Original Research Article

Effects of Escitalopram on C reactive protein in patients of depression

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Abstract

Objective: To study the anti-inflammatory activity of Escitalopram in newly diagnosed patients of depression. **Materials and Methods**: 100 Newly diagnosed patients of Depression as per ICD 10 (International classification of diseases) DCR (Diagnostic criteria for research) were selected for study after applying strict inclusion and exclusion criteria. Baseline Hamilton depression rating scale (HAMD) and baseline C reactive protein (CRP) was assessed and antidepressant treatment was started. After 8 weeks, again HAMD and CRP were assessed. **Results**: Mean of Baseline CRP was higher in patients in those who have no response after antidepressant treatment and it was significant. The relationship between baseline HAMD and baseline CRP was found to be significantly positively correlated. Mean HAMD was significantly reduced after 8 weeks of antidepressant treatment. Mean CRP was significantly reduced after 8 weeks of antidepressant treatment. The relationship between baseline CRP and reduction in HAM D (in baseline and after 8 weeks of treatment) found to be negatively correlated and it was significant. **Conclusion:** Escitalopram reduced C reactive protein in depressed patient and result was significant.

Key words- Hamilton rating scale for depression, C Reactive protein, Depression

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Introduction

Depression is a common disorder, affecting over 120 million people worldwide. Even when successfully treated and remission is achieved, depressive disorders still impose a considerable burden on the patient. Remission is rarely accompanied by a total disappearance of all symptoms. Residual symptoms, especially cognitive impairment or social dysfunction, can continue to reduce performance and cause considerable distress. The burden of depressive disorder extends far beyond the disorder itself influencing the mortality risk of the patient. The most common theory about the neurochemical etiology of depression is Monoamine hypothesis**.** According to it, depression occurs due to a deficiency of the brain monoaminergic transmitter norepinephrine, serotonin, and dopamine [1]. Monoaminergic systems are responsible for many behavioral symptoms, such as mood, vigilance, motivation, fatigue, and psychomotor agitation or retardation.

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Abnormal function and the behavioral consequences of either depression or the manic state may arise from altered synthesis, storage, or release of the neurotransmitters, as well as from disturbed sensitivity of their receptors or subcellular messenger functions.

Currently available antidepressant medications largely target monoamine pathways, but treatment of depression is only effective in about a third to a half of patients [2].

Identification of other pathophysiological pathways involved in depression is needed for the development of alternative treatment strategies. Increasing interest has been directed to immune dysregulation in depression. Some studies have indicated that immune activation could also be present and might even play a role in the onset of depressive symptoms.

Recently, two meta-analyses have shown that inflammatory marker levels such as C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor

alpha (TNF) are increased in depressed persons compared with nondepressed subjects [3, 4]. As summarized by Miller et al, several studies showed that antidepressant treatment, mainly selective serotonin reuptake inhibitor, was associated with decreases in inflammatory markers [5].

The aim of this study was to examine the possible differences and changes in the concentrations of inflammatory cytokines CRP before and after antidepressant therapy.

Materials and Methods

This study was carried out at department of psychiatry at MGM medical college & associated M.Y. hospital, indore.

138 newly diagnosed patients of Depression as per ICD 10 (International classification of diseases) DCR (Diagnostic criteria for research) were selected for study after applying strict inclusion and exclusion criteria.

Inclusion criteria

- Patient giving written informed consent
- Patients fulfilling criteria of depression according to ICD 10 DCR
- Patient were selected of age group of 18-50 years

Exclusion criteria

- Patients not giving informed consent
- Patients who were on any other medication that affects CRP (anti-inflammatory drugs, oral contraceptive drugs, etc.).
- Patients having severe medical illnesses (Who are incapable for interview, need intensive care, in delirium),
- Patients with any infection, e.g., bacterial/viral/fungal
- Patients of known autoimmune disease, Diabetes mellitus, renal insufficiency, pregnancy and tuberculosis. and having other disorders that cause raised CRP
- Patients having the habits of alcohol intake or smoking.
- Patients with any inflammatory disease such as rheumatoid arthritis, juvenile chronic arthritis, ankylosing spondylitis, psoriatic arthritis etc
- Pregnant woman.
- Patient having Mental Retardation.

