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Research Article

Beneficial Antidepressant Effect of Aceclofenac Add-on Therapy to Sertraline for Treatment of Depression

Hardik G Dodiya[1]* (GTU PhD Scholar), Ramashanker R Yadav[2] and Sunita S Goswami[1]

[1]Department of Pharmacology, L M College of Pharmacy, Ahmedabad, Gujarat, India

[2]Department of Psychiatry, Shubham Multispecialty Hospital, Ahmedabad, Gujarat, India

***Corresponding author:** Hardik G Dodiya (GTU PhD Scholar), Department of Pharmacology, L M College of Pharmacy, Navarangpura, Ahmedabad, 380009, Gujarat, India

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Abstract

Numerous clinical studies reported effectiveness of add-on non-steroidal anti-inflammatory agents in patients with depression. In the present study, we investigated efficacy and safety of add-on aceclofenac alone or in-combination with serratiopeptidase to sertraline in patients with depression. A total of 102 patients with depression were assigned to three different treatment groups: A) add-on aceclofenac monotherapy (200mg/day) to sertraline B) add-on fixed-dose combination (FDC) of aceclofenac and serratiopeptidase (200+30mg/day) to sertraline C) sertraline (150mg/day). Efficacy measures included the HAM-D_{17} score, MADRS score and biomarkers levels like interleukin-6, cortisol and brain-derived neurotrophic factor (BDNF). Treatment with add-on aceclofenac monotherapy or its combination with serratiopeptidase to sertraline showed significant reduction in HAM-D_{17} score at week 8 and week 12 as compared to sertraline monotherapy. Add-on therapies also showed reduction in MADRS score at week 12. Interleukin-6 levels significantly reduced in patients treated with add-on aceclofenac monotherapy or add-on FDC treatment with that of sertraline monotherapy at week 12. Both add-on treatments to sertraline also showed significant improvement in BDNF levels as compared to sertraline monotherapy at week 12.The antidepressant activity and neuroprotective potential of add-on aceclofenac monotherapy or its combination with serratiopeptidase to sertraline can be attributed to its capability of reducing IL-6 and cortisol levels and augmenting levels of BDNF.

Keywords: COX inhibitor; Aceclofenac; Serratiopeptidase; Depression; Biomarkers; Clinical Study

Introduction

Depression is a common illness worldwide and potentially debilitating mental disorder, predicted to be the most leading cause of morbidity by the year of 2030 [1]. As per National Mental Health Survey (NMHS), 5.6% lifetime prevalence is observed for mood disorders in India [2]. Women have higher incidence rate of depression as compared to men [3]. The target of antidepressants was found to reduce 50% depressive symptoms [4]. However, inadequate response to currently available antidepressants, disability associated with disease and higher prevalence are serious concerns for the management of depression [5]. Previous findings estimated that 30-50% of the depressive patients showed inadequate response to currently available antidepressants due to either lack of efficacy or intolerable side effects [6]. Recently, the role of neuroinflammation in depressive symptoms gained momentum as a potential target of treatment [6]. Growing evidence suggests that pro-inflammatory cytokines play a major role in the pathophysiology of depression [7]. Numerous studies reported elevated levels of pro-inflammatory cytokines such as tumor-necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-1 (IL-1) and interleukin-6 (IL-6), in patients with depression [8-16]. These elevated levels of pro-inflammatory cytokines trigger an inflammatory cascade in the brain which includes the induction of cyclooxygenases. Based on this finding, it has been hypothesized that treatments targeting the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) could have a beneficial effect in patients with depression with an elevated level of pro-inflammatory cytokines [17].Various clinical studies evaluated the benefit of add-on non-selective COX inhibitors (eg. aspirin, diclofenac) and add-on selective cyclooxygenase-2 (COX-2) inhibitors (eg. celecoxib) to treat neuroinflammation in patients with depression [18-26]. However, the efficacy of add-on COX inhibitors is still controversial and should be further elucidated as a potential therapeutic approach in depression with an inflammatory component [27-29]. Further, it is recommended that instead of targeting one inflammatory pathway in depression (COX), multiple pathways (inflammatory pathway, oxidative and nitrosative stress (O&NS) pathway, neurodegeneration pathway) could be a better treatment strategy in depression [29-30].

