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ORIGINAL RESEARCH

A study of hepatoprotective effect of N-acetyl cystein on the patient receiving ATT in tertiary care centre

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ABSTRACT

Aim: *To hepatoprotective effect of N-acetyl cystein on the patient receiving at in tertiary care centre.*

Material & Methods: *Study will be conducted on 50 newly diagnosed pulmonary TB and treatment naïve patient from the Department of TB and CHEST at Index Medical College, Research centre and Hospital, Indore and all the tests will be performed with due permission from the Institutional Ethical Committee and informed consent from the subjects or their legal relatives. Subjects were included on the basis of their diagnosis of TB as per RNTCP guidelines. A rise of five fold in ALT over upper normal limit in the absence of symptoms and any increase in serum bilirubin.*

Results: *For the Sample size of 50 patients, 24 used the NAC drug & 26 were not administered NAC Drug. Without the use of NAC Drug : The Mean SGOT variation was observed from 40.23 to 123.65 from the 1st week to 3rd week, Mean SGPT from 34.31 to 77.38 and MeanBilirubin variation was from 0.37 to 0.48. As per the study, to study the hepato-protective effect of N-acetyl cystein on liver injury induced by anti TB drugs 24 patients were administered NAC drug. It was observed & documented that Mean SGOT variation from the 1st week to the3rd week, the change was from 26.92 to 29.92, Mean SGPT variation was from 23.67 to 29.0 and the Mean Bilirubin variation observed was from 0.40 to 0.46. The percentage change is very visible on comparison of the use of NAC drug vis-à- vis NAC drug not administered. The percentage change of SGOT was 111.15% in NAC used patients (p-value 0.0036) & 307.36% in patient not given NAC drug (p-value 0.0009). SGPT percentage change was 122.51% (p-value 0.0005) as compared to 225.56% for Patient not on NAC drug (p-value 0.0009) and Bilirubin percentage change was 115.30% for patient on NAC drug (p-value 0.0050) & 127.31% for patient not onNAC drugs (p-value 0.0301).*

Conclusion: *Isoniazid, rifampicin, and pyrazinamide, the first-line antituberculosis (anti-TB) drugs are associated with hepatotoxicity. Patients treated with antituberculosis drugs may experience hepatotoxicity ranging from simple hepatic enzyme elevations to severe clinical hepatitis. According to our study results, it could be concluded that NAC acts as an effective antioxidant in the prevention of ATT-induced hepatotoxicity. Administration of NAC produced a significant hepatoprotective effect and effectively reduced lipid peroxidation.*

Keywords: *ATT, hepatotoxicity, NAC.*

Introduction

Liver injury is a common complication of first-line anti-tuberculosis therapy. Isoniazid, rifampicin, and pyrazinamide, the first-line antituberculosis (anti-TB) drugs are associated with hepatotoxicity.[1]

The reasons for this higher rate of hepatotoxicity are not completely clear. Ethnic variations, advanced age, female sex, alcoholism, underlying liver disease, acetylator phenotype, hepatitis B and C virus, HIV infection, extensive pulmonary parenchymal disease, and hypoalbuminemia have been observed to be the risk factors for the development of drug-induced hepatotoxicity (DIH) because of anti-TB treatment. Patients treated with antituberculosis drugs may experience hepatotoxicity ranging from simple hepatic enzyme elevations to severe clinical hepatitis.[2-4] ATT induced DIH usually benign but may result in serious morbidity and mortality. The free radicals are probably generated during the metabolism of the various anti TB drugs The mechanism of DIH induced by anti-TB treatment is not yet fully understood. [5-8]

