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ANALYSIS OF LIVER FUNCTION TESTS AND RENAL FUNCTION TESTS IN MAJOR DEPRESSIVE PATIENTS ON IMIPRAMINE, SERTRALINE AND ESCITALOPRAM THERAPY: AN OBSERVATIONAL STUDY IN A TERTIARY CARE HOSPITAL, AJMER, RAJASTHAN

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Keywords:

Depression, LFT, RFT, Imipramine, Sertraline and Escitalopram

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ABSTRACT: Depression is the major cause of disability Worldwide. Antidepressant medications remain a mainstay of treatment for major depressive disorder. Our aim in this study was to analyze the LFT & RFT in patients of major depressive disorder taking imipramine, sertraline and escitalopram. A total of 810 such patients meeting the inclusion and exclusion criteria were randomly divided into three groups *i.e.* group I, II & III containing 270 patients in each group and treated with imipramine, sertraline and escitalopram as per scheduled dose respectively. LFT & RFT parameters during enrolment visit as well as follow up at 4 weeks, 8 weeks, and 12 weeks were recorded and analysed as per appropriate statistical method. After 12 weeks of treatment mean value of SGOT, SGPT, serum bilirubin, serum alkaline phosphate, serum albumin and total protein level were increased in all study groups but these were within normal range. In RFT; mean value of blood urea, uric acid and serum creatinine increased whereas serum sodium level and serum potassium level was reduced from base line after 12 weeks of treatment in all groups; however all these changes were observed within normal limits. **Conclusion:** In term of LFT & RFT, we found that all study drugs (Imipramine, Sertraline and Escitalopram) are safe in major depressive patients. We suggest, for safety of patients, LFT & RFT should be done before initiation of treatment and regularly during treatment to rule out any hepatic and/or renal discrepancy.

INTRODUCTION: Depression is the major cause of disability Worldwide. According to the WHO, every year, 5.8% males and 9.5% females experience episodes of depression worldwide [1]. Major depression is experienced by 10-15% people in their lifetime [2]. Overall prevalence of 15.9% for depression was reported in Indian context [3].

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American psychiatric association treatment guidelines recommend that initial treatment should be individually tailored based on factors including severity of symptoms, co-existing disorders, prior treatment experience, and patient preference.

Options may include pharmacotherapy, psycho-therapy, exercise, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) or light therapy. Antidepressant medication is recom-mended as an initial treatment choice in people with mild, moderate, or severe major depression, and should be given to all patients with severe depression unless ECT is planned [4]. Drug-induced liver injury (DILI), the fourth leading cause of liver

damage in Western countries. It is a matter of concern in the context of increasing drug availability and prescription [5]. The incidence of drug induced liver injury (DILI) is between 1 per 10000 and 1 per 100000 patient-year [6, 7]. DILI can be classified as hepatocellular, cholestic or mixed depending on the underlying liver injury [8].

In hepatocellular injury, there is abnormally high serum alanine aminotransferase (ALT) titers with a small or no increase in alkaline phosphatase (ALP) titers and associated with high serum bilirubin level [9]. Cholestatic liver injury is characterized by high serum ALP titers associated with only slightly higher than normal ALT levels; serum bilirubin concentrations may also be high. In cases of mixed injury, both ALT and ALP levels are abnormally high. Therefore, ALT values > 3 x upper limit of normal (ULN) or ALP values > 2 x ULN are indicative of DILI [10]. Various studies were performed to analysis the impact of antidepressants on liver function tests (LFT). Antidepressants induced liver injury is generally considered to be dose independent.

Many research studies were performed in depressive patients with renal impairment (acute or chronic) person to observe the effects of antidepressants. It is evident from various studies that oxidative stress and uric acid levels also play an important role in the pathophysiology of mood disorder [11, 12]. It is also evident in some studies that psychotropic agents may cause hyponatraemia [13]. Several case reports also shown an association between the use of SSRIs and hyponatraemia [14 -16]. In some studies, low serum creatinine was observed in depressive patients [17].

We found very little studies in which LFT and renal function tests (RFT) were analysed in major depressive patients receiving imipramine, sertraline and escitalopram. Paucity of such type studies especially in Indian scenario prompts us to take present study.

Aims and Objectives: Our aim in this study was to analyze the LFT & RFT in patients of major depressive disorder taking imipramine, sertraline and escitalopram.

Methodology: This prospective, open label, comparative and observational study was conducted after obtaining the approval from the institutional ethics committee (order no. 1685/ Acad-III/MCA/2014 dated 20/10/2015) & approval from Rajasthan University of Health Sciences, Jaipur (RUHS).

Source of data: Patients of depressive disorder visiting OPD (Out Patient Department) of psychiatric department of JLN Medical College & associate group of Hospitals, Ajmer (Rajasthan). Patients were included since August 2016 as per inclusion and exclusion criteria of this study.

