Original Research Paper

Volume - 10 | Issue - 12 | December - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Ophthalmology

PENTOXIFYLLINE: A BOON FOR ISCHEMIC AND INFLAMMATORY NEUROPATHIES

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ABSTRACT **AIM:** The aim of study was to compare the visual outcome in patients of optic neuritis given intravenous methyl prednisolone with and without oral pentoxifylline. **PATIENTS AND METHODS:** This was a randomized prospective interventional study. After obtaining ethical committee's clearance and informed consent, 60 patients were enrolled and divided into two groups, first group was given intravenous methyl prednisolone for 3 days with oral pentoxifylline 400 mg bd for 3 months and another group was given methyl prednisolone alone. Both the group were analysed using unpaired t test. GraphPad in stat 3 software programmers was used for statistical analysis. **RESULTS:** There was improvement seen in both the groups of patients however patients given pentoxifylline there was much more significant, continuous and sustained improvement in visual acuity till 3rd month of follow up. **CONCLUSION:** Pentoxifylline causes improvement in visual acuity by increasing the vascular supply of optic nerve and reducing the inflammation thus causing long-term improvement and prevent recurrence of the disease.

KEYWORDS : Optic Neuritis, Visual Acuity, Methyl Prednisolone, Pentoxifylline.

INTRODUCTION

Optic neuritis is an inflammatory condition affecting the optic nerve, usually affecting young adults, especially females, between 18 and 45 years of age. Although it has been reported from almost all parts of the world, regions with the highest incidence include northern Europe, southern Australia and middle part of North America.[1,2]

Most of the cases are idiopathic in nature; however, it could be associated with demyelinating lesions, of which multiple sclerosis (MS) is the most common cause. Other less common etiologies include infectious and para-infectious causes, inflammatory and para vaccination immunological responses.

Typical optic neuritis in adults usually presents as acute monocular loss of vision progressing over several hours to days, often associated with ocular pain that worsens on eye movement. Presenting vision can range from 20/20 with mild visual defects to no light perception. A Study reported a vision of 20/20 or better at presentation in 10.5% of the patients of optic neuritis, and no perception of light in 3.1% of the cases.[3] Although vision loss is usually monocular, involvement of both eyes can occur, usually in children.[4] A relative afferent pupillary defect is present in almost all unilateral cases, but absence of the defect suggests a pre-existing or coincident optic neuropathy in the fellow eye. Although retrobulbar optic neuritis is more common,[5] quite a substantial proportion of patients have disc edema (papillitis) .A variety of visual field defects ranging from commonly seen diffuse depression and centrocecal scotoma to rarely seen quadrantic defects and altitudinal defects are present in patients with optic neuritis. Subnormal color vision or contrast sensitivity is noted in the affected eye and at times in the fellow eye and is suggestive of subclinical involvement of the fellow eye. Atypical features include absence of pain, which may be seen in only 8% of the patients with typical optic neuritis; marked swelling of the nerve with retinal exudates and peripapillary hemorrhages; severe visual loss to no light perception; progression of visual loss or pain for more than 2 weeks; and lack of recovery after 3 weeks.[6,7,8] Bilateral optic neuritis may occur, either simultaneously or sequentially,[9] which would also be an unusual feature in typical optic neuritis.[10] Patients with atypical optic neuritis are at lower risk of developing MS and should be extensively evaluated for other causes of optic neuropathy.

Optic neuritis usually improves on its own. In some cases, steroid medications are used to reduce inflammation in the optic nerve. Possible side effects from steroid treatment include weight gain, mood changes, facial flushing, stomach upset and insomnia.

Steroid treatment is usually given intravenously. Intravenous steroid therapy quickens vision recovery, but it doesn't appear to affect the amount of vision you'll recover for typical optic neuritis.

