Nicotinic Acid in Retinal Vein Occlusion

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Abstract

**Purpose:** To evaluate the effect of nicotinic acid (as a possible vasodilator) in treatment of retinal vein occlusions (CRVO or BRVO).

**Setting:** Mashad University of Medical Science (MUMS); Khatam-Al-Anbia eye hospital.

**Design:** Prospective non-randomized pilot study

**Patients & Methods:** Twenty two eyes of 21 patients with CRVO or BRVO, participated to receive incremental doses of niacin starting from 300mg/day up to 3g/day for 3 months.

**Main outcome measures:** Changes in visual acuity, visual fields, amount of vascular congestion, hemorrhage and macular edema in fundus photographs, and systemic complications of nicotinic acid.

**Results:** Mean follow up was 8.6±2.7 months. Mean BCVA was 0.11±0.14 before treatment, 0.12±0.11 (P=0.30) at 1 month and 0.27±0.22 (P=0.009) at 3 months after treatment. At last follow up visit, mean BCVA was 0.26±0.23 (P=0.02). All patients had resolution of hemorrhages, cotton wool spots, macular edema, disc edema, venous tortuosity and dilation on basis of fundus photographs, 3 months after treatment. MD index or automated primgity improved from -29±9 before treatment to -24±7 (P=0.007) at three months and -28±9 (P=0.01) in the last follow up. Four patients were lost to follow up before 3 months and two other patients were excluded due to hypersensitivity to nicotinic acid and severe hyperglycemia. The only other notable side effect of nicotinic acid was flushing which was well tolerated by all patients.

**Conclusion:** Nicotinic acid treatment for 3 months led to significant clinical improvement in CRVO and BRVO. Niacin, by induction of vasodilatation, may possibly provide enough time for collateral vessels to develop. Niacin is well tolerated and is associated with mild systemic side effects.

**Key words:** Nicotinic Acid, Niacin, Retinal Vein Occlusion, CRVO, BRVO.

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Introduction

Retinal vein occlusions are common in clinical practice. Central retinal vein occlusion (CRVO) is a potentially blinding disorder in which the thrombus formation typically occurs at or near the lamina cribrosa. Current treatment of CRVO is based on findings from the Central Vein Occlusion Study (CVOS) and is aimed at preventing or treatment of complications and does not improve vision. Management of BRVO is based on the recommendations of the Branch Vein Occlusion Study (BVOS). This strategy is also aimed at treatment of complications. Recently, treatment strategies have focused on restoring venous outflow from the affected eyes by administering recombinant tissue plasminogen activator (t-PA) via cannulation of a retinal vein, creating a surgically or laser-induced chorioretinal anastomosis, transvitreal optic nerve surgery to relax constriction of the central retinal vein by incising the scleral fibers of the lamina cribrosa or releasing the pressure on the affected branch by arteriovenous sheathotomy. Other nonsurgical treatments involving the use of hyperbaric oxygen and hemodilution have also been advocated. Nicotinic acid has three roles. One is as a vitamin. The other is as a broad-spectrum anti-lipid drug and it has been used for many years to treat hyperlipidemia. The third role of nicotinic acid as a vasodilator is less well known. Data support the hypothesis that the vasodilating effect of nicotinic acid is largely dependent upon an increased vascular formation of prostaglandins especially PGD2. In addition, niacin induces high HDL levels. HDL increases endothelial nitric oxide synthase expression. Nitric oxide contributes to vasorelaxation. A few reports suggest that niacin has anti-coagulant effect. In 1992, three patients with significant clotting factor synthesis deficiency and coagulopathy (prothrombin times, greater than 1.5 time's control) due to use of sustained-release niacin were reported. Vasodilation may help restore some venous outflow in retinal vein occlusions and niacin seems to be a good choice in this regard because it has anti lipid action which is needed in many of these patients and has few side effects.