Inclusion/Exclusion Criteria: Patients of either sex aged between 18-65 years, newly diagnosed patients of major depressive disorder fulfilling the diagnostic and statistical manual of mental disorder, 5th edition (DSM-V) criteria. Patients with >/= 14 to 28 on BDI (Beck Depression Inventory Rating Scale- BDI-II) score, Patients giving written informed consents were included in present study.

Patients who were treated more than one antidepressant and having additional or other disorder/medical conditions and those patients who do not fulfil inclusion criteria were excluded from present study.

Sample Size: Sample size was calculated by ANOVA test using statistical analysis software primer version 6.0. We obtained a number of 802. For convince a total of 810 patients with depressive disorder meeting the inclusion and exclusion criteria of present study were selected. They were randomly allocated into three groups contain 270 patients in each group and treated in following manners:

Group I: Study subjects were treated with imipramine orally in a dose of 75 mg BD.

Group II: Study subjects were treated with sertraline orally in a dose of 150 mg daily (*i.e.* 50 mg in morning and 100 mg in night).

Group III: Study subjects were treated with escitalopram orally in a dose of 10 mg BD.

LFT & RFT parameters during enrolment visit as well as follow up at 4 weeks, 8 weeks and 12 weeks were recorded and analysed as per appropriate statistical method. Values of LFT & RFT parameters were estimated by standard

methods given by Dumas BT *et al*., Gornal AG *et al*., Fawcett JK *et al*., Fossati P *et al*., etc. [18 - 23]

RESULTS: A total of 187 patients in group I, 228 in group II and 237 patients in group III completed this study; rest of the patients were withdraw from present study due to adverse effects or unknown reasons.

At baseline and 4 week follow up, no significant intergroup differences in mean value of SGOT (U/L) were observed. However, at 8 and 12 weeks, intergroup differences were significant. At 8 weeks, inter group difference observed for the pair III *vs.* I while at 12 week interval intergroup difference observed for pairs I *vs.* II and I *vs.* III **Chart 1a**. After the completion of treatment (12 weeks), a significant increase in mean values of SGOT (U/L) was observed in all the three groups ($p<0.001$). Mean was maximum in Group I and minimum in Group II **Chart 1b**.

At baseline, week 4 and week 12 follow up intervals, statistically no significant intergroup difference was observed in mean value of SGPT. Only statistically significant difference was observed at week 8 ($p=0.014$). At this interval, mean value in Group III was significantly higher as compared to that in Groups I and II ($p<0.05$) **Chart 2a**.

After completion of treatment (12 weeks), all the three groups showed a significant increase in mean values of SGPT ($p<0.001$) **Chart 2b**.

At baseline, and 4 week follow up interval, a significant intergroup difference in mean value of serum bilirubin (mg/dl) was observed. While at 8 week and 12 week follow up intervals, no intergroup difference in serum bilirubin (mg/dl) was observed. On evaluating the between group difference, significant difference in mean values of serum bilirubin was observed between Groups I and III at baseline and 4 weeks **Chart 3a**.

After completion of treatment (12 weeks), an increase in mean value of serum bilirubin was significant only for group II and III ($p\leq0.001$) **Chart 3b**. From **Chart 4a**, Serum Alkaline Phosphate at baseline as well as all the follow up intervals, no significant intergroup difference was observed among the three study groups. In all the three groups a significant increase in mean value was observed after completion of treatment ($p<0.001$) **Chart 4b**.

At baseline as well as all the follow up intervals, no significant intergroup difference in serum albumin was observed among the three study groups **Chart 5a**. However in all the three groups a significant increase in mean value was observed after completion of treatment ($p<0.001$). The result indicates that mean value of serum albumin (mg/dl) significantly increased **Chart 5b**.

It is evident from **Chart 6a**; at baseline as well as all the follow up intervals, no significant intergroup difference in mean value of total protein was observed among the three study groups. For Group I and Group II significant increase in the mean values of total protein was observed as p values are less than 0.05 **Chart 6b**.

Chart 7a shows that at baseline as well as all the follow up intervals, no significant intergroup difference in mean value of blood urea was observed among the three study groups. At all the time intervals, the three groups were comparable statistically ($p>0.05$). However all the three groups have a significant increase in mean value after completion of treatment ($p<0.001$) **Chart 7b**.

In **Chart 8a**, at baseline as well as all the follow up intervals, no significant intergroup difference in mean value of uric acid was observed among the three study groups as p values are less than 0.05. All the three groups a significant increase in mean value was observed after completion of treatment ($p<0.001$) **Chart 8b**.

It is evident from **Chart 9a**, mean value of serum creatinine at baseline as well as all the follow up intervals, no significant intergroup difference was observed among the three study groups. In all the three groups a significant increase in mean value of serum creatinine was observed after completion of treatment ($p<0.001$) **Chart 9b**.