Study was conducted from March 2015 to February 2016. The study protocol was approved by institutional scientific and ethical committee. Written informed consents were taken before the patients were included in study. A complete clinical assessment done to confirm diagnosis and clinical profile and data entered in semi-structured Performa.

- Apply HAM-D [6] scales to quantify the depression severity.
- Blood sample of participants was obtained and CRP was assessed in pathology lab of M.Y. hospital Indore.
- Patient referred back to treating clinician for further management.
- Escitalopram (10mg/day), a selective serotonin reuptake inhibiter (SSRI) commonly used to treat depression, was prescribed to all patients for the uniformity.
- After 8 weeks patient will again be reviewed and severity assessed in HAM-D and again blood sample was taken and CRP was assessed.
- Response was defined as at least 50% reduction in HAMD score.
- Less than 50% reduction in HAMD was defined as no response

Tools

1. Semi structured data entry performa: This performa is being used for detailed evaluation of the patients. It includes socio-demographic details of the patient, age, gender, place of residence, marital status, religion, education, occupation, income, family type, depression characteristics included depressive symptoms severity as measured by the Hamilton Scale for Depression (HAM-D) score, and depressive symptoms duration.This Performa was completed on the basis of information given by the patient, his or her accompanying relative

2. Hamilton Rating Scale for Depression-17 (HRSD): it is a seventeen item questionnaire used to provide an indication of depression, and as a guide to evaluate recovery. Hamilton rating Scale for Depression (HAM-D) is used in most of study so easy to compare the results with other studies. It generally takes 15-20 minutes to complete the interview and score the results.

Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine are scored from

0-2.It has been useful for many years as a way of determining a patient's level of depression before, during, and after treatment

3. High sensitivity C-reactive protein*:* Blood samples were obtained from cases during diagnosis of depressive episode in outpatient department. Blood was centrifuged at 3000 × g for 10 minutes and stored at −20°C until analysis.

Serum hs-CRP was measured by latex-enhanced immunoturbidimetry using monoclonal anti-CRP antibodies (Infinite Turbilatex CRP, Accurex biochemical private limited Mumbai IND 401506) (hs-CRP reference level, ≤ 6mg/L).

Statistical Analysis- Data obtained in our study were analyzed using the Statistical Package for Social Sciences (SPSS for Windows) software, version 21.

Paired t test was employed to compare the HAM-D at baseline and at 8 weeks. Paired t test was employed to compare the CRP at baseline and at 8 weeks. The correlation between severity of depression (HAMD) and inflammatory marker (CRP) was analysed by Pearson correlation. To compare the CRP or HAMD in between two groups, student *t* test was used. To compare the CRP or HAMD in more than two groups, ANOVA was applied. Average values were reported as mean ± standard deviation (SD). Difference can be considered statistically significant when $P < 0.05$.

Results

Table-1: Mean of CRP at baseline and treatment response.

Treatment response	CRP at baseline (Mean)	(SD)
No response	4.43	2.33
Response	1.17	1.00

Mean of Baseline CRP was compared in patients in those who has no response on treatment and those who has response, by using student t test. It is found to be significant. (p value <0.05)

Table-2: Association of Baseline CRP and baseline HAM D.

		Baseline HAM-D
Pearson Correlation	Baseline CRP	.187
Sig. (1-tailed)	Baseline CRP	.032
N	Baseline CRP	100

The relationship between baseline HAMD and baseline CRP was analysed by pearson correlation and found to be positively correlated and it was significant (r=0.187, p=0.032)

Table-3: Change in Severity of depression and CRP with treatment.

	At baseline Mean(SD)	At 8 weeks Mean(SD)	Level of significance (p value)
HAMD	19.54 ± (3.71)	12.06 ± (3.92)	<0.05
CRP(mg/l)	2.35 ± (2.24)	1.65 ± (1.51)	<0.05

Mean HAMD in depressive patients on the day they presented to the hospital (baseline) was 19.54 ± (3.71) and after 8 weeks of antidepressant therapy, it was 12.06 ± (3.92) and the difference in HAMD score was analysed by paired t test and it was statistically significant. (p<0.05).

Mean CRP value at baseline was 2.35 ± (2.24) mg/l and after 8 weeks of antidepressant therapy, it was 1.65 ± (1.51); the difference in CRP values was analysed by paired *t* test and it was statistically significant. (p<0.05).

Table-4: CRP baseline and reduction in HAM D.

