VISUAL FIELD DEFECTS IN PATIENTS OF TUBERCULOSIS ON ETHAMBUTOL

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ABSTRACT

BACKGROUND

Ethambutol causes retrobulbar neuritis that is related to the dose and duration of treatment, hence we undertook a prospective study of optic nerve function in patients on ethambutol.

MATERIALS AND METHODS

This study was conducted with a sample size of 100 patients. Patients diagnosed who were having tuberculosis and to be started on ethambutol along with other ATT drugs according to RNTCP regimen underwent detailed relevant history, examination and investigation. The best corrected Visual Acuity (VA), Colour Vision (CV) with Ishihara and visual field examination with Interzeag Octopus 1-2-3 automated perimeter were recorded and repeated every month. Mean Cumulative Dose (MCD) of ethambutol was calculated for each patient and statistical significance was done using Chi-square and paired t-test.

RESULTS

Out of 160 eyes (20 lost for follow up), 10 (6.25%) eyes developed Visual Field Defects (VFD) and abnormal VA was present in 10 (6.25%) eyes. MCD of patients with abnormal VA was more than MCD of patients with normal VA, but the difference was not statistically significant. CV abnormalities were present in 6 (3.7%) had strong association with VFD ($p<0.00001$) was dose dependent ($p<0.001$).

CONCLUSION

The study has demonstrated that visual field testing by automated perimetry is more sensitive and specific for detecting early ocular toxicity of ethambutol as compared to VA testing. The toxic effect of ethambutol on the eye can't be predicted on an individual basis, there is a need for a complete ocular evaluation of every patient on ethambutol.

KEYWORDS

Tuberculosis, Ethambutol, Visual Field Defect.

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BACKGROUND

Apart from the direct ocular manifestations of tuberculosis, visual loss can occur during treatment with drugs that have potential ocular toxicity.

Ethambutol can produce a retrobulbar neuritis that is related to the dose and duration of treatment.[1] Though retrobulbar neuritis is considered to be rare and reversible when treatment guidelines are adhered to, optic neuritis has been reported even when guidelines for 'safe doses' are followed. Extensive literature review revealed very few reports from India.[2] Hence, we undertook a prospective study of optic nerve function in patients on ethambutol.

AIMS

1. To determine the effect of cumulative dosage of ethambutol on visual fields.
2. To determine the association of age and sex on visual fields in patients on ethambutol.
3. To determine the association of smoking, anaemia and diabetes on visual fields in patients on ethambutol.

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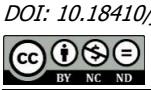


MATERIALS AND METHODS

This study was undertaken in a tertiary care teaching hospital. Sample size of 100 patients obtained by simple random sampling were enrolled. Patients diagnosed to have clinical tuberculosis confirmed by investigations and to be started on ethambutol along with other antitubercular drugs according to Revised National Tuberculosis Control Programme (RNTCP) regimen were enrolled in the study.

A detailed history of smoking and alcohol intake, history of any drug intake and past history of ocular disease if any, was taken. An informed consent was obtained for every patient. Investigations for diabetes mellitus, anaemia and renal function were carried out.

A detailed slit lamp examination including pupillary reflexes and funduscopy was performed. The intraocular pressure was recorded with the applanation tonometer. The best corrected visual acuity for distance and near was recorded for each eye separately. Colour vision was noted in each eye using the pseudoisochromatic plates of Ishihara. Visual field examination was conducted with Interzeag octopus 1-2-3 automated perimeter. The following protocols

were observed- the GIX program with a white on white, Goldmann size III target was used for visual field evaluation. All the patients underwent full threshold (normal) strategy. Examination was repeated until reliable fields were obtained. Only those fields that were reliably performed were included in the analyses.

Exclusion Criteria

Patients with CNS manifestations of tuberculosis-like meningitis, tuberculomas, etc., patients on drugs having known neurotoxic effects. Patients having lenticular opacities more than grade II according to the lens opacities classification system(LOCS) classification. Patient with known colour vision defects were excluded from the study.

Following the above criteria, 100 patients (200 eyes) were enrolled in the study out of which 20 patients were lost for follow up.

All the 80 patients were followed up at monthly intervals till the patient was taking ethambutol. Any symptoms of blurring of vision while on treatment were reviewed and assessed. Visual acuity, colour vision, pupillary reflexes, fundus and visual fields were assessed at each visit. Any single line drop in best corrected visual acuity with stable refraction was considered abnormal and was documented.

Any patient who misinterpreted or failed to recognise two or more colour plates was regarded to have colour vision defects.