It is observed from **Chart 10a**, at baseline, there was no significant intergroup difference in mean value of serum sodium ($p=0.404$), statistically significant intergroup differences were observed from 4 week follow up interval onwards. At 4 weeks, Group I had significantly higher mean value

as compared to Groups II and III. At week 8, Group I had significantly higher mean value as compared to Group III whereas Group II had significantly higher mean value as compared to both Groups I and III. At 12 weeks, Group I and Group II had significantly higher mean value as compared to Groups III.

In all the three groups following completion of treatment (12 weeks), a decrease in mean values of serum sodium was observed ($p<0.001$) (chart 10 b). It is evident from **Chart 11a** that at baseline as well as all the follow up intervals, no significant intergroup difference in mean value of serum potassium was observed among the three study groups. At all the time intervals, the three groups were comparable statistically ($p>0.05$). In all the groups a decrease in mean values was observed **Chart 11b**.

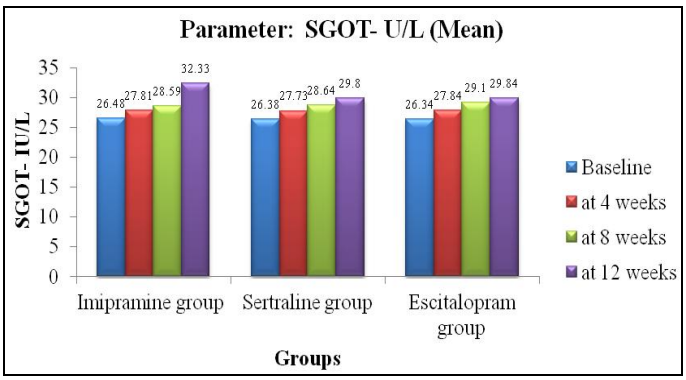

CHART 1A: INTER AND BETWEEN GROUP COMPARISON OF SGOT (U/L)

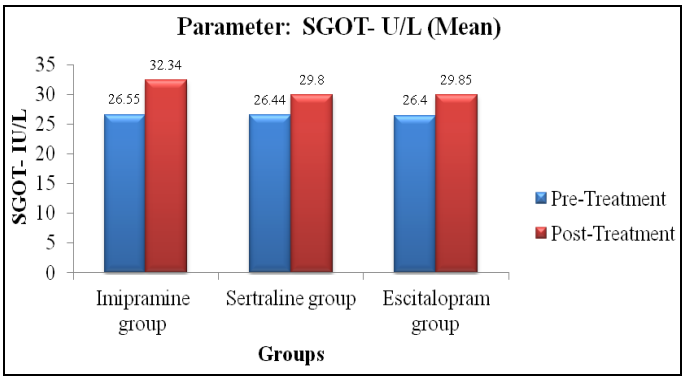

CHART 1B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

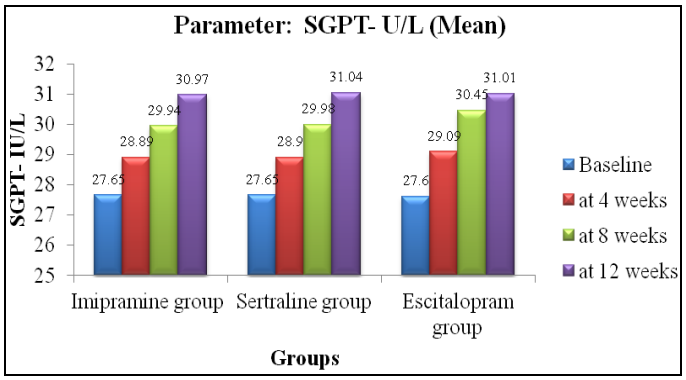

CHART 2A: INTER AND BETWEEN GROUP COMPARISON OF SGPT (U/L)

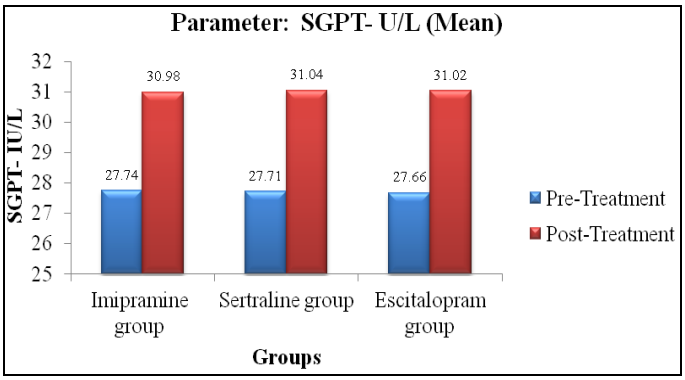

CHART 2B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

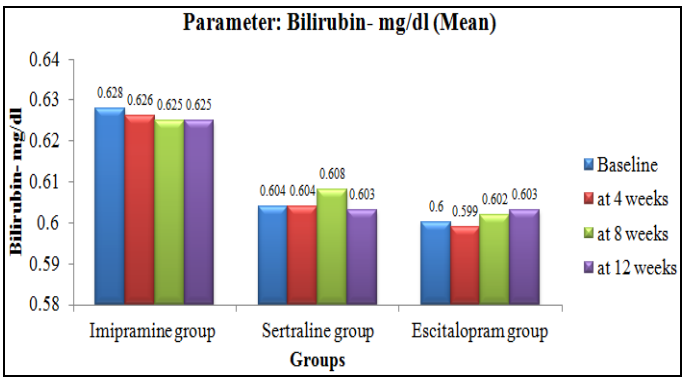

CHART 3A: INTER AND BETWEEN GROUP COMPARISON OF *S. BILIRUBIN* (mg/dl)