Patients and Methods

Between May 2004 and July 2005, 21 patients with CRVO or BRVO were enrolled. Written informed consent was obtained from all subjects before entrance to the study. Complete medical and ophthalmic history, including risk factors such as hypertension, diabetes, open-angle glaucoma, hyperlipidaemia was taken. Systemic workup was considered in those that were younger than sixty or had previous vein occlusion in fellow eye, previous systemic thrombotic disease, family history of thrombosis, or other symptoms suggestive of a hematologic or rheumatologic condition. Eyes with retinal neovascularization, neovascular glaucoma, history of previous laser photocoagulation and vitreous hemorrhage were excluded from the study as were patients with gout or active peptic ulcer disease.

Best-corrected visual acuity (BCVA) with E charts, swinging flashlight test to detect the presence of RAPD (qualitative measurement between +1 to +4, +1=barely detectable, +4=no direct pupillary response, +2 and +3 between them), and slit-lamp examination, gonioscopy, measurement of intraocular pressure (IOP) using Goldmann applanation tonometry, indirect fundoscopy, fundoscopy with slit lamp by noncontact lens (90D) and fundus photography were obtained at baseline and at monthly follow-up visits. Patients with visual acuity >= 1/10 (20/200), no to +1 RAPD were considered to have nonischemic CRVO, while those with visual acuity less than 1/10 (20/200) and RAPD >=+2 were considered to have ischemic CRVO. Fundus photographs were also used for classification. Eyes with few numbers of dot and flame retinal hemorrhage, normal disc appearance and no to few cotton wool spots were classified in the nonischemic group. In contrast, those with extensive retinal hemorrhages in all four quadrants, optic disc swelling and numerous cotton wool spots were classified in the ischemic group. Laboratory investigations including FBS, triglyceride, LDL and HDL levels were done before treatment and at each follow-up visit. Humphrey automated primetry was also done at baseline and during each follow up visit. Because fluorescein angiography was not necessary for starting the treatment, it was only performed if the
patient accepted its risks. Foveal thickness was measured using the OCT in one patient before and three months after treatment. Four patient were lost to follow-up. Drug was discontinued in two other patients due to side effects. Therefore, data of 16 eyes (15 patients) are reported.

Laser treatment was done if neovascular complications occurred during the study (except patient #1, who refused from laser treatment). For patients who underwent laser treatment, visual acuity and other outcome data before laser therapy, were included in the study results.

Drug and dosage: Incremental doses of oral nicotinic acid were given to all patients starting with one tablet (100mg) every 8 hours (300mg daily), increasing the dose 300 mg/day (one tablet every 8 hours) each week up to total dose of 3000mg/day in the 10th week (10 tablets every 8 hours). This dose was continued for 2 weeks and then the drug was discontinued abruptly at the end of 12th week. To improve compliance of patients to skin flush, aspirin (100mg/day) was prescribed to be used in the morning for the first month.

Results
Twenty one patients (12 males and 9 females) affected by retinal vein occlusion at least in one eye were treated with nicotinic acid. Average age of patients was 58.5±12.0 SD years (range: 29-82 years). Five patients were hypertensive and one was diabetic. One patient (patient #1) had antiphospholipid antibody syndrome and presented with bilateral multiple BRVOs 6 months after onset of symptoms (Figure 1). Fourteen patients had ischemic CRVO, five had nonischemic CRVO and one patient presented with macular BRVO. There was serum lipid abnormality (TG>200mg/d, LDL>160 or HDL<40mg/dl) in 7 patients. Average duration of symptoms at the time of treatment was 50.32±62.71 days (range 8-240 days). Demographic data, systemic risk factors and lipid profile abnormalities are listed in Table 1.

Table 1. Demographic data, systemic risk factors and lipid profile abnormality. TG more than 200mg/d, LDL more than 160 and HDL less than 40mg/dl were considered as an abnormal.

