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Original Research Article

Electrocardiographic changes of antidepressant medication in depressive episode

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ABSTRACT

Introduction: Depressive disorder is leading cause of mortality in the world, with the help of recent therapeutic strategies it is easily manageable. Antidepressant medication is the most commonly used for management of depressive disorders. Among the side effects of antidepressant, cardiovascular effects of antidepressant deserve close monitoring. Invariably, it is observed that patients undergoing antidepressant therapy are not screened for pre-existing cardiovascular diseases and more so for cardiotoxicity. Various antidepressant medications are available, with different cardiac side effects profile. Ignorance, over clinical burden, poor follow up and under evaluation of cardiovascular side effects could be attributable to an ultimate surveillance of such cases. So, this study conducted to evaluate electrocardiographic changes in therapeutic doses of antidepressant medication.
Methods: An Open label-controlled study was conducted on 386 subjects to evaluate the antidepressant-induced electrocardiographic changes. Treatment seeking subjects for the depressive episode was recruited from outpatient and inpatient section of Psychiatry department after fulfilling inclusion and exclusion criteria. Data was collected on socio-demographic characteristics, and detailed pre-treatment and post-treatment clinical evaluation and electrocardiographic assessment were done.
Results: Data collected and analyzed from 204 subjects, mean age of subjects taking tricyclics and SSRI (Fluoxitine) 43.6±7.5 years vs 41.5±9.6 years respectively. The study sample consists of 66% females, 33% males. Among them, 35% study subject expose to tricyclics and 65% subjects taking SSRI. 19% study subjects presented electrocardiograph changes especially tachycardia among them 55% was taking the tricyclic antidepressant. Only 10% subjects taking SSRI had post-treatment abnormal electrocardiograph changes.
Conclusions: Conclusively, antidepressant form a safe therapeutic modality for the management of major depression. Its cardiovascular side effects warrant against indiscriminate use of particularly in high dose and old aged person and preexisting cardiac disease.

Keywords: Antidepressant, Cardiovascular side effects, Depression, Electrocardiograph, SSRI, TCA

INTRODUCTION

Depressive disorder will be the second leading cause of disease-related burden up to 2020.[1] An episode of depression leads to increased risk of absenteeism from work, decreased productivity and the treatment-related costs.[2] Depression is a common and treatable condition and various pharmacological and non-pharmacological antidepressants. Management of depressive episode various treatment modalities including antidepressant medications, somatic therapies and psychotherapeutic interventions is available, but pharmacotherapy is considered as the most commonly used modalities worldwide.[3] Antidepressants are main therapeutic agents

used for the management of depressive episode. Increasing numbers and types of antidepressant and dimensional approach of depression show that different symptom of depression mediated by different neurotransmitter and to enhance remission rates in depression the clinician uses antidepressants according to symptoms and patient characteristics in clinical practice. Like the other drug, antidepressant has several side effects, few simply pharmacological in nature and few are toxic cardiovascular side effects. Among these, cardiovascular side effects deserve close monitoring.

A large number of mortalities and morbidities are on record due to toxic as well as the therapeutic dose of antidepressants.[4-7] Invariably it is being observed that patient undergoing antidepressant therapy are not properly screened for pre-existing cardiovascular disease and more so for possible cardiotoxicity. Ignorance, over clinical burden, poor follow up and poor existing facilities could be attributable to an ultimate surveillance of such cases. In the view of potential cardiovascular side effects of antidepressant, the present open controlled study was conducted to evaluate electrocardiography changes by different antidepressant medications among subjects suffering from the depressive episode.

METHODS

Subjects, study design and sample

Data for this study were collected from Department of Psychiatry, Shyam Shah Medical College, Rewa. A research protocol was framed, and institutional ethics committees approved the study. This was a cross-sectional study. Treatment-seeking subjects aged ≥18 years with an ICD-10 diagnosis of the depressive episode, and clinically stable were purposively recruited, from outpatient and inpatient services, for this study.