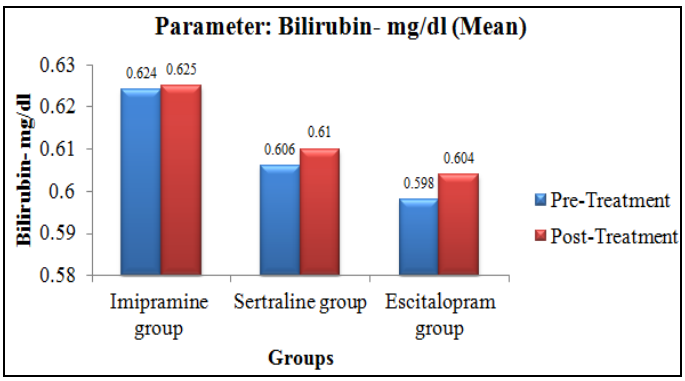

CHART 3B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

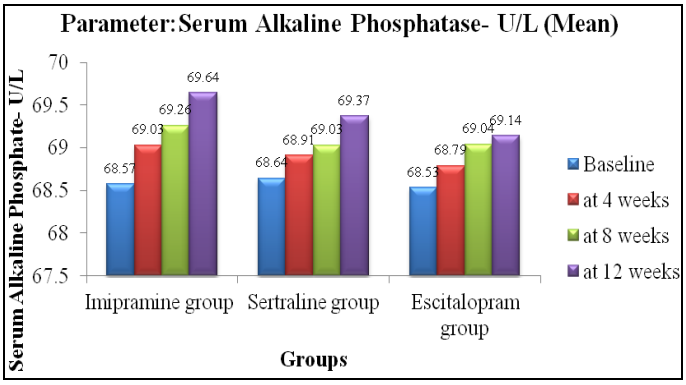

CHART 4A: INTER AND BETWEEN GROUP COMPARISON OF SERUM ALKALINE PHOSPHATASE (mg/dl)

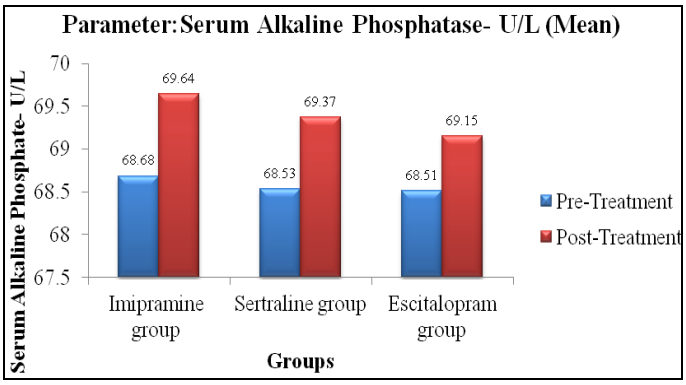

CHART 4B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

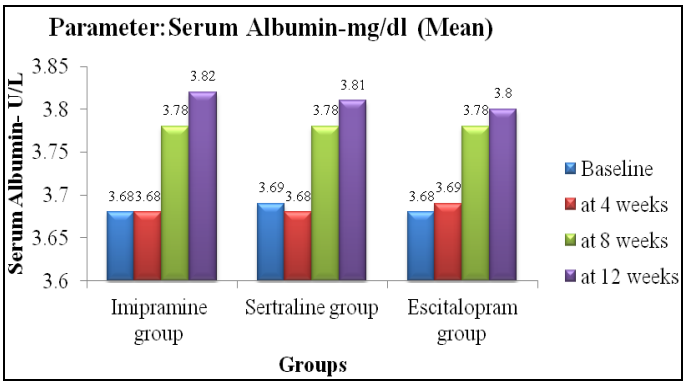

CHART 5A: INTER AND BETWEEN GROUP COMPARISON OF S. ALBUMIN (mg/dl)