Studies have shown that INH-RIF-induced oxidative injury can be prevented by supporting the cellular anti-oxidant defense mechanism by N-acetylcysteine (NAC). However, there are no published data regarding the protective effect of NAC against hepatotoxicity induced by anti-TB drugs in humans to our knowledge. Therefore, we designed a clinical trial with the aim to see whether NAC could protect against anti- TB DIH. Drug induced hepatotoxicity is a health problem and is expected to increase as the number of drug being consumed increases both prescription and non- prescription as well as pharmacological active substances in complementary and alternative medicine. Many cases of drug induced liver injury are idiosyncratic i.e. unpredictable based on the known pharmacological properties of the substance, and hence easily missed during preclinical stages of development.[9] Drug induced liver injury may present with several different clinical features; hepatitis / hepatocellular, cholestatic or mixed. They often have the basis in an adverse immune response, for instance towards reactive metabolites of the drug that may bind to cellular proteins and macromolecules, hence form neo antigens, that are recognized by the immune system. reactive metabolite have direct detrimental effect on cellular function, many times affecting mitochondrial function.[10]

In this context, the purpose of this study is to study the hepatoprotective effect of N-acetyl cystein on liver injury induced by anti TB drugs on Patients on ATT and to investigate the short-term effects upto a period of 16 months (January 2021 till May 2022) and possible complications during treatment.

Material & Methods

All patients between 18 years to 65 years of age admitted in Chest ward in the Department of Respiratory Medicine of Index Medical College, Indore, with symptoms of TB between January 2021 to May 2022 .

Study will be conducted on 50 newly diagnosed pulmonary TB and treatment naïve patient from the Department of TB and CHEST at Index Medical College, Research centre and Hospital, Indore and all the tests will be performed with due permission from the Institutional Ethical Committee and informed consent from the subjects or their legal relatives.

Subjects were included on the basis of their diagnosis of TB as per RNTCP guidelines.

Diagnosis of ATT induced hepatotoxicity is considered with the presence of the following criteria was defined as DIH:

A rise of three folds times the upper limit of normal levels of serum aspartate aminotransferase (ALT) reporting jaundice and /or hepatitis symptoms suchas nausea, vomiting, abdominal pain. or A rise of fivefold in ALT over upper normal limit in the absence of symptoms and any increase in serum bilirubin.

Inclusion criteria

- Age 18 to 65 years.

- Newly diagnosed pulmonary or extrapulmonary tuberculosis based on symptoms, radiological features and/or laboratory evidence and requiring first line ATT.
- LFT values less than or equal to 3 times of the normal reference values (SGOT less than or equal to 105 U/L, SGPT less than or equal to 120 U/l, ALP less than or equal to 390 U/l) and total bilirubin less than or equal to 2 mg / dl.

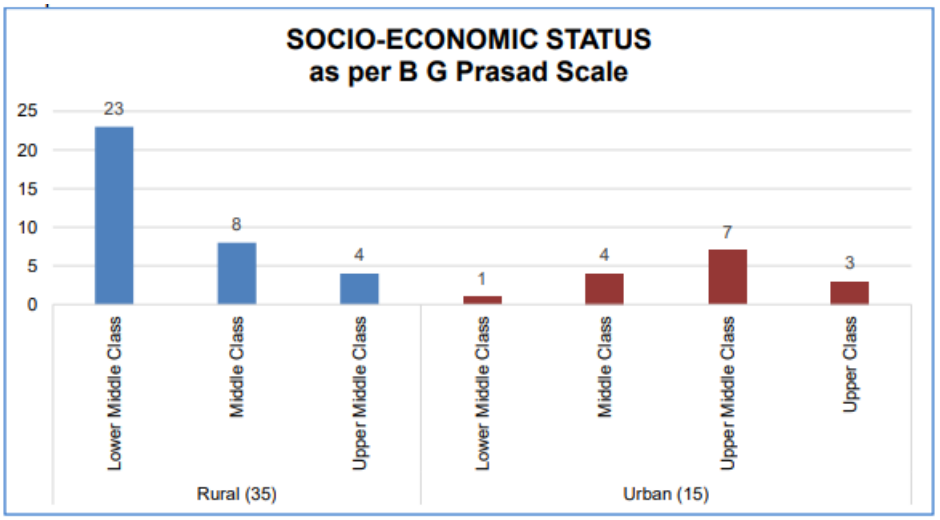
Exclusion criteria

- Pregnant and lactating women.
- History of hypersensitivity to the study drug.
- Subject with history of liver disease, kidney disease , COPD, asthmaand HIV
- History of chronic smoking or chronic alcoholism.
- Patients on any concomitant medications known to affect hepaticfunction within the past 3 months