Aceclofenac is non-steroidal anti-inflammatory drug (NSAID) with an efficacy similar to that of other NSAIDs. Clinical studies reported that aceclofenac seems to possess an improved gastrointestinal tolerability as compared to other NSAIDs [31]. Aceclofenac showed slightly superior selectivity towards COX-2 inhibition as compared to celecoxib [32]. Besides this COX-inhibition, aceclofenac also inhibits proinflammatory cytokines activity (IL-6, IL-1, TNF-α) [33-34]. Serratiopeptidase (SP) is a proteolytic enzyme belonging to serine proteases class and possessing an anti-inflammatory property [35]. BDNF plays an important role in the maintenance and survival of neurons and in synaptic plasticity. Depressive patients have shown lower level of BDNF. Serratiopeptidase has never been studied in patients with depression. However, oral administration of

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serratiopeptidase in a rat model of Alzheimer's disease (AD) resulted in a significant increase in brain-derived neurotrophic factor (BDNF) levels as compared to untreated AD-induced rats indicating its neuroprotective property [36]. These findings suggest a hypothetical antidepressant mechanism for aceclofenac and serratiopeptidase in patients with depression. Till date, no study to our knowledge has explored antidepressant effect of add-on aceclofenac monotherapy or fixed-dose combination (FDC) of aceclofenac and serratiopeptidase to sertraline in patients with depression. Therefore, the purpose of present investigations is to assess efficacy and safety of add-on aceclofenac alone or in-combination with serratiopeptidase in patients with depression.

Material and Methods

Study Setting

This study was conducted at Shubham Multispecialty Hospital (Ahmedabad) between August 2019 and August 2021. The institutional ethics committee (IEC) of Shubham Multispecialty Hospital approved the study protocol (Registration number: ECR/853/Inst/GJ/2016/RR-20). The study was conducted according to the Declaration of Helsinki and its subsequent revisions, good clinical practice (GCP) guidelines and new drugs and clinical trials rules 2019. The patients were free to withdraw from the study at any time without compromising their relationship with their study doctor. The study was registered at clinical trials registery-India (Registration number: CTRI/2019/08/020562).

Study Patients

Men and women aged 18 to 65 years, with a diagnosis of depression attending the psychiatry outpatient department (OPD) in the hospital were screened according to eligibility criteria in the study. Patients were required to have depression according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria at the time of randomization and have a Hamilton depression rating scale (HAM-D_{17}) score ranging from 14 to 17 (both inclusive) [37]. All patients were stable on sertraline treatment (150 mg/day) at least the last 4 weeks prior to screening and not responding to sertraline treatment. Non-response was defined as the failure to reach a 50% decrease on the HAM-D_{17} score after at least 4 weeks of sertraline treatment (150 mg/day). All patients and their legally authorized representatives signed an informed consent form before starting any study activities. Exclusion criteria were as follows: patients having history of hypersensitivity or allergy to aceclofenac/SP/sertraline, history of gastro-intestinal bleeding/perforation or active/suspected gastrointestinal ulcer within the past 2 years, history of renal or hepatic impairment, history of angle closure glaucoma, mania/hypomania, hyponatremia, psychotic symptoms, or other DSM axis I and II psychiatric disease, history of active or recent infection within past 2 months, alcohol or substance use disorder (with the exception of nicotine and caffeine), active suicidal ideation or high risk of suicide as per study doctor discretion, history of any clinically significant concomitant medical illness or ongoing concomitant drugs (within the past 4 weeks) which may interfere with study outcome or compromises the safety of patient, receiving any other non-pharmacological therapy within the past 4 weeks, pregnant or lactating women and women of child bearing age who do not agree to use an approved method of contraception during the course of the study [31,38].

Study Design

This is single-center, 12-weeks, randomized, assessor-blind, controlled, parallel-group clinical study. In the present study, we evaluated antidepressant effects of add-on aceclofenac monotherapy or its combination with serratiopeptidase to sertraline in patients with depression. Written informed consent was obtained from all patients prior to study entry. The principal investigator recruited patient according to eligibility criteria. Sub-investigator allocated treatment to all the eligible patients as per randomization schedule. To randomize the patients, a computer random number generator was used. All patients were kept blinded for their allocated treatment. All efficacy and safety assessments of every enrolled patient in the study are performed by blinded sub-investigator to study treatment at baseline/first visit, week-4, week-8 and week-12 intervals. A window period of ±2 days was provided at week-4, week-8 and week-12 for study visits. Random allocation and assessment of the patients were done by separate sub-investigators.

Interventions

Eligible patients were randomly assigned to three different treatment groups in a 1:1:1 ratio: A) aceclofenac monotherapy (Tablet Akilos, Unison Pharmaceuticals Private Ltd, 100 mg) twice daily B) FDC of aceclofenac and serratiopeptidase (Tablet New Craze, Curewell Drugs & Pharmaceuticals Private Ltd, 100+15 mg) twice daily C) sertraline monotherapy (Tablet Serta, Torrent Pharmaceuticals Private Ltd, 50 mg). Treatment group A and B includes add-on therapy to sertraline 150mg/day whereas patients randomized to treatment C received sertraline monotherapy (150mg/day) with no any add-on placebo. Total treatment duration was 12 weeks. Patients were not allowed to use any other psychotropic/antidepressant medication or undergo behavioral intervention therapy during the study course. Medication adherence was measured using weekly tablet counts justified against patient reports of medication intake to calculate the proportion of dispensed medication doses that were actually ingested.