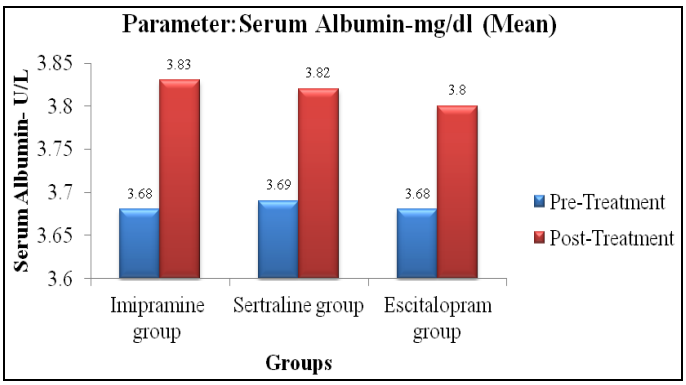

CHART 5B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

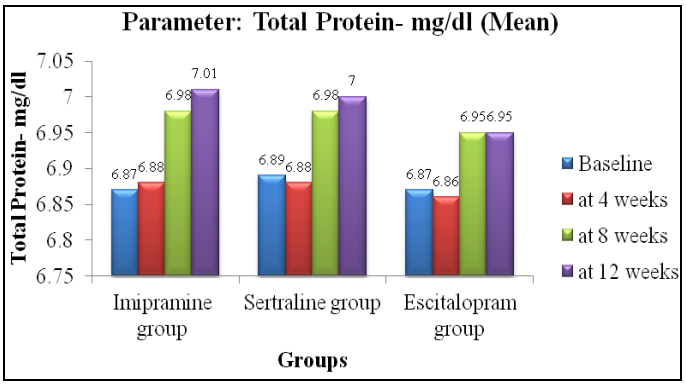

CHART 6A: INTER AND BETWEEN GROUP COMPARISON OF TOTAL PROTEIN (mg/dl)

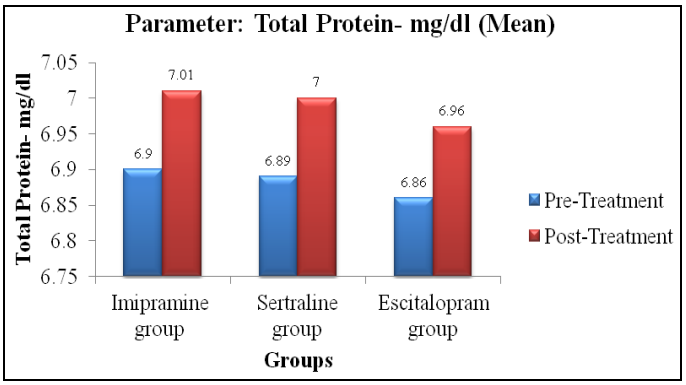

CHART 6B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

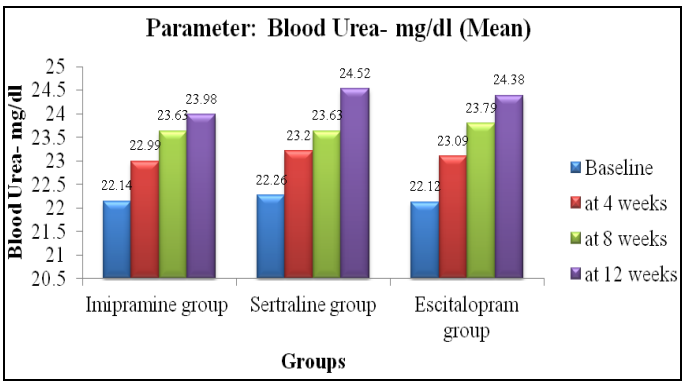

CHART 7A: INTER AND BETWEEN GROUP COMPARISON OF BLOOD UREA (mg/dl)

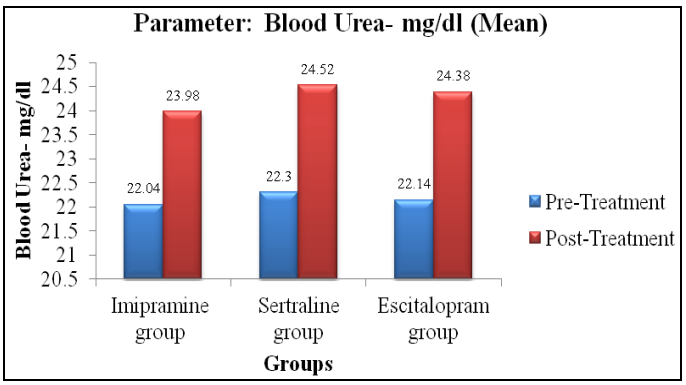

CHART 7B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

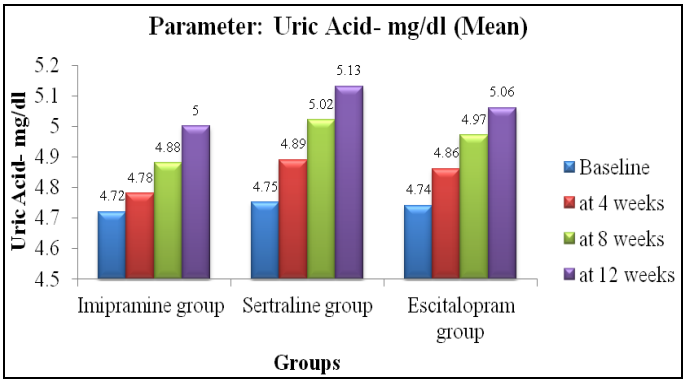

CHART 8A: INTER AND BETWEEN GROUP COMPARISON OF URIC ACID (mg/dl)