RESULTS

For the Sample size of 50 patients, 24 used the NAC drug & 26 were not administered NAC Drug. Without the use of NAC Drug : The Mean SGOT variation was observed from 40.23 to 123.65 from the 1st week to 3rd week, Mean SGPT from 34.31 to 77.38 and MeanBilirubin variation was from 0.37 to 0.48. As per the study, to study the hepato-protective effect of N-acetyl cystein on liver injury induced by anti TB drugs 24 patients were administered NAC drug. It was observed & documented that Mean SGOT variation from the 1^{st} week to the3^{rd} week, the change was from 26.92 to 29.92, Mean SGPT variation was from 23.67 to 29.0 and the Mean Bilirubin variation observed was from 0.40 to 0.46. The percentage change is very visible on comparison of the use of NAC drug vis-à- vis NAC drug not administered. The percentage change of SGOT was 111.15% in NAC used patients (p-value 0.0036) & 307.36% in patient not given NAC drug (p-value 0.0009). SGPT percentage change was 122.51% (p-value 0.0005) as compared to 225.56% for Patient not on NAC drug (p-value 0.0009) and Bilirubin percentage change was 115.30% for patient on NAC drug (p-value 0.0050) & 127.31% for patient not onNAC drugs (p-value 0.0301). The study revealed that N-acetyl cystein has a Hepato-protective effect on Liverinjury induced by anti TB drugs. The Comparison of SGOT, SGPT & Bilirubin values of 1^{st} week & 3^{rd} week in Patients not on NAC drug & on NAC drug are statistically significant.

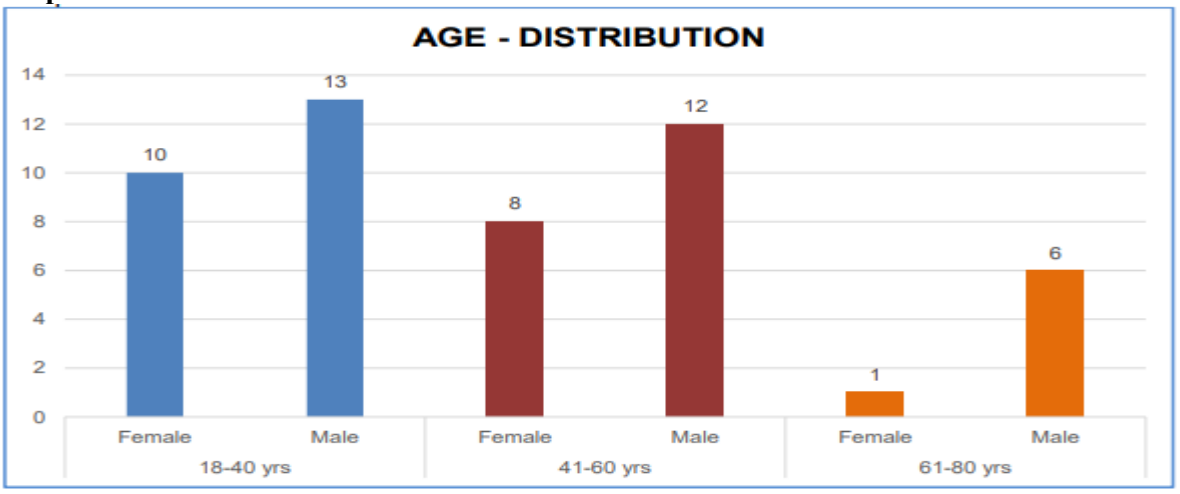
Graph No 1



For the sample size of 50 – 35 belongs to Rural Area & 15 from Urban area. Only 3 patients were from the Upper Class living in the Urban area and 1 from Lower Middle Class. The Rural area patients were mostly of Lower Middle Class. The Socio-