Outcomes

Patients were evaluated using HAM-D_{17} score at screening, baseline and at week 4, week 8 and week 12. HAM-D_{17} is a validated 17-item rating scale that has been widely applied in psychiatric studies to measure the severity of depressive symptoms and also has been used to evaluate treatment efficacy and severity of depressive symptoms in several clinical studies [39]. The primary outcome measure was to evaluate the efficacy of add-on aceclofenac monotherapy or its combination with SP to sertraline with that of sertraline monotherapy in improving depressive symptoms using HAM-D_{17} score (baseline versus week 12). The secondary outcome measures include comparison of changes in HAM-D_{17} score from baseline to each time point (week 4 and week 8), comparison of changes in Montgomery–Asberg depression rating score (MADRS) from baseline to week 12, response rate (defined as ≥50% reduction in the HAM-D_{17} score) and remission rate (defined as HAM-D_{17} score ≤7) for all the study groups. MADRS is 10-item scale (apparent sadness, reported sadness, feelings of tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel emotions, pessimistic thoughts and suicidal thoughts) which is widely used clinician-rated measure of depressive

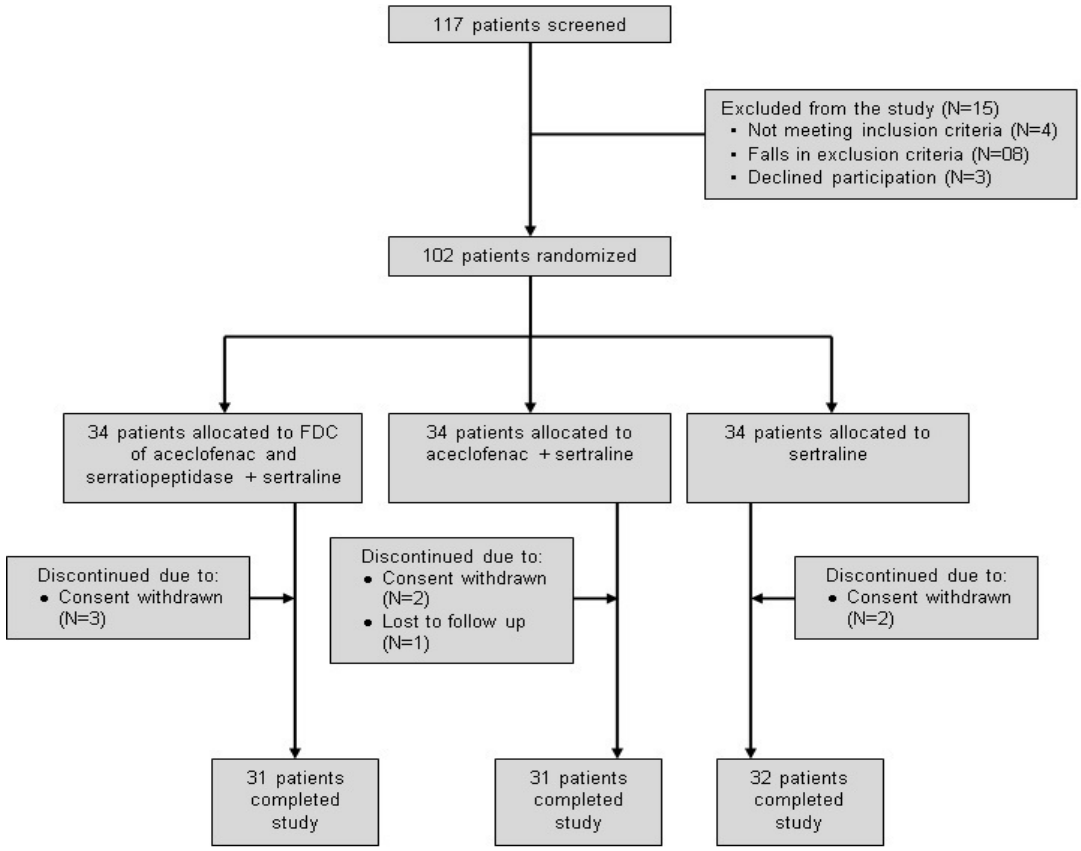

Figure 1: Disposition of patients.

severity [40]. Adverse events were systematically evaluated at each time point using a checklist. Furthermore, patients were first asked an open-ended question about any adverse event that was not mentioned on the checklist. Patients were also asked to immediately inform the research team of any unexpected symptom during the study duration.