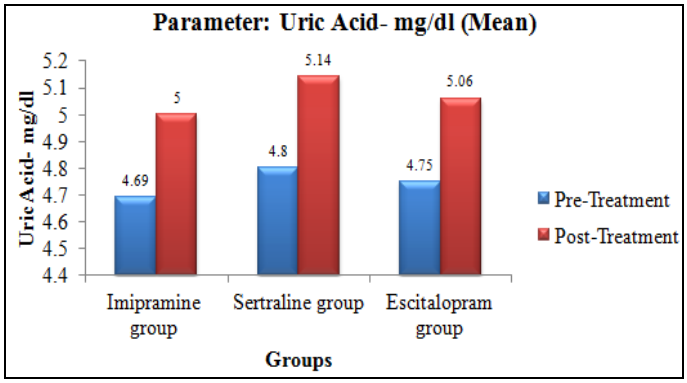

CHART 8B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

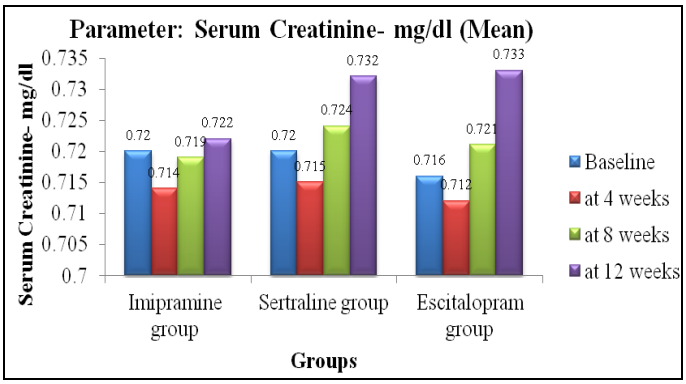

CHART 9A: INTER AND BETWEEN GROUP COMPARISON OF S. CREATININE (mg/dl)

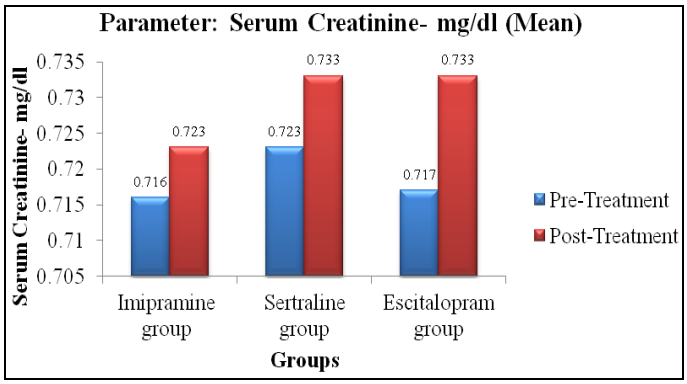

CHART 9B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

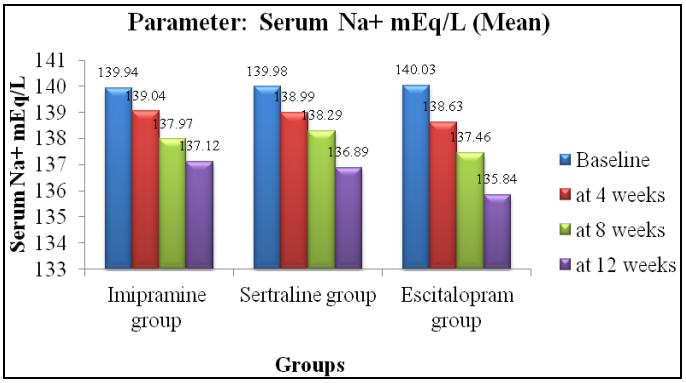

CHART 10A: INTER AND BETWEEN GROUP COMPARISON OF S. SODIUM (MEQ/L)