<table>
<thead>
<tr>
<th>Patient NO</th>
<th>AGE (year)</th>
<th>GENDER</th>
<th>Risk factor</th>
<th>Lipid profile abnormality</th>
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</thead>
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<td>3</td>
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<td>High TG, High LDL, Low HDL</td>
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<tr>
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<td>Hypertension</td>
<td>Low HDL</td>
</tr>
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<td>Male</td>
<td>-</td>
<td>High LDL</td>
</tr>
<tr>
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<td>63</td>
<td>Male</td>
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<td>67</td>
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<td>8</td>
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<td>-</td>
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<tr>
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<td>-</td>
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<td>-</td>
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One patient experienced generalized urticaria due to nicotinic acid and was excluded from the study. We discontinued niacin because of uncontrollable high blood glucose levels two months after treatment in a diabetic case. Four patients did not follow the treatment protocol for 3 months and their data were excluded from the study. Therefore, results of treatment in 16 eyes (15 patients) are reported. These patients had mean age (±SD) of 59.56 (±11.12) years (range: 35-82 years). Average duration of symptoms at presentation was 59.69±71.60 days (range 10-240 days). Average follow-up was 8.6±2.7 months (range 1-12 months).

In the last visit, 1 eye (6%) had a lower vision than baseline, two maintained the pre-treatment vision and 13 (81%) showed an increase in visual acuity. Mean BCVA (±SD) for distant vision was 0.11±0.14 before treatment, 0.12±0.11 (P=0.30) at 1 month, 0.18±0.16 (P=0.08) at 2 month and 0.27±0.22
mean TG and LDL levels decreased to 151±35 mg/dl (P=0.003) and 139±19 mg/dl (P=0.07) and mean HDL increased to 52±9 mg/dl (P=0.04) (Figure 2). In the last follow up visit (an average of 4.2 months after niacin discontinuation), lipid profile did not show statistically significant difference from pre-treatment values (P>0.05). Change in BCVA did not correlate with TG, LDL, or HDL levels. Mean fasting blood glucose (FBS) level increased from 93mg/dl to 102mg/dl three months after treatment (P=0.00). As mentioned earlier, there was one diabetic patient who developed uncontrollable hyperglycemia 2 months after starting treatment, therefore, the drug was discontinued. After drug cessation, FBS returned to pre-treatment values.

### Table 2. Pre and post-treatment ocular data

<table>
<thead>
<tr>
<th>Patient NO</th>
<th>ONSET (days)</th>
<th>BCVA0</th>
<th>RAPD</th>
<th>TYPE*</th>
<th>BCVA3</th>
<th>Follow up (months)</th>
<th>Last BCVA</th>
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<td>12.00</td>
<td>0.02</td>
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<td>6.00</td>
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</table>

*According to visual acuity, RAPD, and fundus appearance.
I-CRVO=Ischemic CRVO
N-CRVO=Non-ischemic CRVO
M-BRVO=Macular BRVO
Mu-BRVO=Multiple BRVO
BCVA0=BCVA before treatment
BCVA3=BCVA at 3 months follow up visit
Last BCVA=BCVA at more than 3 months follow up visit (for patients with complete therapeutic course of niacin)
HM = hand motion
deviation) as an indicator of general visual field sensitivity. MD index improved from -29±9 before treatment to -24±7 (P=0.007) three months and to -28±9 (P=0.01) in the last follow up visit (Figure 2). Patient #8 had persistent macular edema 8 months after radial optic neurotomy (RON). His lipid profile showed the need for treatment with a lipid lowering agent. Therefore, we considered him to participate in study to evaluate niacin effect on macular edema. Three months after beginning of treatment, vision improved 3 lines, macular edema reduced and the focal field defect in primetry disappeared.

Resolution of hemorrhages, cotton wool spots, macular edema, disc edema, venous tortuosity and venous dilatation were detected in all eyes, approximately 3 months after starting treatment (Figure 1, 3 and 4). Foveal thickness was measured with OCT in one case (patient #4) which was 539μm before treatment and decreased to 319μm 3 months after treatment (Figure 3). Fluorescein angiography before and after treatment, showed resolution of macular and disc edema, reduction of areas of blocked fluorescence (due to hemorrhages) and development of perfused areas in two cases (patient #3 and 4) (Figure 3, 4).