A reliable visual field, which showed depression of thresholds by 5 dB or more in 3 or more contiguous points in the central, paracentral or centrocecal areas was considered abnormal. Also, field which showed depression of thresholds of 5 dB or more in 3 or more contiguous non-edge points as compared to their mirror image points across the horizontal meridian, i.e. nerve fibre bundle defects was considered abnormal. The association of age, sex, smoking, anaemia and diabetes with visual fields in patients on ethambutol was tested using Chi-square test and the numerical variables were tested with Student's t-test.

RESULTS AND ANALYSIS

160 eyes of 80 patients were analysed. The patient's ages ranged from 16-67 years. The male/female ratio was 1.96:1.

Groups	Cumulative Dose	Number of Patients
I	0-29 g	21 (26.25%)
II	30-59 g	17 (21.25%)
III	60-89 g	11 (13.75%)
IV	90-119 g	23 (28.75%)
V	120-150 g	8 (10%)
Total		**80 (100%)**

Table 1. Group Distribution According to Cumulative Dose

The cumulative dosage received by each patient was calculated at each visit and the final cumulative dosage arrived at when the drug was stopped. Patients were grouped from I to V depending on cumulative dose of ethambutol received.

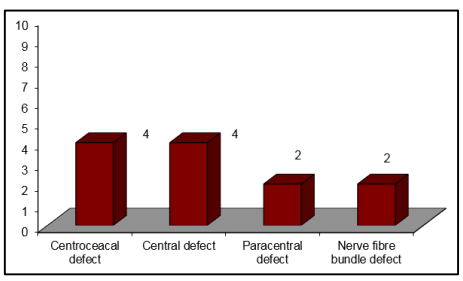
All the patients who developed toxicity had round, regular and reactive pupil as they had bilateral involvement. The fundus of patients showed normal optic disc and macula, which explains retrobulbar nature of the condition.

Groups	Number of Eyes	Percentage	Normal Visual Field	Percentage	Abnormal Visual Field	Percentage
I	42	26.25%	42	100%	0	0%
II	34	21.25%	34	100%	0	0%
III	22	13.75%	16	72.72%	6	27.27%
IV	46	28.75%	42	91.30%	4	8.6%
V	16	10%	16	100%	0	0%

Table 2. Effect of Visual Fields in Patients on Ethambutol

Visual field defects were seen in a total of 10 (6.25%) patients. Table 2 shows the visual field defect picked up by the automated perimetry. In groups I, II and V, no visual fields abnormalities were found. In group III (27.27%) and group IV (8.6%) visual field abnormalities were seen.

All the eyes, i.e. 6 eyes with colour vision defect had abnormal visual field and 4 eyes with abnormal visual field defects had no colour vision defect. Graph 1 shows out of 10 (6.25%) eyes who developed visual field defects.



Graph 1. Type of Visual Field Defects in Patients on Ethambutol

Graph 1 shows out of 10 (6.25%) eyes who developed visual field defects, (40%) had centrocecal defects, (40%) central defect, (20%) had paracentral defects and (20%) had nerve fibre defect.

The MCD received by patients with visual field abnormalities was 89.28 g, which is higher than the MCD received by patients with normal visual field, i.e. 66.14 g. This is statistically significant at the level of $p<0.001$ stating that this is dose dependent.

Abnormal visual acuity was present in 10 (12.5%) eyes out of 160 eyes of patients on ethambutol. These effects were statistically significant at the level of p value less than 0.000001. The mean cumulative dose of patients with abnormal visual acuity was 77.6 g, which is more than mean cumulative dose of patients with normal visual acuity, i.e. 66.67 g. But, this is not statistically significant concluding that this parameter of optic nerve function is not dose-dependent bundle defect.

Colour vision abnormalities were present in 6 (3.75%) eyes of 160 on ethambutol. There is a strong association

between colour vision abnormalities and visual field defects. (p<0.00001). The mean cumulative dose received by patients who developed colour vision abnormalities was 81.6 g, which is more than the mean cumulative dose received by patients who had normal colour vision, i.e., 67.04 g. This was a significant difference (p<0.001) concluding that this association is dose dependent.

In the younger age group of less than 40 years, out of 106 eyes, 2 eyes (18%) developed visual field defect, whereas in age group >40 years, 8 eyes of 44 eyes developed visual field defects, which was significantly high (P<0.0009). Though patient's age more than 40 years received a mean cumulative dose of 75.04 g, which is higher than the mean cumulative dose received by younger age group, i.e. 67.33 g, this is not statistically significant.

The male patients received a mean cumulative dosage of 77.56 g, which is higher than the female patients who received a mean cumulative dosage of 63.73 g, but there is no statistical difference.

29 (36.25%) of the patients were smokers and 51 (63.75%) were nonsmokers. 6 eyes (3.75%) of smokers developed visual field abnormalities whereas 4 eyes (2.5%) of non-smokers developed visual field abnormalities. It was found that smoking and visual field abnormality didn't go hand in hand.