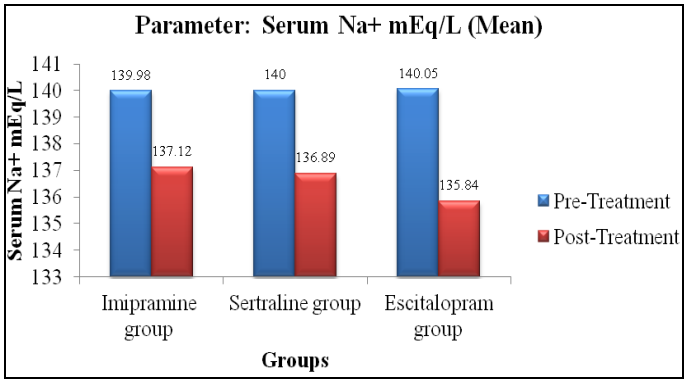

CHART 10B: WITHIN GROUP EVALUATION OF CHANGE AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

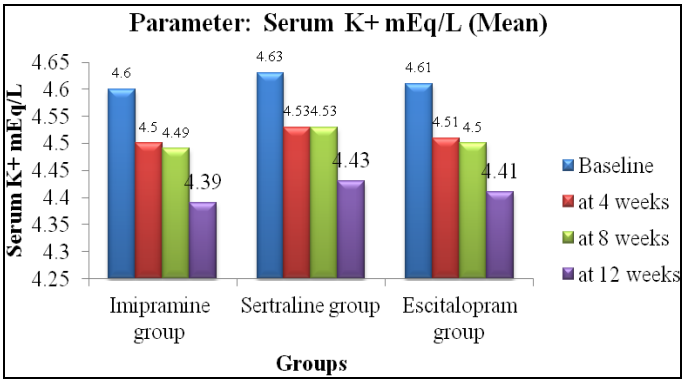

CHART 11A: INTER AND BETWEEN GROUP COMPARISON OF S. POTASSIUM (mEq/L)

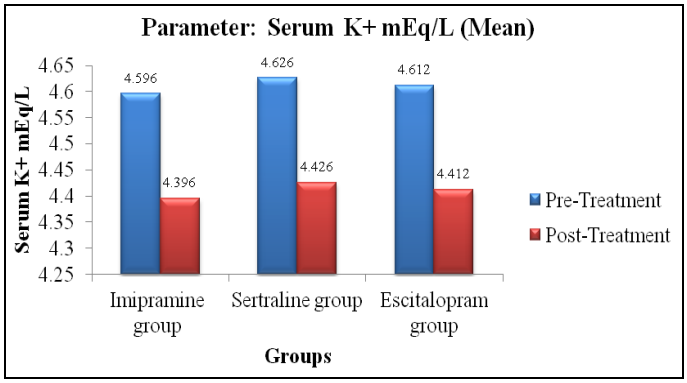

CHART 11B: WITHIN GROUP EVALUATION OF AMONG PATIENTS COMPLETING 12 WEEKS OF TREATMENT

DISCUSSION: LFT: In present study there is no significant intergroup differences observed at baseline and 4 weeks follow up but it was statistically significant on at 8 and 12 weeks follow up. After 12 weeks of treatment, a significant increase in SGOT (AST) mean value was observed in all the three groups ($p<0.001$). Maximum increase in mean SGOT was observed in imipramine group. SGPT (ALT) level was significantly increased in all groups after 12 weeks of treatment ($p<0.001$). In intergroup comparison, it was significantly difference at 12 weeks follow up period only; however all these values remain in normal limits throughout the study period.

Chart 3a shows no intergroup difference in serum billirubin level at 8 weeks and 12 weeks follow up intervals. After completion of 12 weeks treatment, an increase in mean value was significant only for group II and III **Chart 3b**. However in all these group, serum bilirubin level was within normal range. These finding were in accordance with Divya Shree M *et al*., Chetan S Urade *et al*. [24, 25]

Many studies were carried with antidepressants to find out any discrepancy on liver. Some studies found that they are hepatotoxic. A. Mhalla *et al*., found that the ALT activity was significantly higher in patients treated with TCA compared to those treated with the SSRI ($p=0.011$). They also observed an increase in ALT and AST activities in 4.7% of patients treated with TCA and 3.7% of patients treated with SSRI [26]. In present study, no sign of any hepatotoxicity was found during study period.

Antidepressant: induced liver injury is generally considered to be dose independent. Hepatotoxicity caused by sertraline is rare [27]. The mechanism of liver injury associated with antidepressants is metabolic or immunoallergic. A hypersensitivity syndrome (fever, rash, eosinophilia, auto-antibodies) and a short latency period (1 to 6 weeks) [28] suggest immune-mediated hepatic injury, whereas the absence of any hypersensitivity syndrome and a longer latency period (1 month to 1 year) suggests an idiosyncratic metabolic mechanism [29]. In present study no patients were found to include in DILI criteria. Liver function tests were within recommended range in all study patients.

Some studies establish a relationship between serum albumin, total protein and depression. Hypoalbuminaemia has been reported more in patients with major depressive disorder than in normal volunteers [29 - 33]. Tiao-Lai Huang observed lower serum albumin level during the acute phases of mania and major depression in Taiwanese psychiatric inpatients [34].

S. Salimi noted that albumin and total serum protein were significantly lower in depressed patients than in normal control group. Few researches suggested that depression is accompanied by activation of the inflammatory response system (IRS). Proinflamatory cytokines such as IL-6 & IL-1b and interferon G activates IRS. Activation of IRS results in decrease in serum albumin concentration [35].

In present study; serum alkaline phosphatase, serum albumin and total protein were increased after 12 weeks of treatment in all groups but this was found within normal range during entire study period. Present study indicated that as the treatment progress, patients condition improves and serum alkaline phosphatase, serum albumin and total protein level rises but within recommended range. Based on previous research and our finding it is suggested that for safety of patients, liver function tests should be done before the initiation of a treatment and regularly during treatment to rule out any hepatic discrepancy.