Figure 2. Lipid profile changes: TG, LDL reduced, and HDL increased 3 months after treatment. The changes were statistically significant. At the last follow up visit (by average 4.2 months after niacin discontinuation), lipid profile did not show statistically significant difference from pre-treatment values.

Primetry was performed in 10 patients before treatment and at 3 months follow up visit. Visual field improvement was seen in all except two. In other patients, primetry was not reliable because of poor vision or poor cooperation. We considered MD (mean

Figure 3. Fundus photograph, fluorescein angiography and macular OCT in patient #3 before treatment (A) and at three months follow up visit (B). Foveal thickness was 539 μm pre-treatment and decreased to 319 μm 3 months after starting the treatment.
Side effects were mild and well tolerated. Generally, systemic and ocular complications were well managed in all patients, except for one patient who developed neovascularization of the iris. No other complications were reported.

Three months after the beginning of treatment, macular hole detected in the fellow eye of the patient presented by vitreous hemorrhage, which resolved after the first month in all patients. No other complications were reported.

Figure 4. Foveal and macular stains in a diabetic patient, 4 months after treatment.

Figure 5. Foveal and macular stains in a diabetic patient, 7 months after treatment.
Discussion

We found only one abstract\textsuperscript{26} with incomplete data regarding niacin use in retinal vein occlusion in Medline and we think our study must be the first to probe the issue in detail. The natural course of CRVO, in eyes presenting with vision less than 1/10 is poor. Pan-retinal laser photoacoagulation appears effective only in managing neovascular complications, while grid macular laser decreases macular oedema without changing the final vision.\textsuperscript{3} There is 80% chance that eyes with initial visual acuity of worse than 1/10 will have final visual acuity less than 1/10 without treatment\textsuperscript{27}, but this chance was only 45% in the current series which seems significantly better than natural history of the disease. Percentage of patients with best-corrected vision worse than 1/10 decreased from 68% (14 patients) at presentation to 37% in the last follow-up.

Fluorescein angiography was done in only two patients because of its potential risks. One can argue that classification of patients to ischemic and nonischemic groups, according to BCVA, RAPD and fundus appearance may not be correct. Hayreh et al.\textsuperscript{28} investigated the reliability of various clinical tests (visual acuity, visual fields, RAPD, electroretinography, ophthalmoscopy and fluorescein fundus angiography) in differentiating definitely the two types of CRVO. They found that four of five functional tests (i.e. visual acuity, visual fields, relative afferent pupillary defect and electroretinography) when taken together are far more reliable in making such a differentiation than fluorescein angiography alone. In fact, the information derived from fluorescein angiography may actually be misleading, particularly during the early stages of CRVO.

One major concern is persistence of the salutary effects of the drug after its discontinuation. Mean BCVA at 3 months follow up and last visit were 0.27±0.22 and 0.25±0.23 (P=0.62) respectively. Mean MD at 3 months follow up and last visit were -12.05±7.81 and -10.63±9.31 (P=0.84) respectively. Although, data showed that the effect of niacin persisted after discontinuation of the drug, longer follow up may prove a temporary effect.

All ocular complications occurred in the ischemic group. Neovascular complications developed in 30% of the ischemic group which is lower than the 60% rate reported in the natural history of ischemic CRVO.\textsuperscript{27} Duration of follow up seems to be adequate and this factors does not seem to have any influence on reduction of the neovascular complication rates because in the study reporting the natural history of the disease\textsuperscript{27} most, neovascular events occurred 3-4 months after vein occlusion and our patients had more 6 months follow up.

