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Original Research Article

Effect of Sertraline on biomarker alterations in patients of multidrug resistant tuberculosis with depression: a prospective clinical trial

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ABSTRACT

Background: Lipid profile parameters may be used as biomarker for depression. Sertraline belongs to selective serotonin reuptake inhibitors (SSRIs), the most commonly used group to treat the depression in multidrug resistant tuberculosis patients.

Methods: A prospective clinical trial was carried out in department of Psychiatry and department of Tuberculosis and Respiratory disease G.S.V.M. Medical College, Kanpur. Diagnosed MDR TB patients were screened for depression applying Hamilton Depression Rating Scale (HDRS) and these patients were referred to Psychiatrist for diagnosis of depression. Total 25 diagnosed patients of MDR TB with mild to moderate depression were selected. HDRS Score and morning blood sample of 5ml were collected to analyze biomarker for depression before intervention. Same test was repeated in 18 patients who completed the study at day 30 and 120 after administering Sertraline (50mg). Data were compiled and analyzed using SPSS 20.0 and paired t - test.

Results: The mean decrease in HDRS score from base line at day 30 and 120 of administering Sertraline were 6.22 (±1.26) and 2.72 (±0.67) which were significant (p<0.001). The mean increase in serum cholesterol at day 30 was 153.94 (±19.31) and at day 120 was 157.83 (±19.36) which were significant (p<0.001). Rest of Tg, HDLc, LDLc and VLDL cholesterole levels were not increased significantly.

Conclusions: As the depression symptoms improved by sertraline. The biomarkers of depression were also increased (within the normal range) from baseline but significant increase was observed in serum cholesterol only.

Keywords: High density lipoprotein, Low density lipoprotein, Sertraline, Serum cholesterol, Triglyceride

INTRODUCTION

Multidrug resistant tuberculosis (MDR-TB) is a major health problem worldwide. According to the WHO Global TB Report- 2016, TB remained one of the top 10 causes of death worldwide. There were an estimated 480 000 new cases of MDR-TB and India, China and the Russian Federation accounted for 45% of these cases.[1] India accounts for one fourth of the global TB burden. An estimated 1.3 lakh incident multi-drug resistant TB patient emerge annually in India which included 79000 MDR-TB Patients estimated among notified pulmonary cases.[2]

There is a high prevalence of psychiatric illness in TB patients, but primary care physicians and specialists do not screen this association.[3] It has been shown in most of the National and International studies that among the mental illness; commonest diagnosis being depression which is usually followed by personality disorder alone or co morbid with other psychiatric illnesses.[4] The co-

prevalence of depression with MDR tuberculosis leads to increased medical cost, poor medical adherence, morbidity and mortality.[5] It is estimated that 20% of patients with somatic disease suffer from major depression.[6] Failure to manage such mental health problems increases the patients's probability of suffering from complications. Reported rate of depression in MDR-TB varies from 6.2% to 22%.[4]

Currently, selective serotonin reuptake inhibitors (SSRIs) are recommended as the first line treatment for depression and tend to be favoured over other pharmacologic treatments such as by Tricyclic antidepressants (TCAs) and Monoamine oxidase inhibitors (MAOIs) because of their relatively benign side effect profiles.[7] Sertraline have been available since the beginning of the 1990s.[8] In 2013, it was the most prescribed antidepressant and second most prescribed psychiatric medication (after Alprazolam) on the U.S. retail market, with over 41 million prescriptions.[9]

Cholesterol has several important functions in the central nervous system. It is a constituent of the neuronal membrane, and plays a significant role in the process of neurotransmission and in the second messenger system in the brain.[10] Low cholesterol level is believed to enhance the risk of depression due to the neuronal dysfunction occurring because of changes in micro viscosity of the cellular membrane or disorders in signal transduction.[11] Serum Lipids may be used as peripheral biomarkers that can be used for diagnosis, monitoring response to treatment and patient stratification.[12] The levels of serum cholesterol and cholesterol-containing molecules like LDL, HDL have been linked to Major depressive disorder (MDD). Decrease in total serum cholesterol is commonly observed in depressed patients suffering from MDD when compared to healthy controls.[13] Various researches have demonstrated that MDD patients often show a decrease in high-density lipoprotein, an increase in low-density lipoprotein and an increase in LDL/HDL ratio.[14]

Depression is common findings in MDR TB patients and serum lipid profile may be used as a biomarker for depression. Therefore, present study has been planned to observe the effect of Sertraline a commonly prescribed antidepressant drug on biomarker (lipid profile) along with clinical improvement of depression in these patients.

METHODS

A prospective clinical trial was carried out in department of Psychiatry and department of tuberculosis and respiratory disease G.S.V.M. Medical College, Kanpur over a period of 12 months from January 2016 to December 2016. Total 74 diagnosed MDR TB patients attending O.P.D and I.P.D of department of Tuberculosis and Respiratory diseases were screened for depression applying Hamilton Depression Rating Scale after which patients were referred to Psychiatry OPD for diagnosis of depression. Total 25 diagnosed patients of MDR TB with

mild to moderate depression were selected after getting written informed consent.