Intervention

All the subjects underwent pre-treatment assessment at baseline followed by they were administered tricycle antidepressant or serotonin reuptake inhibitors (Fluoxetine) depending upon the clinical profile of subjects, as advice by treating psychiatrist. The initial dose of tricyclics and Fluoxetine were 75 mg/day in divided doses and 20 mg of Fluoxetine per day respectively. On the third week again, clinical assessment was made to evaluate the severity of depression. Inpatient having nonresponder, the dose was further increased to 150 mg per day for tricyclics and 40 mg per day of Fluoxetine.

Assessment

Clinical assessments were carried out by face-to-face interviews conducted and clinical examination done at baseline in form of hemodynamic stability, freedom from any systemic illness and finally, electrocardiography recording was performed. Depression rating scales used to quantify the severity of depression and assessment of antidepressant response. Subjects were excluded if they had a history of diabetes mellitus, pre-existing cardiovascular disease, hypertension before initiation of treatment for the depressive episode. All patients underwent pre-treatment assessment and post-treatment assessment with electrocardiography recording at baseline and third week of antidepressant treatment.

Evaluation tools

Data were collected on a specifically designed proforma to record sociodemographic and clinical details such as comorbid medical illness, history of alcohol use. Clinical examination and recording of blood pressure were done by mercury sphygmomanometer in the supine position after completing the clinical interview. All patients underwent 12 lead electrocardiography performed pre-treatment and post-treatment clinical assessment and E.C.G. finding was interpreted by the clinical expert.

Statistical analysis

Means with standard deviations and frequencies with percentages were used to summarize continuous and categorical variables, respectively. Student's t-test (continuous variables) and chi-squared test (categorical variables) were used for comparative analyses and correlation between the groups. Statistical significance was fixed at $p = 0.05$.

RESULTS

Data collected from 386 subjects, fulfilling inclusion and exclusion criteria of study and underwent clinical evaluation and pretreatment evaluation. Among 204 subjects included for analysis 186 subject excluded from the study (Figure 1).

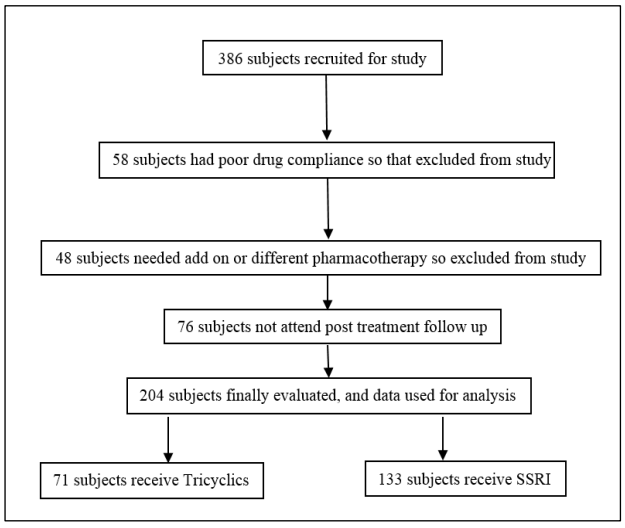

Figure 1: Enrollment and disposition of participant in study.

Socio-demographic and clinical characteristics

As seen in Table 1 mean age of subjects taking tricyclics and Fluoxetine 43.6±7.5 years versus 41.5±9.6 years respectively. Mean education year up to the level of high school. Majority of the subject were in the age range of 21-30 years (40%). The bulk of the patient were also below the age of 50 years (86%).

Only 14% patient was above 50-year of age. In the range of 31-40 years, females were statically significant higher as compared to male. This is well in confirmation with earlier observation reporting the higher incidence of depression in the female, many times as high as double of the males (Lewis et al 1992).

Table 1: Socio-demographic and clinical characteristics.