Patients with CRVO especially the ischemic type have a higher risk of cardiovascular events.\textsuperscript{26} Therefore, it is very important to diagnose and treat cardiovascular risk factors in these patients. There was a high rate of serum lipid abnormality in the current series and although the first step in treatment is modifying regimen and motility but because of its possible beneficial effects on ocular venous return, niacin may be indicated as a first line therapy. Use of niacin to prevent or treat atherosclerotic cardiovascular disease is based on strong and consistent evidence from clinical trials. Trials have shown that niacin monotherapy reduces myocardial infarction and cerebrovascular events. After long-term (15 years), follow-up, total mortality was also found to be decreased.\textsuperscript{30} Therefore, niacin may help improve serum lipid profile and reduce risk of cardiovascular accidents in addition to its effect on CRVO.

From an ophthalmologic point of view, niacin appears to be a relatively safe medication but one concern is induction of cystoid macular edema (CME) which was first described by Gass and subsequently documented in additional case reports.\textsuperscript{31,33} It occurs primarily in patients receiving more than 3 g/day niacin. Duration of treatment to cause CME is from 6 weeks to 1 year\textsuperscript{32} CME is most common in men in the third to fifth decades of life, and usually disappears within 2 weeks after discontinuation of the drug.\textsuperscript{33}

Mechanism of development of CME is unknown. A possible etiology is prostaglandin-induced toxic response of Muller cells or intracellular accumulation of fluid secondary to some as yet undetermined derangement of intracellular metabolism.\textsuperscript{34}
We were unable to document niacin induced CME in the current series because:

1. Fluorescein angiography is the only tool that may help differentiate between CME of CRVO with prominent vascular leakage from that induced by niacin without capillary permeability alterations and leakage and we did not perform it in all cases.

2. Niacin was used only for a short time that may not be enough for induction of CME. Patient #8 showed resolution of macular edema and vision improvement after niacin treatment for 3 months. He had persistent CME after radial optic neurotomy (RON) 8 months before niacin administration. In addition to 3 line increase in BCVA, focal field defect in primetry disappeared.

In this study, aspirin was used to reduce cutaneous reactions from niacin administration and to increase patient tolerance. As mentioned earlier, the vasodilatory effect of nicotinic acid seems to be mediated by release of endogenous prostaglandins and is dissociated from its lipid modifying effect. Aspirin, as a prostaglandin inhibitor, can reduce the vasodilatory effect of niacin on skin vasculature and also its potential vasodilatory effect on retinal vessels. The recommended dose of aspirin is 325 mg/day but we used aspirin with lower dose of (100mg/day) and for a short time because of its possible effect in counteracting niacin induced retinal vasodilation. Despite this low dose of aspirin, systemic side effects were mild and well tolerated. Role of systemic anticoagulation in CRVO is unclear, as there is no evidence that agents, such as aspirin or heparin, can prevent or alter the natural history of CRVO. However aspirin may act as confluent factor in this study.

Our study has the following limitations:

- It is not a blind study and significant bias may be present in data collection.
- Method of treatment may need to be modified. We are also not certain about the optimum dose of niacin and aspirin and about persistence of drug effects. Longer follow up may show reduced or even, rebound effect.
- Improved visual acuity on follow-up does not necessarily reflect a genuine visual improvement. Visual acuity measured at the first visit can be unreliable and deceptively poor, because the patient, having suddenly lost vision, may be emotionally upset and poorly cooperative. In due course, the patient learns by experience to read the test chart better, looking around and fixing eccentrically. This problem probably didn't affect results of the current study to a great extent, because the average duration of symptoms at presentation was 59.69±71.60 days (range 10-240 days) which seems more than adequate for adapting such behaviour.

- We did not use low vision chart. By use of routine E chart, poor visual acuity evaluation is prone to error. Qualitative measurement of RAPD is another defect of the study. Quantitative measurement by neutral density filters is more reliable.

- It may be difficult to evaluate the visual field in patients with low vision. MD may not be a suitable indicator of visual field sensitivity in these patients. (It was primarily introduced for glaucoma patients).