Biomarkers Analysis

Five milliliter (ml) of venous blood was drawn from each patient for measurement of biomarkers (IL-6, cortisol and BDNF) at baseline and week 12. The blood was transferred into tubes without anticoagulants and centrifuged for 15 min at a speed of 2850 RPM. All serum samples were stored at −70°C before use. IL-6, cortisol and BDNF concentrations in the serum were determined by the sandwich enzyme immunoassay method, using Diaclone human IL-6 kit (Diaclone SAS, France), DRG human cortisol kit (DRG international, USA) and Fine human BDNF kit (Wuhan Fine Biotech Co., Ltd., China), respectively. All samples were tested in the same run, which also included a set of standards that were measured in duplicate. The amount of IL-6 (pg/mL), cortisol (µg/dL) and BDNF (µg/L) in each sample was calculated using the standard curve method [41].

Sample Size Determination

According to guidelines, a difference in outcome of at least 3 points on the HAM-D_{17} can be considered clinically significant [24,42]. Assuming a difference of 3.2 on the HAM-D_{17} score, standard deviation (SD) of 3.8 (based on previous literature), a 2-sided significance level of 5%, a power of 90%, and a drop-out rate 10%, a total sample size of 102 (34 in each arm) was needed [43].

Statistical Analysis

Categorical variables were reported as number (percentage) and continuous variables were reported as mean (±standard error of mean, SEM). A two-way repeated measures analysis of variance (ANOVA) was used to assess the time dependent effect of treatments (for HAM-D_{17} score) used under the study. Additionally, one-way ANOVA followed by Tukey's test was used to compare changes from baseline to end of study period for baseline continuous variables, MADRS score, IL-6, cortisol and BDNF levels between study groups. Within treatment group comparison between baseline and week 12 was done using a paired Student's t-test. Pearson's chi-square test was used to compare the baseline categorical variables between study groups. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistic Version 19.0 (IBM Co.)

Results

Disposition of Patients

A total of 117 patients were screened at hospital. As per protocol, 102 patients were enrolled and randomized to either test arms (either add-on aceclofenac monotherapy to sertraline or add-on FDC of aceclofenac and SP to sertraline) or reference arm (sertraline monotherapy). Among test arms, sixty-two patients completed study treatment up to week 12. The other six patients who discontinued

Table 1: Baseline characteristics of the study patients.

Parameters		Aceclofenac monotherapy + Sertraline	FDC of aceclofenac and serratiopeptidase + Sertraline	Sertraline monotherapy	P Value
Age, year, MEAN±SEM		48.40±2.20	44.70±3.00	49.60±2.40	0.356
Weight, Kg, MEAN±SEM		63.00±1.60	67.30±2.50	63.50±2.20	0.317
Body mass index (Kg/m^2)		25.90±0.80	26.50±1.00	23.90±0.50	0.08
Gender N (%)	Male	16 (47.1)	17 (50.0)	20 (58.8)	0.600
	Female	18 (52.9)	17 (50.0)	14 (41.2)	
Marital Status N (%)	Single	0 (0.0)	2 (5.9)	0 (0.0)	0.337
	Married	32 (94.1)	30 (88.2)	33 (97.1)	
	Widow	2 (5.9)	2 (5.9)	1 (2.9)	
Education Status N (%)	Up to SSC	27 (79.4)	24 (70.6)	28 (82.4)	0.504
	Up to HSC	3 (8.8)	6 (17.6)	5 (14.7)	
	Graduate and Above	4 (11.8)	4 (11.8)	1 (2.9)	
Family income in rupees N (%)	Below 5000	4 (11.8)	3 (8.8)	3 (8.8)	0.927
	5000-10000	16 (47.1)	20 (58.8)	21 (61.8)	
	10000-15000	9 (26.4)	8 (23.6)	7 (20.6)	
	>15000	5 (14.7)	3 (8.8)	3 (8.8)	
Family history N (%)	Yes	3 (8.8)	4 (11.8)	2 (5.9)	0.693
	No	31(91.2)	30 (88.2)	32 (94.1)	
History of alcohol or drug abuse N (%)	Yes	0 (0.0)	0 (0.0)	0 (0.0)	-
	No	34 (100.0)	34 (100.0)	34 (100.0)	
Duration of illness N (%)	<2 years	22 (64.7)	16 (47.1)	19 (55.9)	0.341
	2-3 years	12 (35.3)	18 (52.9)	15 (44.1)	
$HAM\text{-}D_{17}$ score, MEAN±SEM		15.80±0.20	15.80±0.20	15.40±0.20	0.279
MADRS score, MEAN±SEM		23.50±1.00	25.10±0.80	23.10±0.80	0.245
Serum IL-6 levels, pg/ml MEAN±SEM		9.40±0.70	8.60±0.60	8.70±0.50	0.071
Serum Cortisol levels, µg/dL MEAN±SEM		19.20±1.30	18.8-±1.40	19.10±1.30	0.573
Serum BDNF levels, µg/L MEAN±SEM		215±8.30	214±6.80	197±10.90	0.353
Medication adherence, % MEAN±SEM		97.1±0.50	98.0±0.40	96.5±0.60	0.161