Variable	Tricyclics (n = 71)	SSRI (n = 133)	Level of significance
Age, Years mean (SD)	43.6±7.5	41.5 ± 9.6	0.73
Education, years mean (SD)	8.6±3.8	10.4 ± 2.6	0.15
Sex, N (%)			
Male	47 (66.20%)	89 (66.92%)	N.S.
Female	24 (33.80%)	44 (33.08)	
Marital status (N)			
Married	65 (91.55%)	126 (94.74%)	N.S.
Widowed/ Seprated	6 (8.45%)	7 (5.26%)	
Religion (N)			
Hindu	68 (95.77%)	130 (97.74%)	N.S.
Muslim	3 (4.23%)	3 (2.26%)	
Family type (N)			
Nuclear	32 (45.07%)	57 (42.86%)	N.S.
Extended/joint	39 (54.93%)	76 (57.14%)	
Residence (N)			
Urban	32 (45.07%)	56 (42.11%)	N.S.
Rural	39 (54.93%)	77 (47.89%)	
F/H/O psychiatric illness (N)			
Absent	57 (80.28%)	107 (80.45%)	N.S.
Present	14 (19.72%)	26 (19.55%)	
Precipitating factor (N)			
Absent	63 (88.73%)	119 (89.47%)	N.S.
Present	7 (11.27%)	14 (10.53%)	

In the study sample, almost all subjects were Hindu (98%), and 58% subjects were from rural area. This was probably due to greater Hindu predominated population and rural background in this subcontinent and was unlikely due to the preponderance of depression in rural population. Positive family history of neuropsychiatric illness was present in 20% of subjects, and the precipitating factor was present in only 10% of the subjects. Majority of male subjects (56%) were addicted to tobacco, 16.3% were addicted to alcohol. No female patient was addicted to either alcohol or tobacco. Therefore, addiction was not a contributory factor in our subjects and is not a key factor for depression. Electrocardiographic abnormality observed were found mostly in those addicted to tobacco.

Table 2: Electrocardiographic changes.

Electro-cardiographic changes	Tricyclics % (n = 71)	SSRI % (n = 133)	Level of significance
Sinus tachycardia	55%	0	<0.05
Sinus Bradycardia	0	0	N.S.
Atrial Premature Complexes	4	0	<0.05
1st degree heart block	10%	0	<0.05
2nd degree heart block	0	0	N.S.
3rd degree heart block	0	0	N.S.
Increased QRS interval (>0.15 sec)	0	0	N.S.
Abnormal QTc interval	45%	10%	<0.05
Atypical ventricular conduction	10	0	<0.05
Right bundle branch block	0	0	N.S.
Left bundle branch block	15%	0	<0.05
T wave changes	9%	0	<0.05
ST segment changes	20%	0	<0.05

Antidepressant

Majority of patients were taking Fluoxetine (66.3%), Amitriptyline 16.6%, Dothipine 13.3%, or Clomipramine 3.3%. The result indicates that almost no cardiovascular abnormalities precipitated with the use of Fluoxetine in either low or moderate dose. While 60% patient required the moderate dosage of tricyclics to came over depressive symptoms. Although cardiovascular side effect

precipitated even in the low dose of tricyclics within a week, however, changes were not progressive even with the increase of tricyclics dose. It may be concluded that tricyclics can precipitate cardiovascular side effect in both therapeutics range or in higher dosages, within a short period of administration while Fluoxetine had almost no cardiovascular side effects either in therapeutic/high dose.

Electrocardiography changes

Nearly 10% subjects on SSRI shows ECG changes in comparison to 70% subjects on Tricyclics reported ECG changes in three month of antidepressant monotherapy (Table 2).

DISCUSSION

This study was an open controlled study wherein electrocardiography changes induced by the various antidepressant, used in depression were evaluated. A total of 204 subjects taking antidepressant medication were studied.

Electrocardiographic changes

Sinus tachycardia

In 55% patients on tricyclics developed sinus tachycardia, however, none of the Fluoxetine recipients developed either sinus tachycardia or bradycardia, Lawrence et al reported sinus tachycardia in 27% subjects with tricyclic use. As most of the subjects who had sinus tachycardia developed it within 2 weeks and further after increasing the dosage of tricyclics rise could not be traced in proportionately. Although in a small percentage of the patient on Fluoxetine was noted.[8,9] As the high incidence of sinus tachycardia was observed with the use of tricyclics, not with Fluoxetine, it is recommended that tricyclics showed only to used with caution in patients with hyperdynamic circulatory states, ischemic heart disease as increase heart rate further precipitates the ischemia by increasing oxygen demands. In case there is no contraindication, low dose of beta blockers like Propenalol may also be used as an adjuvant to treat stressful palpitation.