- A major limitation of our study is the lack of a well-matched control group to compare for the effect of natural course of the disease.

A randomized study with subgroup analysis based on timing of treatment and longer follow up is required to determine whether niacin actually improves visual outcome in CRVO.

**Conclusion**

Nicotinic acid treatment for 3 months led to a significant clinical improvement in eyes with CRVO and BRVO. Niacin use is well tolerated and is associated with mild systemic side effects. Niacin may possibly induce vasodilation either directly or by means of a prostaglandin mediated release of nitric oxide, a potent vasodilator. While a randomized clinical trial is needed to determine whether niacin actually improves visual outcome in CRVO and BRVO, we suggest niacin as a lipid modifying drug of choice for treatment of hyperlipidemia in patients with CRVO and BRVO.
References


بررسی اثر‌ریختی نیکوتینیک اسید در درمان انسدادهای وریدی شیکیه

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چکیده
هدف: بررسی اثر‌ریختی نیکوتینیک اسید (به عنوان متع مکمل اختمای عروق) در درمان انسدادهای وریدی شیکیه (انساد ورید مرکزی شیکیه (BRVO) و انسداد شاخهای ورید شیکیه).

مکان: دانشگاه علوم پزشکی مشهد، بیمارستان خانم‌الانبیاء (س).
طرح مطالعه: مداخله‌ای، آیین‌نامه‌گیر و غیرمقایسه‌ای.

روش و پیامدها: 22 پاتولوژی از 21 مبتلا به انسدادهای وریدی شیکیه (انساد ورید مرکزی شیکیه (BRVO) و انسداد شاخهای ورید شیکیه) تحت درمان با نیکوتینیک اسید (نیاسین) به مدت 3 سال قرار گرفتند. دوز نیکوتینیک اسید تدریجاً از 300 میلیگرم در روز به 3 گرم در روز افزایش یافت.

پایان‌ها: مدت پیگیری بطور متوسط 88/7 (حداقل 3 ماه و حداکثر 12 ماه) بود. میانگین دید اصلاح شده برای دور، تب از درمان پراپای 0/14/0/11 (درکه، 0/30/0/30) در درکه و 0/30/0/30 (درکه) با اینکه درکه، به پایان و زیمت پراپای 30/0/20 (درکه) در تمام پیامران، حدوداً 3 ماه بعد از درمان افزایش یافته. متوسط دید اصلاح شده در آخرین زیم پراپای 0/20/0/20 (درکه) در آخرین زیم پراپای، حدوداً 3 ماه بعد از درمان، البته از دو سوکوت شیکه، ادامه مادرکی، تماس دیسک و انسای و وریدی از بین رفت. شاخص انحراف متوسط AD (cotton wool spot) در پیامزی 24/4-24/7 (درکه) مالکا ادامه داشت. از دیسک و انسای و وریدی از بین رفت. شاخص انحراف متوسط AD (cotton wool spot) در پیامزی 24/4-24/7 (درکه) مالکا ادامه داشت. از دیسک و انسای و وریدی از بین رفت. شاخص انحراف متوسط AD (cotton wool spot) در پیامزی 24/4-24/7 (درکه) مالکا ادامه داشت.

نتیجه‌گیری: درمان سه ماهه نیکوتینیک اسید موجب بهبود بازی غرسگر و احیای ده که به خوبی در تمام پیامران تحمل شد. نتایج این مطالعه نشان می‌دهد که این دارو به عنوان یک جایگزین گیاهی موثر می‌تواند در درمان انسدادهای وریدی شیکیه از جمله انسداد ورید مرکزی شیکیه (BRVO) و انسداد شاخهای وریدی شیکیه کارآمد باشد.

کلمات کلیدی: نیکوتینیک اسید، نیاسین، انسدادهای وریدی شیکیه، انسداد ورید مرکزی شیکیه، انسداد شاخهای وریدی شیکیه

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