Efficacy of Vitamin Supplementation in Preventing Color Vision Abnormalities among Patients Undergoing DOTS for Tuberculosis

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ABSTRACT

Objective: To determine if vitamin supplementation can prevent the development of color vision abnormalities in patients taking ethambutol as part of DOTS for tuberculosis (TB).

Methods: A randomized, placebo-controlled, single-blind clinical trial was conducted among newly diagnosed category-1 TB patients enrolled in DOTS health centers in the third district of Manila from June 2011 to August 2012. Before starting therapy, the participants underwent a complete eye evaluation including baseline color vision tests using the Ishihara Color Vision Plates (Ishihara), Farnsworth Panel D-15 (FD 15), and Lanthony Desaturated D-15. Only subjects who passed the three color vision tests were included in the study. They were divided into 2 groups: Group A received vitamin supplementation and Group B received a placebo. Follow-up color vision testing was done monthly for 3 months.

Results: There were 105 patients included in the study, 77 males and 28 females, age ranging from 16 to 68 years with a mean of 37 years. Forty three (43) patients received vitamin supplementation (group A) and 62 received placebo (group B). After one month of DOTS, 5 of 43 patients (11. 6%) in group A and 10 of 62 patients (16.1%) in group B developed color vision abnormalities, detected only with the Lanthony Desaturated test. The absolute risk reduction (ARR) of color vision abnormalities by vitamin supplementation was 4.5%, with the number needed to treat (NNT) of 23. After the second month of therapy, ARR was 7.4% and NNT was 14. ARR was highest in the third month at 8.3%, with a corresponding decreased NNT of 12. Among patients who developed color vision abnormalities, reversal of the abnormalities was observed in 80% of 5 subjects in group A, and 40% of 10 patients in group B. By the third month of treatment, all in group A already had normal color vision, while 40% in group B still showed abnormal color vision.

Conclusion: This study showed that vitamin supplementation was effective in reducing the risk of, and in reversing cases of, color vision abnormalities among patients undergoing DOTS therapy for tuberculosis.

Keywords: DOTS, Tuberculosis, Ethambutol, Vitamin B, Color Vision, Optic Neuritis

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Tuberculosis (TB) is a significant health problem, especially in the Philippines where it is the 6th leading cause of morbidity and mortality.[1,2]

Various anti-TB drugs are currently in use, the most common being isoniazid, pyrazinamide, rifampicin, and ethambutol. Of these, ethambutol hydrochloride, a bacteriostatic drug, has been implicated as a cause of toxic optic neuropathy. Toxicity has been reported to occur in 1-5% of patients, with symptoms manifesting 2-8 months after start of therapy. Lim et al[3] reported 3 cases where intake of ethambutol was associated with the development of central or cecocentral scotomas, bitemporal field defects, and even permanent vision loss.

The possible mechanism by which ethambutol causes optic neuropathy was elucidated by Noche et al[4] in a local study done in 1987. The authors postulated that ethambutol and its metabolites formed a complex with zinc and copper. These complexes then entered axons and the increased influx of ions caused a corresponding increased hydration and axonal swelling. Another mechanism might be the effect of ethambutol activating intracellular enzymes resulting to cell membrane damage and vacuolation[5].

A study by Cruz and colleagues showed that color vision abnormalities were detected by the Lanthony Desaturated test in as high as 46% of patients undergoing DOTS therapy for TB. Since none of the patients who developed these color vision abnormalities complained of blurring of vision at the time the color vision abnormalities were detected, the authors suggested that color vision testing may be a good screening tool to monitor for early ocular toxicity of anti-Koch's therapy.[6]

Early detection of toxicity is important because other than stopping the drug, no specific treatment is available. Visual improvement and recovery usually occur after discontinuation of therapy, but this may take weeks to months. There are reports that vision may continue to decline or fail to recover even when the drug is stopped, if damage is severe enough.[7] It is possible that late detection and late discontinuation of the offending drug can lead to permanent damage.

The B complex vitamins have been recommended to prevent the toxic effects of ethambutol, and are often given together with the anti-TB treatment. However, there is a paucity of clinical data on its value in preventing or reversing the toxic effects of ethambutol.

This study determined if vitamin supplementation can help prevent color vision abnormalities, which may be an early manifestation of optic nerve toxicity, among patients undergoing DOTS for tuberculosis.

