior ischemic optic neuropathy; Prostaglandin E1 (PGE1)*

Nonarteritic anterior ischemic optic neuropathy (NAION) is thought to be an ischemic infarction of the prelaminar portion of the optic nerve head (ONH). The main cause is believed to be a drop in the perfusion pressure of the posterior ciliary arteries, and not an embolism or thrombosis, although pathological evidence is not available. This drop in perfusion pressure is thought to result in ischemia to the retinal nerve fibre bundles in the optic disk anterior to the lamina cribrosa. Nocturnal arterial hypotension is considered to be an important risk factor (1). Regarding therapy, a recent study (2) showed that systemic corticosteroids given to patients in the acute phase of NAION can lead to an improvement in their visual acuity (VA) and visual fields (VFs).

Prostaglandin E1 (PGE1) is a potent microcirculation vasodilator. The successful use of intravenous (IV) PGE1 to treat an acute case of ocular ischemia in the form of a branch retinal arterial occlusion has been reported (3). It has also been shown to improve decreased ocular blood flow in patients with peripheral vascular disease and diabetes (4). Because NAION is thought to be caused by ischemia, the use of a potent microcirculation vasodilator may help in its treatment.

The present study describes eight consecutive cases of acute NAION treated with IV steroids and IV PGE1. The results are compared with seven consecutive cases of acute NAION treated with steroids and acetylsalicylic acid. The treatment protocol was the result of a collaboration among two angiologists (MRC, GB), two internists (MDA, SB) and two ophthalmologists (RDS, AP).

METHODS

Eight consecutive cases of NAION were diagnosed and treated. Six of the patients presented to the emergency room at the Ophthalmic Hospital (Rome, Italy) and two presented to the

private practice of one of the authors (RDS) during the same period. Seven of the patients were seen and treated by an ophthalmologist 24 h to 72 h after the onset of the symptoms. One patient was first seen and treated 120 h after the onset of the symptoms. All the patients had a sudden loss of VA in one eye with optic disc edema (ODE). The initial best corrected VA (BCVA) was obtained with the Snellen VA chart. All the patients immediately had a complete dilated eye examination including intraocular pressure measurements, fundus examination and VF assessment. Blood work, including erythrocyte sedimentation rate, an electrocardiogram and a medical examination were also immediately performed. After the diagnosis of NAION was made, therapy commenced immediately without waiting for other eye examinations such as fluorescein angiography (FA) to prevent treatment delay. After explaining the experimental nature of the treatment, written consent was obtained and the patients were rapidly given 40 mg of 6-methylprednisolone IV. Diabetic patients received one-half the dose of cortisone. All the patients were then immediately given 80 µg of PGE1 plus 1 mL of potassium in 250 mL of physiological solution IV over 3 h to 4 h. The pulse and systemic blood pressure (BP) were monitored every 15 min. If the BP decreased, the rate of the IV PGE1 was decreased. On the morning of the following day, the same treatment was repeated, first with 40 mg of 6-methylprednisolone IV, immediately followed by 80 µg of PGE1 plus 1 mL of potassium IV over 3 h to 4 h. No patients needed to interrupt the PGE1 treatment because of hypotension. The patients were then started orally on 25 mg of prednisone per day for one week and 100 mg of acetylsalicylic acid per day for two months. Diabetic patients received 12.5 mg of prednisone per day for one week. The patients were then seen at seven, 21 and 35 days from the onset of the PGE1 therapy. When possible, the patients were then

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TABLE 1
Treated eyes

Patient	Age	Time	Initial	VA other	VA at	Final VA	
	years,	after					
sex	onset, h	Eye	VA	eye	1 week		
1	68 M	48	OD	1/10	10/10	2/10	3/10
2	65 F	72	OS	3/10	7/10	5/10	5/10
3	57 M	48	OD	CF	7/10	1/10	1/10
4	66 M	72	OD	4/10	8/10	7/10	9/10
5	68 M	120	OD	5/10	1/50	7/10	7/10
6	72 M	24	OS	LP	4/10	LP	LP
7	78 F	60	OS	1/10	9/10	4/10	10/10
8	60 F	72	OD	4/10	10/10	5/10	7/10

CF Count fingers; F Female; LP Light perception; M Male; OD Right eye; OS Left eye; VA Visual acuity

followed bimonthly. An FA or VF assessment was performed on follow-up visits when necessary for diagnostic or therapeutic reasons. The first patient treated with steroids and PGE1 had persistent ODE. She needed a low-molecular-weight heparin (LMWH) because of persistent disc edema; nadroparin was used.