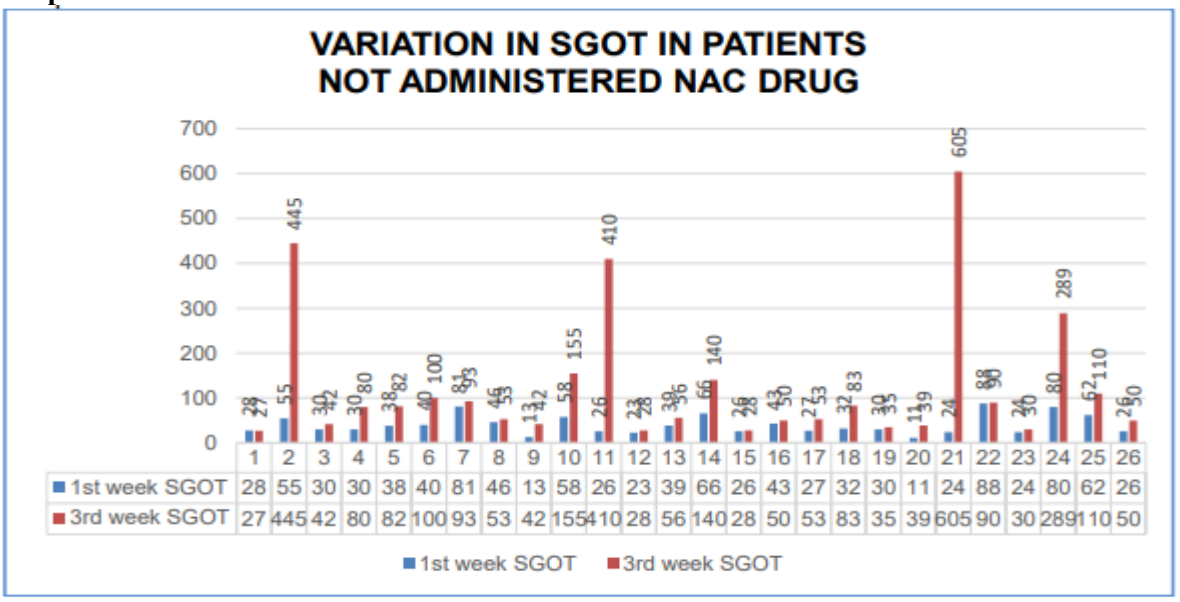
Economic distribution were as per B G Prasad Scale.

Graph No 2



We had 1 female & 6 Male Patients in the Age group of 61-80 yrs. Whereas the 23 patients falls under the Age group of 18–40 years & 20 Patients under 41–60 years.

Graph No 3



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
1st week SGOT	28	55	30	30	38	40	81	46	13	58	26	23	39	66	26	43	27	32	30	11	24	88	24	80	62	26
3rd week SGOT	27	445	42	80	82	100	93	53	42	155	410	28	56	140	28	50	53	83	35	39	605	90	30	289	110	50

Total Sample size for the study is taken as 50 patients. For 26 odd patients, NAC was not administered and LFT parameter was monitored for 1st week & 3rd week. It was observed that only one patient had a decrease in SGOT level from 28 to 27, whereas other 26 patient's SGOT level increased from 2.27% to as high as 2421%. 8 patients had their SGOT values crossed the Critical values.