the study were voluntary consent withdrawal (05) and lost to follow-up (01). Thirty-two patients in the reference arm completed study treatment up to week 12 and two patients withdrew consent voluntarily. The detailed disposition of patients is represented in (Figure 1).

Baseline Characteristics

Baseline characteristics of the patients including age, weight, body mass index, gender, marital status, education status, family income, family history, duration of depression, $HAM\text{-}D_{17}$ score, MADRS score and biomarker levels of all the study groups were found comparable with each other (Table 1). Statistical comparison for history of alcohol or drug abuse among treatment groups could not be analyzed since none of the enrolled patient had history of alcohol or drug abuse in last six months. All patients in treatment groups were compliant to their treatment (>92% compliance to respective treatment).

Efficacy Outcomes

Efficacy outcomes were studied in terms of $HAM\text{-}D_{17}$ score, MADRS score, response rates and remission rates.

***$HAM\text{-}D_{17}$* Score:** Treatment of add-on aceclofenac to sertraline also showed statistically significant improvement for the product of time and intervention interaction term on $HAM\text{-}D_{17}$ score when compared with the sertraline monotherapy during the study ($p<0.01$,Figure 2). However, add-on aceclofenac to sertraline did not reveal any remarkable change in $HAM\text{-}D_{17}$ score at week 4 ($p>0.05$). Patient receiving add-on aceclofenac to sertraline showed statistically significant improvement in $HAM\text{-}D_{17}$ score at week 8 (2.30 ± 0.20 vs. 1.30 ± 0.20, $p<0.05$) and week 12 (3.60 ± 0.30 vs. 1.90 ± 0.20, $p<0.05$) when compared with sertraline monotherapy.

Similarly, our study demonstrated statistically significant effect for the product of time and intervention interaction on $HAM\text{-}D_{17}$ score between treatment groups like add-on FDC of aceclofenac and SP to sertraline versus sertraline monotherapy during the study ($p<0.01$,Figure 2). However, $HAM\text{-}D_{17}$ score was not reduced significantly between treatment groups at week 4 (mean reduction in

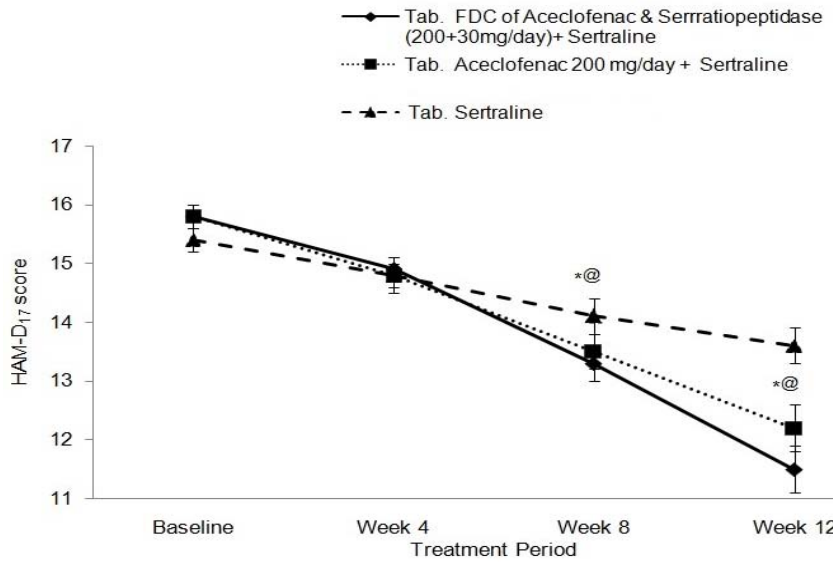

Figure 2: Comparative assessment of HAM-D_{17} score. Data are expressed as mean ± SEM .
@p<0.05 indicates that score difference between add-on aceclofenac monotherapy to sertraline when compared with sertraline monotherapy.
*p<0.05 indicates score difference between add-on FDC of aceclofenac and serratiopeptidase to sertraline as compared to sertraline monotherapy.

Table 2: Frequency of adverse events.