Inclusion criteria

- All patients between age group of 15 to 65 years attending IPD/OPD.
- Patients of MDR-TB (Mycobacterium showed resistant to H and R)
- Patients with mild to moderate depression (International classification of diseases, tenth revision, diagnostic criteria for research)

Exclusion criteria

- Patients of depression with suicidal tendency
- Patients already taking antidepressant drug therapy
- Patients taking any drug other than the prescribed during study
- Cases positive for HIV and Hepatitis B
- Pregnant female
- Patients not willing to participate in the study.
- Patients of MDR-TB with psychiatric illness other than mild to moderate depression.
- Patients with diabetes, hypertension, renal impairment and abnormal liver function test.
- History of allergy to any medication prescribed during the study.

The enrolled patients on Standard MDR-tuberculosis treatment were administered single oral tablet of Sertraline (50mg) and follow up was done at day 30 and day 120. For depression improvement Hamilton depression rating scale score and for biomarker alteration Serum lipid profile (Serum cholesterol, Triglyceride, High density lipoprotein cholesterol, Low density lipoprotein cholesterol and Very low density lipoprotein cholesterol) were done at each follow up.

Data management and statistical analysis

Data was tabulated in Microsoft excel sheet. Data were compiled and analyzed using SPSS 20.0. All categorical variables were analyzed using percentage.

Quantitative variables were analyzed using Mean, Standard Deviation (SD). Before and after scores were compared using paired t - test. p value <0.05 was considered significant.

RESULTS

74 MDR TB patients were screened for depression, out of which 49 were excluded and 25 diagnosed depressed patients were included in the study. They then received Sertraline (50mg/day) single oral tablet. Total 18 patients had completed the study. 3 patients and 4 patients were lost to follow-up at day 30 and day 120 respectively.

Table 1: Change in HDRS score after administration of Sertraline.

Sertraline (50mg/day) (n=18)			
Day '0' HDRS Score (Mean±SD)	Follow up	Change in HDRS Score (Mean±SD)	p* value
13.11±2.29	At day 30	6.22 ± 1.26	<0.001, significant
13.11±2.29	At day 120	2.72 ± 0.67	<0.001, significant

(p* < 0.05 is significant)

Patients characteristics and baseline data

The mean (±SD) values of age were 28 (±11). The numbers of males were 12 (66.66%) and females were 6 (33.33%). The patients of mild depression were 10 (55.55%) and moderate depression was 8 (44.44%). The mean (± SD) of lipid profile parameters were serum cholesterol 145.94±20.33, serum triglyceride (Tg) 76.56±15.07, serum high density lipoprotein cholesterol (HDLc) 44.06±7.63, serum low density lipoprotein cholesterol (LDLc) 46.67±16.79 and serum very low-density cholesterol (VLDL) 22.06±4.96. The mean (±SD) HDRS score were 13.11±2.29 at base line.

Effect of sertraline on depression

The mean (±SD) HDRS score were 13.11(±2.29) at base line. Mean (±SD) HDRS scores at day 30 and day 120 after initiation of Sertraline drug therapy were 6.22 (±1.26) and 2.72 (±0.67) respectively. There were decrease in HDRS score from the day 0 (base line) to subsequent follow-up. The mean decrease in HDRS scores from baseline were significant (p<0.001) at each follow-up (Table 1).

Effect of sertraline on lipid profile

The mean (±SD) Serum cholesterol was 145.94±20.33, Tg was 76.56±15.07, HDLc was 44.06±7.63, LDLc was 46.67±16.79 and VLDL was 22.06±4.96 at base line. At day 30 the mean (±SD) serum cholesterol level was 153.94±19.31, Tg was 76.16±14.92, HDLc was 45.33±5.59, LDLc was 51.89±12.31, VLDL was 22.27±3.23 and at day 120 the mean (±SD) serum cholesterol level was 157.83± 19.36, Tg was 77.72±14.94, HDLc was 45.28±6.75, LDLc was 53.33±5.30 and VLDL was 23.11±2.68. There were significant increase in Serum Cholesterol levels from base line to the followup at day 30 and day 120 (p<0.001), rest of Tg, HDLc, LDLc and VLDL cholesterole levels did not show significant increase from base line (Table 2).

Table 2: Change in mean serum lipid profile levels after administration of sertraline.