MATERIALS AND METHODS

A randomized, placebo-controlled, single-blinded, clinical trial was conducted among newly diagnosed category-1 TB patients enrolled in DOTS health centers (Lanuza, Fugoso, Dimasalang, and San Nicolas) in the third district of Manila from June 2011 to August 2012. The study protocol was approved by the Department of Ophthalmology of Jose R. Reyes Memorial Medical Center (JRMMC), Manila Health Department, and the Division of Tuberculosis control. A total of 105 newly diagnosed category one TB patients, as identified and classified by the stern criteria set by the WHO-DOTS program, were included.

The local DOTS health center provided the drugs for free and made sure the patients took them as prescribed. For the first 2 months, the patients were given a fixed dose combination of 4 drugs– pyrazinamide (400 mg), ethambutol (275 mg), isoniazid (75 mg), and rifampicin (150 mg). After 2 months, if repeat sputum examination revealed negative results, the treatment was reduced to isoniazid and rifampicin. For those with positive sputum, quadruple therapy were extended for another month or until sputum exam turned negative. A DOTS health center staff administered the medicine everyday to ensure 100% compliance with the therapy.

Participants who were at least an elementary graduate were examined at the out-patient department of JRMMC. Informed consent was obtained after thorough explanation of the nature and possible benefits of the study. The participants underwent an eye evaluation consisting of detailed history, best-corrected visual acuity (Snellen chart converted to decimal system), direct funduscopy, anterior-segment slit lamp biomicroscopy, applanation tonometry. The height and weight of the patients were also obtained to compute the body-mass index (BMI), and categorized using the WHO classification as underweight (<18.5), normal (18.5 to 24.9), overweight (25 to 29.9), or obese (30 or greater).

Exclusion criteria included patients who had category-2 TB (multidrug resistant); had undergone

previous anti-TB therapy; had other ocular disease that may alter the parameters being investigated; were taking oral contraceptives, digoxin, and other medications implicated in causing color-vision deficiency; and had color-vision deficiency at baseline.

After the eye evaluation, patients were grouped into two via toss coin method. Group A received a fixed dose of vitamin B complex plus vitamin E and folic acid (vitamin B_1- 300 mg, vitamin B_6 - 300 mg, vitamin B_{12} -1 mg, vitamin E - 100 IU, folic acid - 1 mg) and group B received a placebo drug. Baseline color vision examination was done before the start of the therapy using the full series of the Ishihara Color Vision Plates (Ishihara), Farnsworth Panel D-15 (FD 15), and Lanthony Desaturated D-15 (Lanthony). Testing methods were as follows:

Testing with the Ishihara was done in a room with adequate light. The participant was positioned with the color-vision plates held 75 centimeters away and tilted so that the plane of the paper was perpendicular to the line of vision. A normal reading of all plates was deemed normal. If a subject read 9 or fewer plates correctly, color vision was regarded as deficient.[8]

The FD15 and Lanthony tests were done using the Color Vision Recorder software, version 4 (Optical Diagnostics, Netherlands), and an Acer 4740G computer. The screen color was calibrated based on the standards set by the International Color Consortium (ICC).

In these color-arrangement tests, the subject was offered a series of colors that needed to be sorted either in a sequence or into groups. The patient's task was to identify the cap that most closely resembled the reference cap in color and place it next to the reference cap. This process was repeated until all removable caps were placed in color order. For both FD15 and Lanthony tests, a horseshoe diagram was drawn which was a graphical presentation of the cap order. The type of color deficiency was determined from the horseshoe diagram by evaluating in what directions the crossings were made. The final diagnosis consisted of two parts—the pass/fail diagnosis, which was automatically set by the software based on the number of errors made by the patient, and the type of color deficiency of the patient determined by unresolved crossing. [9]

Both tests were conducted once. Patients requiring assistance with clicking or dragging the mouse were helped while taking care not to affect their responses.

Only participants who passed all three baseline color vision tests were allowed to go on with the study. These participants were each given fourteen pieces of either the placebo or the vitamin supplement to be taken once a day for two weeks. They were asked to come back once they finished taking all the tablets, and were given another set. Color vision examination was done every month thereafter up to three months into their therapy. A single investigator assessed the color vision using Ishihara, FD15, and Lanthony tests. Subjects were tested binocularly while wearing best correction.