A.V. block

10% patients, receiving tricyclics had developed 1st degree AV block while none of the subjects taking Fluoxetine demonstrated this. However, no subject developed second or third-degree AV block either with tricyclics or Fluoxetine. The previous study reported the lower incidence of AV block, on another side Vohra et al reported marked higher incidence of 1st degree heart block, however, these patients were taking Nortriptyline instead of Amitriptyline/Fluoxetine/Dothiepin.[10,11] So different drug with the different pharmacodynamic property may be responsible for such a difference.

QRS interval

Serious side effects in form of tricyclics intoxication is usually associated with prolongation of QRS interval (>0.15 sec).[12] However, in this study, no patient has developed a prolonged QRS interval. The most probable reason for this may be that dosage in our patients was <150mg/day of tricyclics.

QTc interval

Abnormal QTc interval were observed in 45% patients taking tricyclics and in 10% taking Fluoxetine. It may assume that QTc prolongation is a feature of tricyclics toxicity but not of Fluoxetine. Vohra et al noted abnormal QTc in 75% cases in his study with use of tricyclics which is quite more in comparison to the present results, however, Vohra's study was done against Nortriptyline, instead of tricyclics used by us.[11] Abnormal QTc prolongation usually predisposes for various types of ventricular arrhythmias. Therefore, tricyclics should be cautiously used in the patient with congenital QTc syndrome as the later may develop a fatal form of ventricular arrhythmia.

Atypical ventricular conduction

10% subjects taking tricyclics, had an abnormal tracing of electrocardiographic changes in form of Atypical ventricular conduction although none of the patients on Fluoxetine had similar changes. These subjects may become prone to develop the serious ventricular arrhythmia, so in such patient again tricyclics should be used cautiously.

Bundle branch block

15% subjects taking tricyclics developed bundle branch block in comparison to none in patients on Fluoxetine. These bundle branch blocks were in the form of left anterior hemiblock in all subjects. There was right bundle branch block in the present study. Burrows et al 1975 have revealed that tricyclics primarily exert their cardiotoxic effects on his Purkinje system.[13]

ST segment

ST segment changes in form of ST depression were observed in 20% on tricyclics, while no patient on Fluoxetine. The ST segment changes were nonspecific as there were no associated chest symptoms and no reciprocal changes. Although these nonspecific changes were localized in inferior leads. Schou 1983 also reported similar kind of electrocardiographic changes with the use of tricyclics.[14]

CONCLUSION

Antidepressant medications are a safe therapeutic modality for the management of major depression. Its

cardiovascular side effects warrant against indiscriminate use of particularly in high dose and old aged person. In contrast to western studies, the present study revealed fewer cardiovascular side effects and may be incriminated either to its administration in low to moderate dose or lack of deliberate or accidental intoxication. Majority of side effects were innocuous and did not require interruption of therapy. Sinus tachycardia, the most commonly observed side effects of tricyclic, not of much clinical relevance unless patient having hyperdynamic circulatory state or is vulnerable to develop ischemic heart disease.

The present study does not recommend thyroxin as the tricyclic enhancer in such cases. Similarly, the patient reveling first-degree heart block should not be administered certain adjuvant treatment in conjunction with antidepressant therapy, i.e. lithium, propranolol, verapamil etc. All the patients developing QRS widening or right bundle branch block should be closely followed up for any eventual toxic events like the seizure, ventricular arrhythmia, syncope attach etc.

It is our contention that subtle ST and T wave changes induced by tricyclics, although should not be considered alarming to leading drug withdrawal yet required meticulous work to unravel organic cardiac lesion if any. Since a constant research and development strategy has provided us a long list of antidepressants it is prudent to select an optimum antidepressant molecule according to the not only clinical profile of depression but also in light of cardiovascular and overall status. It is, therefore, strongly recommended that all the patients undergoing antidepressant therapy should be subjected to electrocardiographic monitoring particularly in risk-prone persons both in pretreatment and treatment phases.

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