Now Pentoxifylline is a phosphodiesterase inhibitor .[11] It decreases viscosity of the whole blood which results in improved microcirculation.[12] Due to its phosphodiesterase inhibition effect, cyclic adenosine monophosphate (cAMP) levels increase in erythrocytes, endothelium, and surrounding tissues. [13]

It also has immunomodulatory properties which results in vascular endothelial stabilization and autoimmune inhibition.[14] It decreases peripheral nerve injury by preventing free radical production by neutrophil inhibition and decreasing the levels of cytokines, malondialdehyde and myeloperoxidase.[15]

It had been used in several studies to restore the normal function of the vasa vasorum.

Studies showed oral pentoxifylline causes functional improvement in visual acuity without causing any gross structural change in optic disc.[16,17] It also has important role in microcirculation regulation and intravascular cell dynamics. It is also known to increase whole blood filtration rate and deformability of erythrocytes and polymorphonuclear leucocytes in the tissues. [18]

MATERIAL AND METHODS

The study was a hospital based randomized , prospective, interventional study which included all patients diagnosed with optic neuritis at Department of Ophthalmology, G.S.V.M Medical college and LLR hospital, Kanpur, Uttar Pradesh, India. The study and data accumulation were carried out with the approval from the Ethical committee , GSVM Medical College , Kanpur . A total of 60 patients were enrolled and followed regularly till 3 months. All participants provided informed consent to participate in this study was conducted with the Declaration of Helsinki.

INCLUSION CRITERIA

- Patients diagnosed with optic neuritis.
- Patients who give consent for above treatment.

EXCLUSION CRITERIA

- Patients unwilling to participate.
- Known case of diabetes.
- Patient having other neurological diseases.

- Patients having any ocular pathology other than optic neuritis
- Patient contraindicated for steroids.
- Patients less than 15 years of age.
- Patients having any ocular trauma.
- Patients who fail to follow up.

MATERIALS

The diagnosis was made by

- SNELLEN'S CHART AND ETDRS CHART
- APPLANATION TONOMETER
- COLOUR VISION BY ISHIHARA CHART
- CONTRAST SENSTIVITY BY PELLI ROBSON CHART
- SLIT LAMP EXAMINATION WITH +'90' D LENS
- INDIRECT OPHTHALMOSCOPE WITH +20D LENS
- FUNDUS IMAGE CAMERA
- SPHYGMOMANOMETER
- GLUCOMETER

METHODS

Detail history and examination was done with regards to following points of interest

- Visual acuity and best-corrected visual acuity (BCVA) by Snellen's chart and EDRS chart.
- Colour Vision by Ishihara chart
- Contrast sensitivity by Pelli Robson chart.
- Intraocular pressure by Applanation tonometer
- Anterior segment evaluation by slit lamp and optic disc and macula examination by slit lamp and +90D lens
- Contrast sensitivity by Pelli Robson Chart
- Indirect ophthalmoscope examination with +20D lens
- Fundus image of the patient by fundus camera
- Random Blood Sugar by glucometer
- Blood pressure by sphygmomanometer

A standardized ophthalmological examination was performed at baseline, first three days of IV methyl prednisolone, 1 week, 2 week, 1 month and 3 month after dividing the patients into 2 groups:

Group 1: Patient of optic neuritis given 1-gram IV methyl prednisolone in 250 ml of dns for 3 consecutive days followed by oral steroids alone.

Group 2: Patients of optic neuritis given 1-gram IV methyl prednisolone in 250 ml of dns for 3 consecutive days followed by oral steroids and oral pentoxifylline 400mg BD for 90 days.

STATISTICS

For assessing improvement in visual acuity between both the study group from pre-treatment value to the final value at 12 weeks unpaired t –test was applied.

Significant level at 95% confidence limit was kept at 0.05.