Patients who incurred absences within the time period were not dropped from the study as intent-to-treat was part of the data analysis. The patients who failed in either one of the three examinations were kept in the study and subjected to close follow-up for any improvement or deterioration until they completed the three month period.

Statistical Analysis

Sample-population calculation was performed to ensure validity of the target number of subjects. The demographic and clinical data were collated and analyzed and differences between baseline and follow-up findings were noted, with p value equal to or less than 0.05 considered statistically significant. Absolute risk reduction (ARR) and number needed to treat (NNT) were calculated to determine the association of vitamin supplementation in reducing risk of color abnormalities.

RESULTS

There were 105 patients included in the study, 77 males and 28 females, age ranging from 16 to 68 years, with a mean of 37 years (Table 1). Forty three patients received vitamin supplement (group A) and 62 received placebo (group B) for three months.

After one month of DOTS, 5 of 43 patients (11.6%) in group A and 10 of 62 patients (16.1%) in group B developed color vision abnormalities. The abnormalities were only detected using the Lanthony test. The absolute risk reduction (ARR) of color vision abnormalities by vitamin supplementation was 4.5%,

with the number needed to treat (NNT) of 23. For the second month, ARR was 7.4%, higher than the first month and NNT decreased to 14. ARR was highest in the third month with 8.3%, with a corresponding lowest NNT of 12 (Table 2). Among patients who developed color vision abnormalities, reversal of the abnormalities was observed in 80% of 5 subjects in group A, while only 40% of 10 patients improved in group B. By the third month of treatment, all those in group A had normal color vision while 40% of those in the placebo group still showed abnormal color vision. The difference between the 2 groups was statistically significant.

Table 1. Demographic profile of the study population (N=105).

Age (years)	37.1 ± 13.4
Gender **Male** **Female**	 77 28
Weight (kilogram)	49.4 ± 9.5
Height (meter)	1.63 ± 0.7
Body Mass Index (BMI)	19.98 ± 3.3

Table 2. Efficacy of vitamin B complex in reducing risk of color abnormalities.

Vitamin B Complex (N=43)		Placebo (n=62)
FIRST MONTH		
FAIL color tests	5	10
PASS color tests	38	52
Absolute Risk	5/43 or 11.6%	10/62 or 16.1%
Absolute Risk Reduction (ARR)	16.1-11.6 = 4.50%	
Number needed to treat (NNT)	1/ARR = 23	
SECOND MONTH		
FAIL color tests	1	6
PASS color tests	42	56
Absolute Risk	1/43 or 2.3%	6/62 or 9.7%
Absolute Risk Reduction	9.7-2.3 = 7.4%	
Number needed to treat(NNT)	1/7.4 % = 14	
THIRD MONTH		
FAIL color tests	2	8
PASS color tests	41	54
Absolute Risk	2/43 or 4.6%	8/62 or 12.9%
Absolute risk reduction (ARR)	12.9-4.6 = 8.3%	
Number needed to treat (NNT)	1/8.3 = 12	

The number of subjects who developed color abnormalities during the first month of anti-TB drugs and followed up to the third month is shown in Table 3. For group A, 4 of the 5 subjects (80%) improved, and in group B, 4 of the 10 cases (40%) improved. On the third month, all in group A had normal color vision and 40% in group B showed persistently abnormal color vision. The difference in the proportion of subjects who improved on the third month was significantly different between the 2 groups.

We also determined whether age, sex, and BMI were associated with the development of color abnormalities one month after ethambutol intake. Logistic regression analysis showed no significant association among these variables and the outcome (Table 4).

Table 3. Result of vitamin supplementation in improving/ reversing color abnormalities.

	Cases of Color Abnormalities		**p value***
	Vitamin B complex	Placebo	
First month	5	10	
Second month **improved** **not improved**	 4 1	 4 6	0.18
Third month **improved** **not improved**	 5 0	 4 6	0.0
Percent Improvement of old cases	100%	4/10 or 40%	

**** one-tailed t-test***

Table 4. Variable correlation and odds ratio.