The patients treated with PGE1 were compared with seven consecutive patients with NAION who presented to the emergency room at the Ophthalmic Hospital. They were used as controls. All the controls had a complete eye examination, VF assessment, blood work and a medical examination. The controls were treated with 100 mg of acetylsalicylic acid per day and 25 mg of oral prednisone per day for two weeks. The seven consecutive control patients were not randomly assigned with the PGE1-treated cases. The control patients were treated this way while the authors waited for approval of the use of PGE1 to treat NAION from the Ophthalmic Hospital ethics committee. After PGE1 was approved for use, the next eight consecutive cases of NAION were treated with PGE1 as described above.

Fisher's exact test was used for the statistical analysis. Three outcomes were considered: improved VA, decreased VA and unchanged VA.

RESULTS

The mean age of the seven controls was 70 years, and that of the eight PGE1-treated patients with NAION was 67 years. Of the eight PGE1-treated patients, the BCVA improved in seven (Table 1). One PGE1-treated patient had light perception VA with no change before or after treatment. In the seven patients with improved BCVA, three patients had improved VA within 24 h of starting the IV PGE1. Of the seven patients with improved BCVA, three remained unchanged at two months, two continued to improve for up to two months and two continued to improve for up to six months. One of the seven patients with improved BCVA at one week had a second episode of vision loss two weeks after treatment. She was treated with IV 6-methylprednisolone and IV PGE1 for another three days instead of two days. Her VA improved again at her first visit four days from the beginning of the second round of treatment with IV PGE1.

Of the seven controls, four had no further VA loss (5/10 to 5/10, 1/10 to 1/10, 1/50 to 1/50, hand motions to hand

motions) and three had further VA loss (4/10 to 1/10, 5/10 to 2/10, 5/10 to 2/10) at two months.

Of the eight patients treated with PGE1, one had persistent ODE three weeks after treatment, despite an improvement in VA in her left eye (OS) from 1/10 to 4/10. Macular edema of the OS was noted for the first time with the beginning of radial exudates toward the foveola (macular star). Five weeks after PGE1 treatment, her VA was 5/10, but the macular edema and macular star were increasing so she was started on subcutaneous nadroparin calcium, 6000 IU every 12 h for one week. After one week of nadroparin, her VA was 7/10, the ODE had disappeared and the macular star was resolving. The nadroparin was suspended after two weeks. Six months after PGE1 treatment, her OS had a VA of 10/10 with no macular star.

When considering the three possible outcomes (improved, decreased or unchanged VA), the difference in the sample due to the use of PGE1 was significant (Fisher's exact test, $P=0.001$).

DISCUSSION

PGE1 is a safe, potent vasodilator of the peripheral vascular system (microcirculation or capillary system) that is used to treat patients with peripheral vascular diseases such as intermittent claudication and peripheral diabetic ulcers (4-6). It is the same medication used to treat men with erectile dysfunction (7). A two-day IV treatment of PGE1 causes vasodilation of the capillary system that can last for four weeks or longer in patients with peripheral vascular disease (8). It is well tolerated, has few side effects and can be used in hypotensive patients. It is important to monitor the systemic BP frequently (every 15 min to 20 min) during IV administration (4-6,8). The main mechanism of action of PGE1 is vasodilation of the microcirculation (capillary system). PGE1 has a direct action on the smooth muscle of the vascular wall leading to vascular dilation and increased flow. This vasodilation varies by anatomical location and is dose dependent. PGE1 is also known to inhibit platelet aggregation (9). In addition to known effects of PGE1 on platelet aggregation, fibrinolysis, blood flow and viscosity, it also inhibits monocyte and neutrophil function, which suggests anti-inflammatory effects as well. Recent research on gene expression suggests that several genes in vascular smooth muscle cells and fibroblasts are modified by PGE1 at the transcriptional level. This may contribute to tissue protection in ischemic areas (10). These factors together promote an increase in the capillary flow. PGE1 is rapidly metabolized by oxidation during passage through the pulmonary circulation. It is excreted in the urine as metabolites within approximately 24 h (9). This rapid elimination also contributes to its safety.

Because the main cause of NAION is thought to be a drop in the perfusion pressure of the posterior ciliary arteries, and not an embolism or thrombosis, the use of a potent vasodilator to immediately re-establish blood flow may be important. PGE1 has been shown to improve decreased ocular blood flow in patients with peripheral vascular disease and diabetes (4). It has been used to treat an acute case of ocular ischemia in the form of a branch retinal arterial occlusion (3). More recently, it has been used to treat chronic ocular ischemia in high myopia (11). One IV infusion of PGE1 improves blood flow for up to four weeks in patients with peripheral vascular disease (8). For

these reasons, the authors decided to use PGE1 in the treatment of NAION.