Adverse events	Aceclofenac monotherapy + Sertraline N (%)	FDC of aceclofenac and serratiopeptidase + Sertraline N (%)	Sertraline monotherapy N (%)	P value
Burning Sensation in Abdomen	4(12.9)	4 (12.9)	1(3.12)	0.311
Nausea	5(16.1)	3 (9.67)	1(3.12)	0.214
Headache	1(3.22)	2 (6.45)	1(3.12)	0.793
Fatigue	1(3.22)	2(6.45)	1(3.12)	0.760
Decreased appetite	1(3.22)	1(2.22)	2(6.25)	0.789

HAM-D_{17} score for add-on FDC of aceclofenac and SP to sertraline versus sertraline monotherapy: 0.80±0.10 versus 0.60±0.10, p>0.05). Although, statistically significant improvements in HAM-D_{17} score was observed between treatment groups after 8 weeks (mean reduction in HAM-D_{17} score for add-on FDC of aceclofenac and SP to sertraline versus sertraline monotherapy: 2.50± 0.20 versus 1.30 ± 0.20, p<0.01) and 12 weeks of add-on therapy (mean reduction in HAM-D_{17} score for add-on FDC of aceclofenac and SP to sertraline versus sertraline monotherapy: 4.20 ± 0.30 versus 1.90 ± 0.20, p<0.01). In addition to between group analysis, within group analysis of all the add-on study groups to sertraline also showed significant reduction in HAM-D_{17} score at week 8 and week 12 when compared with sertraline monotherapy (p<0.05).

***MADRS* score:** Our results showed significant effect for both add-on treatment groups on MADRS score at week 12 (mean reduction in MADRS score for patients receiving add-on aceclofenac to sertraline versus add-on FDC of aceclofenac and SP to sertraline versus sertraline monotherapy: 5.50±0.40 versus 6.90±0.40 versus 2.30±0.30, (p<0.05) when compared with the sertraline monotherapy (Figure 3).

Response Rates and Remission Rates: Add-on aceclofenac to sertraline also showed 16.1% responders as compared to sertraline monotherapy (3.1%). This finding with add-on aceclofenac (16.1%) did not achieve statistically significance but considered as clinically significant. Further, Add-on treatment of FDC to sertraline showed 19.3% responders (p<0.05) when compared with the sertraline monotherapy (3.1%). Remission rates for add-on aceclofenac to sertraline and add-on FDC to sertraline were 6.45% and 9.67% respectively as compared to sertraline monotherapy (p>0.05).

Biomarker Outcomes

Serum IL-6 levels at the end of study (week 12) were 6.73±0.65 pg/ml, 5.89±0.73 pg/ml and 9.00±0.50 pg/ml in the patients receiving add-on aceclofenac monotherapy to sertraline, add-on FDC of aceclofenac and SP to sertraline and sertraline monotherapy, respectively. Both add-on therapy to sertraline showed statistically significant reduction in IL-6 concentrations at week 12 (p<0.01). Serum cortisol levels did not reduce significantly in patients receiving add-on aceclofenac monotherapy (16.34±1.31 µg/dL, p>0.05) or add-on FDC (15.74±1.52 µg/dL, p>0.05) to sertraline at the end of study as compared to sertraline monotherapy (18.07±1.40 µg/dL). In addition to above, serum concentration of BDNF raised significantly in patients receiving add-on aceclofenac monotherapy (267.7±17.0 µg/L, p>0.05) as well as add-on FDC (281.0±8.61 µg/L,p<0.01) to

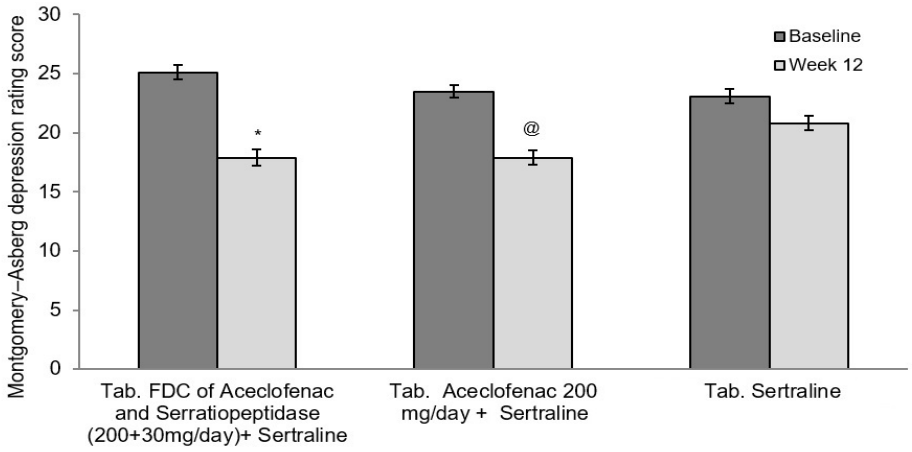

Figure 3: Comparative assessment of MADRS score. Data are expressed as mean ± SEM
@p<0.05 indicates that score difference between add-on aceclofenac monotherapy to sertraline when compared with sertraline monotherapy.
*p<0.05 indicates score difference between add-on FDC of aceclofenac and serratiopeptidase to sertraline as compared to sertraline monotherapy.

sertraline as compared to sertraline monotherapy (228.4±11.50 µg/L).