Sertraline (n=18)					
Lipid profile (Mean±SD)	Day 0	Day 30	p* value	Day 120	p* value
Serum cholesterol	145.94±20.33	153.94±19.31	<0.001	157.83±19.36	<0.001
Serum triglyceride	76.56±15.07	76.16±14.92	0.440	77.72±14.94	0.071
HDL cholesterol	44.06±7.63	45.33±5.59	0.530	45.28±6.75	0.124
LDL cholesterol	46.67±16.79	51.89±12.31	0.139	53.33±5.30	0.082
VLDL cholesterol	22.06±4.96	22.27±3.23	0.763	23.11±2.68	0.354

(p*< 0.05 is significant)

DISCUSSION

The present study investigates simultaneously the effects on depression and serum lipid profile alterations of Sertraline in MDR Tuberculosis patients with depression. When assessing the effect on depression; there was significantly decrease in HDRS score from base line. Amongst the lipid profile parameters, Sertraline showed a significant increase in serum cholesterol at day 30 and day 120. The other lipid profile parameters like Triglyceride (Tg), HDL cholesterol, LDL cholesterol and VLDL also increased at day 30 and day 120 from base line but that was not significant. The anti-depressant Sertraline was well tolerated with none of the patients showed withdrawal.

In this study the change in lipid profile parameter at day 30 and day 120 were serum cholesterol from 145.94±20.33 to 153.94±19.31 and 157.83±19.36 (p<0.001), Tg from 76.56±15.07 to 76.16±14.92 and 77.72±14.94, HDL c from 44.06±7.63 to 45.33± 5.59 and 45.28±6.75,LDLc from 46.67±16.79 to 51.89± 12.31 and 53.33±5.30 and VLDL from 22.06±4.96 to 22.27± 3.23 and 23.11±2.68; it showed that there was significant increase in serum cholesterol after treatment and the increase in Tg, HDL c, LDL c and VLDL was not significant. A study measured serum cholesterol in 92 patients after 1 week and 4 weeks of antidepressant treatment and found that neither a significant change in serum cholesterol levels nor a correlation between cholesterol levels and clinical improvement was found.[15]

In another study on depressive patients, included 40 outpatients 5 men and 35 women and 32 healthy controls.[16] The patients received antidepressant treatment (Sertraline, Escitalopram, Fluoxetine, and Venlafaxine) for 8 weeks. Body measurements were performed, and lipid, fasting blood glucose, and insulin levels were measured before

and after treatment in patients and once in healthy controls. Insulin resistance was evaluated using the homeostasis model assessment (HOMA) index. It was observed that after antidepressant treatment there was increase in serum cholesterol and high density lipoprotein (HDL) cholesterol levels in Escitalopram group whereas in patients treated with Sertraline there was no change in Body mass and lipid levels. Our study differed from this study and it may be because of less no. of female patients and small sample size.

Another prospective clinical trial, used Sertraline in depressive patients.[17] 8 males and 12 females depressive patients, diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, were included in this study. Sertraline therapy (50 mg/day) was started. Patients with diabetes mellitus, heart disease, pregnancy, and those taking other drugs were excluded from the study. Blood glucose, insulin, high-density lipoprotein-cholesterol (HDL c), low density lipoprotein-cholesterol (LDL c), and triglyceride values were measured in patients before, and at the 4th, 8th and 12th weeks after treatment with Sertraline. There was significantly increase in the triglyceride levels at 8th week and 12th week from pre treatment value. In our study 5 females and 13 males were included, with the same dose of Sertraline; the mean change in triglyceride levels from 76.56±15.07 to 77.72±14.94 was observed but it was not significant (p=0.4026). In this study it was observed the triglyceride levels at 30 and 120 days. The difference in our result was due to the more no. of males and because of no history of smoking were taken into consideration and also BMI of the patients are not equally distributed.

Another prospective study was using SSRI to investigate its effect on metabolic syndrome abnormalities in generalized anxiety disorder, Ninety-seven female patients aged 20-41 years without any metabolic or psychiatric co-morbidity were included in the study.[18] Fluoxetine, Sertraline, Paroxetine, Citalopram and Escitalopram were randomly given to the patients. Metabolic parameters including BMI, waist circumference and the levels of fasting glucose, total cholesterol, triglyceride, HDL, LDL and blood pressure were measured before and after 16 weeks of treatment. Patients were controlled for their food intake in terms of continuation of their usual eating habits during study. Blood samples were taken before and after sixteen weeks of treatment and there was significant increase in serum cholesterol levels in Sertraline group. Our study had similar observation with this study that significant increase in serum cholesterol levels (from 146.56±21.49 to 157.83±19.36, p<0.0410) was observed at day 120 after initiation of therapy. The other parameters of lipid profile were also increased but the change was not significant. Our study differed from this study in the aspects that we included both male and female patients with depression, small sample size and age distribution.

CONCLUSION

A prospective clinical trial was conducted to study the effect of Sertraline on biomarker alteration in patients of Multidrug resistant tuberculosis with depression and it was concluded that as the depression symptoms improved by Sertraline treatment, the biomarkers of depression (lipid profile parameters) were also increased (within the normal range) from baseline value but significant increase was seen in serum cholesterol only. The study was small sample sized so further study was needed with large sample size to explore the more rational result outcome.

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