In the present study, after the flow was re-established, further treatment with PGE1 was needed in only one patient, who had a second episode of ischemia. The patients should be followed frequently after the initial treatment in case someone needs a second round of treatment with IV PGE1, as described above. The authors recommend beginning PGE1 immediately after diagnosis and giving a second dose within 24 h. Additional IV doses of PGE1 can be given if necessary. In the present study, when the VA improved, it improved immediately or within one week. One millilitre of potassium was added to each 250 mL IV to avoid cardiac arrhythmias.

IV steroids were given immediately before treatment with PGE1 and continued orally for seven days. Hayreh and Zimmerman (2) have also used systemic corticosteroids to treat patients in the acute phase of NAION. They used oral prednisone and found a significantly higher probability of improvement in VA and VFs in the treated versus the untreated groups (2). In the present study, the authors used IV steroids for two reasons. The first was that ODE was present due to swelling of the axons caused by axoplasmic flow stasis. Swollen axons in a restricted space in the opening in Bruch's membrane and the scleral ring in the ONH can compress the capillaries between the nerve fibre bundles. It is possible that increasing the blood flow with PGE1 in the capillaries could cause more tissue swelling at the level of the ONH. The authors did not want further swelling in an already congested area with the risk of further damage to the nerve fibres, and thought that IV steroids may help reduce the swelling and risk. The second reason for using IV steroids was to try to reduce ischemia-reperfusion injury. Ischemia leads to tissue hypoxia, depletion of energy-rich phosphates, accumulation of metabolic waste products including reactive oxygen species, and cellular edema, all of which may cause cellular injury (12,13). The immediate reinstatement of blood is necessary to prevent further tissue damage, but the reperfusion itself may cause tissue damage (reperfusion injury). Infiltrating leukocytes are thought to play a major role in ischemia-reperfusion injury and were the reason for the use of IV steroids by the authors before IV PGE1 and orally for a week after PGE1 (12,13).

One patient had persistent ODE three weeks after the PGE1 treatment. The presence of macular edema and the beginning of a macular star was noted at three weeks despite visual improvement. At five weeks, the macular edema and macular star were increasing although there was further visual improvement. The authors thought they had increased arterial and capillary flow, as seen with immediate visual improvement, but that the presence of venous stasis at the ONH could explain the persistent ODE and gradual formation of a macular star. The macular star was caused by treatment (iatrogenic). Macular stars are usually seen in neuroretinitis, which usually occurs in children or young adults (14). However, this was not the case here. A LMWH was used by several of the authors to treat retinal vein occlusions. Enoxaparin was used in a dose of 100 IU/kg every 12 h (15). The patient with the macular star in the present report weighed 60 kg and was given 6000 IU of subcutaneous nadroparin calcium every 12 h, with dramatic improvement in the edema and star after only one week. The immediate improvement in the ODE and macular star with a

LMWH supports the hypothesis that they may be due to venous stasis of the ONH after the improved arterial blood flow with PGE1. Hayreh and Zimmerman (16) have also treated ODE, but started steroids within two weeks of the onset of NAION. They observed a more rapid time of resolution of the ODE in the treated patients (17). The rapid resolution of the ODE with nadroparin in the present patient lead the authors to believe that the persistent ODE may have represented a form of venous stasis that could justify the use of LMWH. Other treated cases of NAION will be necessary to provide a better understanding of the appropriateness of LMWH for treating persistent ODE.

The VA in these patients was measured using the Snellen VA chart. VA was measured initially and at all follow-up visits. VFs were initially assessed in all patients and controls. Hayreh and Zimmerman (16) have emphasized the need for both VA and VF end points in NAION to reduce the effect of bias and unmasked treatment arms. BCVA was evaluated at follow-up in all patients. VFs were assessed at follow-up when possible, but not all patients were willing to return for repeat VF assessment. For this reason, VA was the only parameter used in the present article to follow the treatment. The presentation of the patients with NAION was considered to be an ocular emergency by the authors of the present article. IV therapy was immediately started after the initial ocular examination, VF assessment and medical workup were performed. FA, optical coherence tomography and other ocular examinations were not immediately performed to prevent therapy delay. Within 24 h of receiving the first IV treatment, the patients frequently reported a reduction in the size or intensity of their scotoma, or an improvement in their VA. The authors were able to measure this early improvement in three patients who could return immediately after treatment for follow-up. The other four patients with improved VA could not return for follow-up until one week later, so the authors were unable to establish the timing of their visual improvement.

The treatment program presented here was possible because of a collaboration among ophthalmologists, angiologists and internists. The authors believe this type of collaboration is necessary for PGE1 treatment to be effective in problems of ocular and ONH ischemia.

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