Adverse Events

None of the patients, in either group, experienced serious adverse events. However, five side-effects ranging from mild to moderate in severity were recorded during the study and were resolved without sequel before the end of study. Also, there was no statistically significant difference in the frequency of the side effects among all treatment groups (Table 2).

Discussion

In the present study, we evaluated effectiveness of FDC of aceclofenac and SP and aceclofenac monotherapy as an add-on treatment to sertraline in patients with depression. An inflammatory state is found in depressed individuals along with the increased in risk of depression [27]. They demonstrated promising results in clinical trials for depression, mainly involving patients with inflammatory disease co-morbidities [28]. NSAIDs can be used as an add-on treatment option against depression in combination with antidepressants because of common anti-inflammatory mechanisms probably due to cyclooxygenase-2(COX-2) inhibition [21]. Besides COX-2 inhibition, other potential mechanisms of NSAIDs concerning antidepressant properties include reduction in oxidative and nitrosative stress, prevention of increase of pro-inflammatory cytokines and increment of central serotonin levels [7].

The findings of the present study showed superior antidepressant property (as assessed by the primary outcome measure HAM-D_{17} score) of FDC of aceclofenac and SP and aceclofenac monotherapy when used as add-on treatment to sertraline in patients with depression. Patients receiving add-on aceclofenac monotherapy or its combination with serratiopeptidase showed significant reduction in HAM-D_{17} score at week 8 and week 12 as well as reduction in MADRS score over a 12-weeks course of treatment. Therefore, our study provides statistically significant support for an enhancement of the antidepressant effect of sertraline by concomitant add-on treatment with aceclofenac monotherapy or FDC of aceclofenac and SP. Several previous clinical studies have shown significant improvement in depressive symptoms amongst the patients receiving celecoxib or aspirin as an add-on treatment to respective antidepressants, supporting our findings [18-26]. It has also been reported that NSAIDs are unlikely to affect the efficacy of SSRI or other antidepressants when given concomitantly [43]. In the present study, FDC treatment showed greater reduction in MADRS score as compared to aceclofenac monotherapy treatment although statistically insignificant.

In the present study, our study results demonstrated 16.1% and 19.3% responders with the add-on aceclofenac monotherapy and add-on FDC treatment respectively. Previous clinical studies showed responders in the range of 57% to 95% after 4-6 weeks add-on treatment with celecoxib to respective antidepressants [19-23]. Also, Mendlewicz and co-workers reported 52.4% responders after 4 weeks treatment with add-on aspirin. Paradoxically, add-on celecoxib has also reported only 4% responders after 6 weeks treatment along with sertraline [24]. In addition to above, researchers have reported 35% to 45% remission rate after 6 weeks treatment with add-on celecoxib whereas 43% remission rate after 4 weeks treatment with add-on aspirin [18-21,23]. Our observations have shown 6.45% and 9.67% remission rates after 12 weeks treatment with add-on aceclofenac monotherapy or add-on FDC to sertraline, respectively. Therefore, contrary to published results on responders and remitters by treatment with add-on celecoxib or aspirin, our study participants had a lower responder rate and lower remission rates. This might be attributed to the effectiveness of add-on aceclofenac monotherapy or its combination with SP as compared to the reports of celecoxib or aspirin.

Currently, there is no published literature available for aceclofenac monotherapy or add-on FDC of aceclofenac and SP in reducing depressive symptoms. Evidence has shown that depressive patients may have an underlying immune deregulation that could explain the lack of therapeutic benefit from antidepressants [6]. Stimuli like inflammation and infection can trigger the activation of pro-inflammatory cytokines. These cytokines activate microglia of the hypothalamic–pituitary-adrenal (HPA) axis and produce imbalance in the serotonergic and noradrenergic circuits. Further, these cytokines also increase the activity of the enzyme indoleamine-2,