Variable	Coefficient	Standard Error	Odds Ratio	p value
Age	0.006	0.021	1.049	0.78
Sex	-1.076	0.813	1.677	0.19
Body Mass Index	-0.013	0.085	1.167	0.88

DISCUSSION

The patients in our study received a combination of drugs, including pyrazinamide, rifampicin, isoniazid, and ethambutol. Both isoniazid and ethambutol have been implicated in toxic optic neuropathy but ethambutol has been reported as a more common cause[10]. Ethambutol is known as a metal chelator that inhibits myco-bacterial cell wall synthesis by interfering with iron-containing complex I and copper-containing complex IV, disrupting oxidative phosphorylation and mitochondrial function. Because of the similarity of mammalian mitochondrial DNA and ribosomes to those of bacteria, protein synthesis in mitochondria may be inhibited. Chronic impairment of energy

production and accumulation of reactive oxygen species eventually lead to apoptosis and optic nerve degeneration.[11] Neuronal cell death is manifested as retinal nerve fiber thinning and can be detectable by OCT.[12]

A study by Noche et al showed decreased levels of vitamin B, particularly B_6 or pyridoxal phosphate, in rabbits receiving ethambutol. It was suggested that ethambutol and/or its metabolites could assume a conformation similar to pyridoxine and thus compete with the absorption of this vitamin resulting in decreased absorption of the latter.[4] Aside from animal studies wherein levels of vitamin B_6 in the retina was quantified and found to be reduced,[4] the exact relationship between the two remained unclear.

Our results showed that patients who received vitamin supplementation (group A) had an absolute risk reduction of 4.5 to 8.3% of developing color vision abnormalities while undergoing DOTS compared to the group that received placebo (Table 2). The vitamin supplementation group also reverted back to normal color vision faster than the control group (Table 3).

Group A received a combination of vitamins which have been reported to have some neuroprotective effects, namely vitamins B_1, B_6, B_{12}, folic acid, and vitamin E. A commercial preparation that had the highest vitamin B_6 content was used for this study since the available literature point to pyridoxine deficiency as a possible mechanism of toxicity. The histopathologic evidence of Noche's study demonstrated the presumptive role of vitamin B; yet, there was no recommended standard dosage for the treatment or prevention of toxicity from ethambutol.

Because our patients received a combination of vitamins, we could not definitely identify which specific component was responsible for the positive effects of the drug in reducing the risk of and reversing the color vision abnormalities. Further studies are needed to elucidate specific effects of the vitamins.

Similar to the findings of Cruz,[6] none of the patients who developed color vision abnormalities in this study had blurring of vision during the 3 month observation period. This could indicate that color vision abnormalities may precede the decrease in visual acuity usually associated with toxic optic neuropathy. Yehoshua suggested that significant color vision loss with relatively preserved visual acuity could be an indication that the cause of the visual loss was an optic neuropathy.[13] Thus, it is important to monitor color vision among patients undergoing anti-TB therapy so that early signs of toxicity may be detected.

This study used 3 different types of color vision tests but all the abnormalities were detected only by the Lanthony Desaturated test, similar to the findings in an earlier study by Cruz.[6] Though the FM 100 hue test is at present the gold standard for color vision testing, the FD 15 and the Lanthony tests have been reported to adequately predict the severity of color deficit at a fraction of time of the 100 hue test. Thus, they are more suitable for routine screening and monitoring of color-vision deficiency.[14] In this study, the color arrangement tests were done once to remove bias and the possibility of a learning curve by the participants.

This study also determined if certain variables like age, sex, and BMI had any effect on the development of ocular toxicity. The results showed that they were not associated with the development of color vision abnormality.

While vitamin B is often used clinically in cases of toxic optic neuropathy, it is often given empirically and there is no standard dosage recommendation. There is a scarcity of objective data with respect to its beneficial clinical effects, as well as the dose necessary to achieve them. The dosage used for this study was based on the highest commercially available preparation.

In summary, this study showed that vitamin supplementation (vitamin B complex, folate, and vitamin E) was effective in reducing the risk of, and in reversing cases of, color vision abnormalities among patients undergoing DOTS therapy for tuberculosis. Color vision examination, particularly the Lanthony Desaturated test, may be a good screening tool for the early detection of toxicity related to anti-tuberculous therapy. It is, therefore, recommended that patients undergoing DOTS must be regularly screened for color vision abnormalities. Based on the positive effects shown in our results, we recommended vitamin supplementation, especially in those receiving higher doses of the drug, or in prolonged treatment due to advanced or resistant disease, to prevent possible toxic optic neuropathy.

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