GraphPad in stat 3 software program was used for statistical analysis. Value of α error for the study was 5%.Power of the study was 80%. For sample size calculation for the study, following formula was used-

Number of patients $\{n\} = \frac{2x\left(z\left(1-\frac{\alpha}{2}\right)-z\beta\right)^2 x\sigma^2}{\Delta^2}$

Where α=significance level; β= power, probability of detecting a significant result; σ=SD of data; Δ= size of difference. p-value of <0.05 was considered significant at 95% confidence interval.

RESULTS

Mean improvement in LogMAR visual acuity in both groups over 3 months were as follows:

TABLE 1

	Pre-treatment logmar	Post 3 days	Post 1 week	Post 2 weeks	Post 1 month	Post 3 months
Mean Logmar visual acuity in pts on methylprednisolone and pentoxifylline	1.32± 0.49	0.87± 0.31	0.87± 0.31	0.80± 0.28	0.45± 0.25	0.29± 0.22
Mean Logmar visual acuity in pts on methylprednisolone	1.18± 0.37	0.81± 0.29	0.81± 0.29	0.74± 0.31	0.63± 0.31	0.63± 0.31

LogMAR mean visual acuity of the group given oral pentoxifylline with intravenous methyl prednisolone showed significant improvement from 1.32±0.49 to 0.29±0.22 . The group given only intravenous methyl prednisolone also showed significant improvement in LogMAR mean visual acuity from 1.18±0.37 to 0.63±0.31 over the total duration of 3 months.

Un-Paired t-test was applied between 2 groups which showed significantly improved LogMAR visual acuity ($p<0.05$) in patients receiving pentoxifylline along with methyl prednisolone as compared to patients who received only methylprednisolone from the pre-treatment value to final acuity at 3 months.

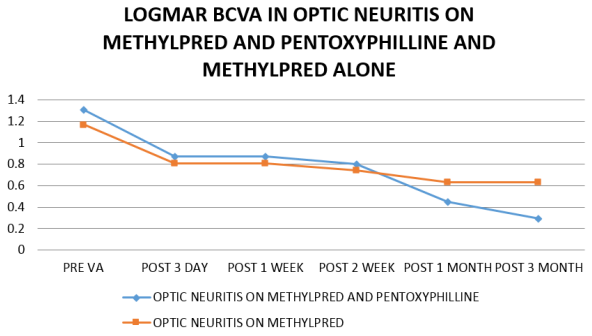

FIGURE 1: Graphical representation of the above data showing gradual improvement in visual acuity.

DISCUSSION

The study conducted clearly shows that when pentoxifylline administered orally along with intravenous methyl prednisolone is much more efficacious treatment option for optic neuritis as compared to intravenous methyl prednisolone alone.

This improvement in visual acuity is owing to the fact that there is significant improvement in LogMAR visual acuity in both the groups of patients however in patients given both intravenous methyl prednisolone along with oral pentoxifylline there is a continuous uniform improvement in visual outcome from day 1 of post treatment till 3 months of our follow up as compared to patients given intravenous methyl prednisolone alone which showed improvement in visual outcome till 1 month of follow up but it remained same on further follow up of patients till 3 months.

In addition, pentoxifylline caused improvement in visual outcome without producing any serious systemic and ocular side effects and is much more well tolerated by the patients.

CONCLUSION

There are many hypothesis regarding the mechanism of action of pentoxifylline and its cellular and molecular effects, based on human and animal studies. This includes effects on immune modulation, anti-tumor necrosis factor-α (TNF-α) effects, hemorheological effects, anti-fibrinolytic effects, along with effects on endothelial cells and adhesion molecules.

All these properties can be used for accelerated and enhanced improvement in neuropathies caused due to inflammation and vascular insufficiencies when used along with steroids like radiation-induced neuropathy, post infections neuropathies (HIV neuropathy) and many more.

LIMITATION

- Small study group.
- Short duration of follow up.

FUNDING

No funding received for the study either from government or from any private organization.

CONFLICTING INTEREST STATEMENT

No conflict of interest among the investigators and authors.

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