3-dioxygenase (IDO), resulting in depletion of serotonin levels. Therefore, the production of quinolinic acid is increased and leading to depression [6]. If this cytokines-based hypothesis is proven true, the patients of depression with increased levels of pro-inflammatory cytokines, mainly IL-6, TNF-α and IL-1β, can be treated with an anti-inflammatory intervention [6]. There is also a report of strong correlation between increased IL-6 concentrations and its relation to the severity of depressive symptoms [21]. Preclinical study also reported positive correlation between plasma IL-6 levels and 5-hydroxyindoleacetic acid/serotonin ratio. Hence, IL-6 is probably capable of increasing serotonin metabolism and thereby inducing neurotoxicity [21]. In agreement to this hypothesis, our study findings have shown statistically significant reduction in IL-6 concentration in patients receiving aceclofenac monotherapy or add-on FDC of aceclofenac and SP to sertraline. In the light of above, we can suggest that add-on aceclofenac monotherapy or its combination with serratiopeptidase exhibit antidepressant mechanism through their anti-inflammatory actions via reduction of pro-inflammatory cytokines like IL-6.

Hypercortisolism is one of the relevant mechanisms involved in response to stress and is present in many people with depression and in animals subjected to stress in the laboratory. Previous studies have reported positive correlation between stress levels and development of depression. Individuals suggest that these could be due to a dysregulation of the HPA axis function [44,45]. Our study showed reduction in serum cortisol levels after 12 weeks treatment with either add-on aceclofenac monotherapy or add-on FDC of aceclofenac and SP to sertraline. Therefore, the mechanism of treatments under the study might be attributed to prevention of dysregulation of the HPA axis. However, it has been recommended that longer treatment period (>12 weeks) with the present study design can help us to study the actual mechanism under the study.

As per literature, neuroprotectants with anti-inflammatory properties could be an effective treatment option for depressive patients [21]. A number of studies suggest that BDNF is involved in depression, such that the expression of BDNF is decreased in depressive patients [40]. The present study has shown statistically significant improvement in BDNF levels at the end of study using add-on FDC of aceclofenac and SP to sertraline. Contrary to this finding, add-on aceclofenac monotherapy to sertraline have not shown statistically significant improvement in BDNF levels at week 12 as compared to sertraline monotherapy although observed as clinically significant. This augmented level of BDNF with add-on aceclofenac monotherapy or its combination with serratiopeptidase to sertraline suggesting a neuroprotective role of add-on therapies and thereby preventing neurodegeneration in patients with depression. Several studies have shown anti-inflammatory effect of SP in varieties of inflammatory conditions [36,38,46].This anti-inflammatory action of SP may represent an additional mechanism for alleviating depressive symptoms via increasing BDNF levels under the study. We also did not observe any serious or severe adverse events during the study. However, our study showed higher rates ($p>0.05$) of gastrointestinal adverse events (burning sensation in abdomen and nausea) in patients treated with aceclofenac or its combination with serratiopeptidase as compared to sertraline monotherapy. These gastrointestinal (GI) adverse events were in-line with the available safety literature of the NSAIDs and can be minimized with concomitant administration of anti-secretory agents [31,38].

In line with previous evidences, we observed that add-on aceclofenac or its combination with serratiopeptidase to sertraline showed significant reduction in HAM-D_{17} score, MADRS score, IL-6 concentration and cortisol concentration as compared to sertraline monotherapy. Further, both add-on treatments have also shown good improvement in BDNF levels without causing any notable adverse events. These findings confirm safety and efficacy of add-on aceclofenac or its combination with serratiopeptidase to sertraline in depressive patients with higher level of pro-inflammatory cytokines. However, our study revealed low percentages of remission and response rates with aceclofenac and its combination with serratiopeptidase. Therefore, further research will be warranted to establish benefit of add-on aceclofenac or its combination with serratiopeptidase in patients with depression.

Limitations and Future Directions

The present study has shown anti-depressant action of add-on aceclofenac or its combination with serratiopeptidase to sertraline. However, it certainly has several limitations. We have not measured changes in serum quinolinic acid levels which might help to demonstrate cytokines-induced depletion of serotonin levels. Further, we administered add-on investigational drugs up to 12 weeks only with limited sample size. Long term studies (24 weeks or 48 weeks) using larger sample size may give good results in terms of reduction in inflammatory biomarkers (interleukin-6 and cortisol), higher level of brain-derived neurotrophic factor and monitoring kidney and liver function.

Conclusions

In conclusion, we suggest that the antidepressant activity and neuroprotective potential of add-on aceclofenac monotherapy or its combination with serratiopeptidase to sertraline could be attributed to its capability of reducing IL-6 and cortisol concentrations and raised levels of BDNF. Thus, it is suggested that add-on aceclofenac or its combination with serratiopeptidase to sertraline are safe and effective in depressive patients with an elevated level of pro-inflammatory cytokines. Further studies will be needed to confirm benefits of NSAIDs in patients with depression.

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Conflict of Interest

The authors declare no conflict of interest.

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