Out of 40 eyes of 20 patients of anaemia, 2 (5%) developed visual field defects. Out of 112 eyes of 80 patients of non-anaemics, 8 (6.6%) eyes developed visual field defects, but no statistical significance was observed.

Out of 80 patients, 11 patients (15%) were diabetes and 56 patients (85%) were nondiabetics. 2 (8.3%) eyes of 11 patients showed visual field abnormalities. 8 (5.8%) eyes of 56 patients showed visual field abnormalities The mean cumulative dose received by nondiabetics was 72.48 g while mean cumulative dose of diabetics was 69.6 g, but difference was not significant.

DISCUSSION

Visual acuity was tested using Snellen's optotypes. Of the 160 eyes examined, 150 eyes had no alteration of visual acuity. Ten eyes (12.5%) showed a drop in visual acuity ranging from one line to three lines on Snellen's chart. These patients received ethambutol at a mean cumulative dose of 77.6 g (30 mg/kg on alternate day). This drop in visual acuity was not statistically significant concluding that abnormal visual acuity was not dose dependent.

In a study by Leibold et al analysing patients with ethambutol toxicity, visual acuity ranged from 6/30 to the ability of counting fingers at close range only at a dosage of 43 mg/kg/day. However, in the same study, it was found that in low dosage group, i.e. less than 30 mg/kg/day, only two patients (3.38%) developed toxicity. Visual acuity loss ranged from 6/12 to 6/30.[1] However, the present study has found no dose-dependent visual loss.

Citron et al had concluded that routine testing of visual acuity during ethambutol therapy was unhelpful, since ocular toxicity may occur without changes in visual acuity, and small changes in visual acuity maybe seen, which do not reflect toxicity similar to our study.[3]

Bobrowitz et al in a study of comparison of Eth-INH Vs. INH-PAS in original treatment of pulmonary tuberculosis commented that there were many patients in his study in whom there were fluctuations in the reading of the Snellen's eye chart. He concluded that these variations occurred with similar frequency in all regimens with or without ethambutol. These fluctuations probably do not reflect the side effect of the drugs, but rather the influence of other factors among which one might include factors like patient fatigue, intelligence and cooperation, variations in lighting conditions at the time of testing, technical errors, temporary refractive error due to temporary changes in the refractive indices of the eye during treatment. Further, he emphasised that a drop in visual acuity from optic nerve or retinal damage would be expected to show associated changes in the visual field pattern. If this did not take place, there was no certain visual toxicity in the cases.[4]

Harcombe A et al supported the view of British Thoracic Society that routine visual acuity testing is unhelpful in detecting toxicity, but it may serve as a useful reminder to both patient and doctor particularly during prolonged courses of treatment that ocular complications remains a potential problem.[5]

Colour vision was tested using the pseudoisochromatic plates of Ishihara. Out of 160 eyes, six eyes (3.75%) showed colour vision abnormalities. The mean cumulative dose of patients who developed colour vision defect was 81.6 g, which is higher compared to patients with normal colour vision, i.e. 67.04 g. This is statistically significant (p<0.001) concluding that this is dose dependent.[1]

Leibold et al[1] reported colour vision defect in 7 patients (11.86%) taking ethambutol at a dose of 43 mg/kg/day. He reported that all the patients lost the ability to see green colour while a few had difficulty with red. In patients taking ethambutol less than 30 mg/kg/day, only two patients (3.38%) developed colour vision abnormality. This correlated well with the present study, which also has found significant dose-dependent relation of colour vision defect with ethambutol.

Woung et al studied 36 ethambutol-induced axial optic neuropathy over a three year period. They assessed colour vision 100 Hue test 6 and reported 14 eyes (38.3%) with deuteron/tritan defect.[6] Kaimbo et al studied the colour vision defect in patients on ethambutol and found normal colour vision when measured by the Ishihara pseudoisochromatic plates, but 7% abnormality in colour vision testing using d-15 test and 36% using Farnsworth-Munsell 100 Hue test.[7] Since, the present study was done using the Ishihara pseudoisochromatic plates, the subtle colour vision defects may not have been detected.

The effect of ethambutol on central 30° visual fields was studied with automated static perimetry using Octopus 1-2-3. Of the 160 eyes tested, only 10 eyes (6.25%) showed field defect in the form of relative centrocecal defect, central defect, paracentral defects and nerve fibre bundle defect. Mean cumulative dose of patients with visual field defect was

89.28 g, which is higher than the mean cumulative dose of patients with normal visual fields. This is statistically significant ($p<0.001$) concluding that these defects were dose dependent.