		Baseline CRP	Reduction in HAMD
Baseline CRP	Pearson Correlation	1	-.551
	Sig. (2-tailed)		.000
	N	100	100
Reduction in HAMD	Pearson Correlation	-.551	1
	Sig. (2-tailed)	.000	
	N	100	100

The relationship between baseline CRP and reduction in HAM D (in baseline and after 8 weeks of treatment) was analysed by pearson correlation and found to be negatively correlated and it was significant. ($r= -0.551$, $p<0.001$)

Discussion

Mean of Baseline CRP was higher in patients in those who have no response after antidepressant treatment and it was significant. It was in accordance with a meta analysis by Strawbridge et al. He found that treatment non-responders tend to have higher baseline inflammation elevated levels of inflammation are contributory to treatment resistance [7].

The relationship between baseline HAMD and baseline CRP was found to be significantly positively correlated. That shows that if baseline inflammation increases then severity of depression also increases so baseline CRP could be one of the biochemical marker to judge the severity of depression. Yunsheng Ma et al (2011) also found that depression score appears to be positively correlated to CRP [8]. Mean HAMD was significantly reduced after 8 weeks of antidepressant treatment.

Mean CRP was significantly reduced after 8 weeks of antidepressant treatment. Various previous studies support our findings. In one study, Nilesh Chavda [9] et al (2010), After 2 months of treatment with either fluoxetine or escitalopram, there was significant reduction in the levels of inflammatory markers in both the treatment groups. In fluoxetine group, pre treatment CRP was 4.04 and post treatment CRP was 3.92. In escitalopram group, pre treatment CRP was 4.04 and post treatment CRP was 3.91. These findings were consistent with our study.

In another study by Danijel et al (2012) on serum CRP variable in the group of depression patients (n=38, 16 male and 22 female) on the day they presented to the hospital and on day 30 of antidepressant therapy CRP level was significantly lower after antidepressant therapy [10]. Sinead m. O'brien et al (2006) C-reactive protein was measured in 20 patients with major depression were treated for 3 weeks with either fluoxetine (20 mg), paroxetine (20 mg) or sertraline (50 mg). Levels of C-reactive protein dropped significantly following treatment. The pre-treatment level was 12.0mg /l and the level following treatment was 8.0mg/l [11]. In other study S. Lanquillon et al (2000) among 24 patients, amitriptylline was used as antidepressant throughout the study. In this study, pre treatment CRP was 5.45 and post treatment CRP was 2.95 [12].

The significant difference in CRP in these studies indicates the importance of this acute phase inflammatory reaction protein as one of the very valuable and definite markers of depression. Accordingly, it is valuable information that the patients' CRP concentration was reduced after one month of antidepressant therapy and this result is definitely worth of further studying. Since antidepressants significantly decreased CRP concentration, thus proving that antidepressants strongly inhibit this pro inflammatory protein.

The possible explanation of CRP reduction by antidepressant medication, there are some pathways through which inflammatory cytokines can lead to reduced synaptic availability of the monoamines, which is believed to be a fundamental mechanism in the pathophysiology of depression. These are by decreasing tetrahydrobiopterin, by activation of the enzyme indoleamine 2,3-dioxygenase, by stimulating glutamate release or by decreasing BDNF [13]. Antidepressant interrupts these pathways of inflammatory cytokines and reduces CRP. Other possible mechanisms involves serotonergic pathways.Intracellular serotonin and low concentrations of extracellular serotonin are necessary for optimal production of cytokines and normal immune functions, whereas higher concentrations of serotonin

(e.g. supra-physiological) are immunosuppressive and inhibit cytokine production. Antidepressants (especially SSRIs) that inhibit the reuptake of serotonin may further increase serotonin concentrations in culture medium. This may result in high extracellular serotonin concentrations and the subsequent inhibition of cytokine production.[14] This is the explanation why in our study, we have got similar results using escitalopram, an SSRI.

The relationship between baseline CRP and reduction in HAM D (in baseline and after 8 weeks of treatment) found to be negatively correlated and it was significant. It shows that patients who has higher baseline CRP, they show less reduction in HAMD. Hence combining inflammatory biomarkers might prove a useful tool to improve diagnosis and detection of treatment refractoriness. There are some limitations in our study. Control group should be followed up for better comparison of results. Large sample size could have given more accurate results.

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