RFT:

Blood Urea and Uric Acid: There is no significant intergroup difference was observed for blood urea and uric acid level at base line as well as follow up interval among study group. However after treatment these groups have a significant increase in mean value. This increment in mean value was within normal range **Chart 7a, 7b, 8a & 8b**. These results are in accordance with chetan S. *et al*., 2015 and Mojtaba Keshavarz *et al*., 2016 [25, 36].

It is evident in many studies that oxidative stress is involved in the pathophysiology of mood disorders. It has been demonstrated that oxidative stress markers are increased in MDD and BD [12]. Uric acid is a natural antioxidant, with high levels of free-radical scavenging activity in the blood [37] and brain [38].

It has been suggested that low uric acid levels are associated with the development and progression of a variety of central nervous system (CNS) diseases [39]. It has been prove in many studies that mood-stabilizing agents augment antioxidant defences [40, 41]. Pharmacotherapy may increase uric acid to protect neuronal cells against oxidative stress damage in mood disorders. In view of previous research and present study; uric acid, is an indicator of the purinergic and oxidative stress systems, may be a new target for the development of drugs that could accelerate treatment responses in mood disorders.

Serum Creatinine, S. Sodium & Potassium level: In present study, at base line as well as follow up intervals, no significant intergroup difference was observed in serum creatinine value among study group. All the three groups show a significant increase in mean serum creatinine after completion of 12 weeks treatment; however this increment was within normal range. It is evident in few studies that depressive patients had lower serum creatinine value [17]. In present study, as therapy progress, serum creatinine level increased showing improvement in patient's condition. However this increment was within normal recommended range. Our results are in accordance with Heng Jung Hsu *et al*., 2013 and Chetan S. Urade *et al*., 2016 [17, 25]. It is observed from chart 10 (a) that statistically significant intergroup difference of serum sodium level was noted from 4 week follow up interval onwards. In all the three groups after completion of 12 weeks treatments, a significantly decrease in mean value of serum sodium level was observed ($p<0.001$).

There is no significant intergroup difference of Serum potassium level was observed among study group. Similar results were also found in previous studies done by Divyashree M et al 2014, Singh AK *et al*., 2011, Catalano MC *et al*., 2000 [24, 42, 43]. In present study, no patients complained of any symptoms due to hyponatraemia or hypokalaemia in all three groups. However above electrolyte values remain in normal range. Signs and symptoms of hyponatraemia generally do not appear until the serum concentration falls below 130 m mol^{-1} of chronic hyponatraemic patients remain asymptomatic even with serum concentration lower than 125 m mol/l [44].

Usage of psychotropics, diuretics and antiepileptics are associated with hyponatraemia [13, 45, 47]. Antideprassants are known to cause syndrome of inappropriate antidiuretic hormone secretion (SIADH) which constitute hyponatremia and hypokalaemia [24]. Numerous case reports show an association between the use of SSRIs and hyponatraemia [14 - 16]. Siegler and colleagues found that use of fluoxetine and tricyclic antidepressants (TCAs) was significantly associated with hyponatraemia, with fluoxetine showing a higher risk than TCAs [48].

The pathogenesis of hyponatraemia in patients treated with antidepressants in general and with SSRIs specifically is unknown. Some animal studies have shown that serotoninergic mechanisms are involved in the regulation of antidiuretic hormone secretion [49, 50]. The syndrome of inappropriate antidiuretic hormone secretion has often been mentioned in case reports as the cause of antidepressant-associated hyponatraemia. Further research is needed to elaborate the mechanism through which antidepressants cause hyponatraemia. Based on previous case reports/research and our study results; it is concluded that physicians should be aware of SSRI-induced hyponatraemia in daily clinical practice. It is advice to measure serum electrolytes on a regular basis also.

CONCLUSION: After 12 weeks of treatment mean value of SGOT & SGPT were increased in all study groups. Maximum increase in mean SGOT was observed in imipramine group. As the therapy progress; serum bilirubin, serum alkaline phosphate, serum albumin and total protein level rises but it was within normal range. We did not find any case of hepatotoxicity due to above prescribe antidepressants. Mean value of blood urea, uric acid and serum creatinine increased whereas serum sodium level and serum potassium level was reduced from base line after 12 weeks of treatment in all groups. However liver enzymes were more increased with imipramine. However, all changes were found within normal limits. No sign of hyponatraemia was seen in any patients of any group. In term of LFT & RFT, we found that all study drugs (Imipramine, Sertraline and Escitalopram) are safe in major depressive patients.

Based on previous research and our study results, escitalopram was found safer than imipramine and sertraline. Regarding LFT & RFT, further studies are needed to evaluate the effects of imipramine, sertraline and escitalopram on long term use. We suggest, for safety of patients, LFT & RFT should be done before initiation of treatment and regularly during treatment with an antidepressants to rule out any hepatic and/or renal discrepancy.

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