Woung et al observed paracentral scotoma, arcuate scotoma and enlargement of blind spot in 58.6% patients with established ocular toxicity over a 3 year period.[6]

Loss of visual acuity correlated significantly well with visual field defects ($p<0.000001$) and colour vision defects also showed strong correlation with visual field defect ($p <0.0001$). In the present study, the incidence of visual acuity loss was not dose dependent, whereas that of colour vision abnormality and visual field defects were dose dependent.

Taking all the three parameters of optic nerve function, ethambutol toxicity was seen in 6.25% of eyes on standard drug regimen of 30 mg/kg on alternate day in our study.

However, patients who received MCD of 120 mg - 150 mg in this study did not develop any abnormality, this can be deduced two ways. The subset of patients in this category was 10%, which is not sufficient to conclude and again one may also conclude that ethambutol toxicity is unpredictable and an idiosyncratic reaction may cause neuritis at so called safe doses.

In one report by Carr et al among 18 patients treated with ethambutol at 60-100 mg/kg per day, eight patients (44.4%) developed toxicity.[8]

Leibold et al reported the incidence of ethambutol toxicity depending on dosage. It was found to be 18% in patients taking ethambutol more than 35 mg/kg/day, 5% in patients on 25 mg/kg/day, 3% among those on 20 mg/kg/day while negligible toxicity was seen in patients taking ethambutol 15 mg/kg/day stressing the importance of dosage on toxicity.[1]

Krishnaswamy et al did not find any case of retrobulbar neuritis in their series of number of patients while Roy et al and Sharma et al found 3% toxicity in cases using 25 mg/kg/day. On the other hand, Narang et al in their study of 640 cases treated by ethambutol 25 mg/kg/day along with a companion drug came across only four cases (0.62%) of retrobulbar neuritis.[9]

Mathur et al reported 6.3% ocular toxicity when the drug was given in dose of 20 mg/kg/day.[9]

Though previous reports stated that ethambutol toxicity is virtually negligible in patients on dosage of 15 mg/kg/day in several recent series, patients experienced severe, irreversible vision loss from ethambutol toxicity. Vision loss occurred often despite frequent and regular monitoring.[10]

Kumar et al described a series of seven patients treated with 25 mg/kg/day. All patients experienced sudden onset of decreased vision despite careful ophthalmologic follow-up.[2]

Tsai and Lee described 10 patients with ethambutol toxicity who were treated with presumably 'safe' dosage of ethambutol.[11]

In our study, we found an incidence of ethambutol toxicity in 6.25% of patients at a dosage of 30 mg/kg on alternate day, which is higher compared to the above reports described. When the above studies are analysed, it is found that the toxic effect of ethambutol on the eye is highly unpredictable and probably idiosyncrasy also could play a part.

A cumulative dose of 150 g is considered critical dose for ethambutol toxicity.[12] Patients who developed ethambutol toxicity in this study received cumulative doses less than 150 g, i.e. an average of 89.28 g (range 72-115.2 g). Eight eyes (15.38%) of more than 40 years of age developed ethambutol toxicity. The visual field defects seen were centrocecal defect, central defect, paracentral defects and nerve fibre bundle defect. The mean cumulative dose of patients with visual field defect was 89.28 g, which is higher than the mean cumulative dose of patients with normal visual fields. This is statistically significant ($p<0.001$) concluding that these defects were dose dependent.

Woung et al observed paracentral scotoma, arcuate bundle defect statistically significant ($p<0.0009$)[7]. This finding is in concurrence with the study by Filipouie et al, who concluded that older age is a significant risk factor for the development of toxic optic neuropathy.[13]

6 eyes (5.3%) of males and four eyes (7.4%) of females developed ethambutol toxicity. Our study showed that gender had no association with ethambutol toxicity. However, in a Korean study, males were found to be more susceptible than females.[14]

Only two diabetic eyes (8.3%) developed ethambutol toxicity. On the contrary in a study by Carr E. R. et al, they found a statistically significant association between diabetes and ethambutol toxicity.[8]

CONCLUSION

The present study however, had few shortcomings of a small sample size, short period of observation, automated perimetry done with only white target and not colour targets and colour vision being tested on Ishihara's plate instead of the far more sensitive Farnsworth-Munsell 100 Hue test.

Nevertheless, the present study has conclusively demonstrated the fact that visual field testing by automated perimetry is far more sensitive and specific for detecting early ocular toxicity of ethambutol as compared to visual acuity testing. Indian eyes were found to have toxicity at lower mean cumulative dose as compared to Western eyes. Since, the toxic effect of ethambutol on the eye can't be predicted on an individual basis, there is a pressing need for a complete ocular evaluation of every patients on ethambutol. Thus, a detailed periodic eye checkup must be made an integral part in the management of tuberculosis of every patient.

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