Graph No 4

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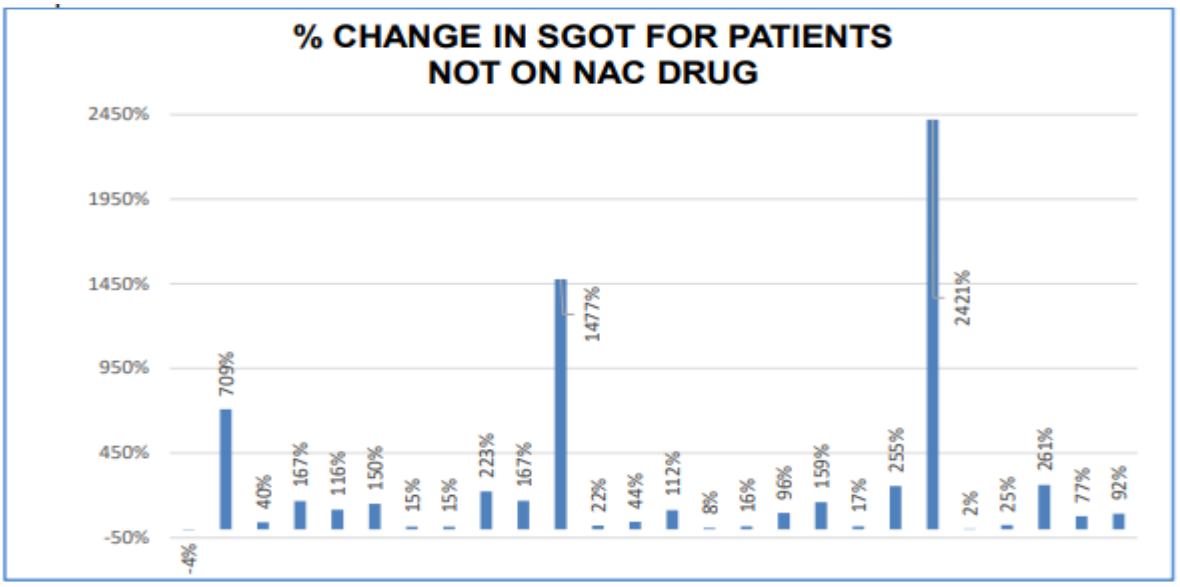
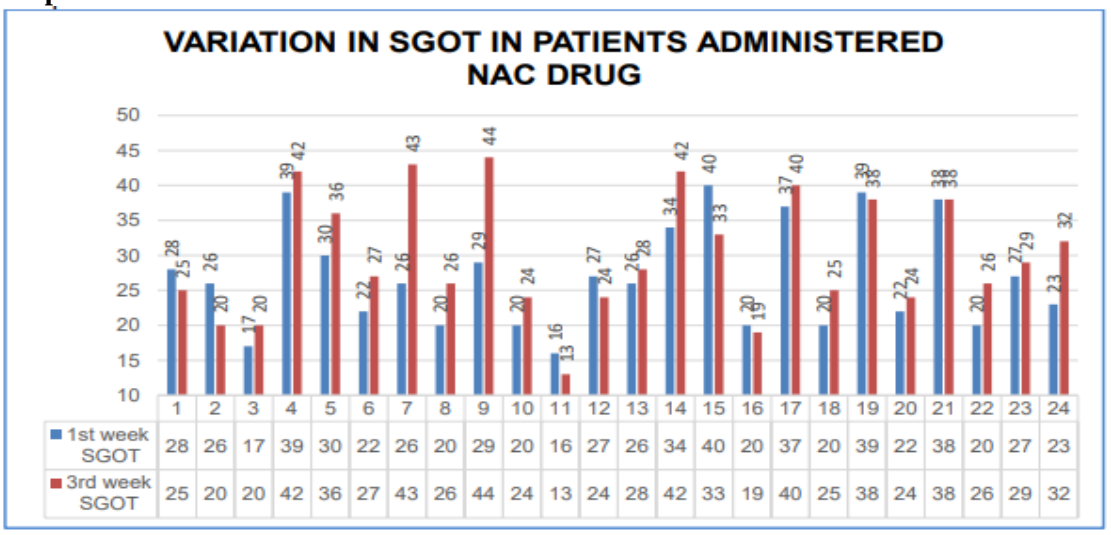


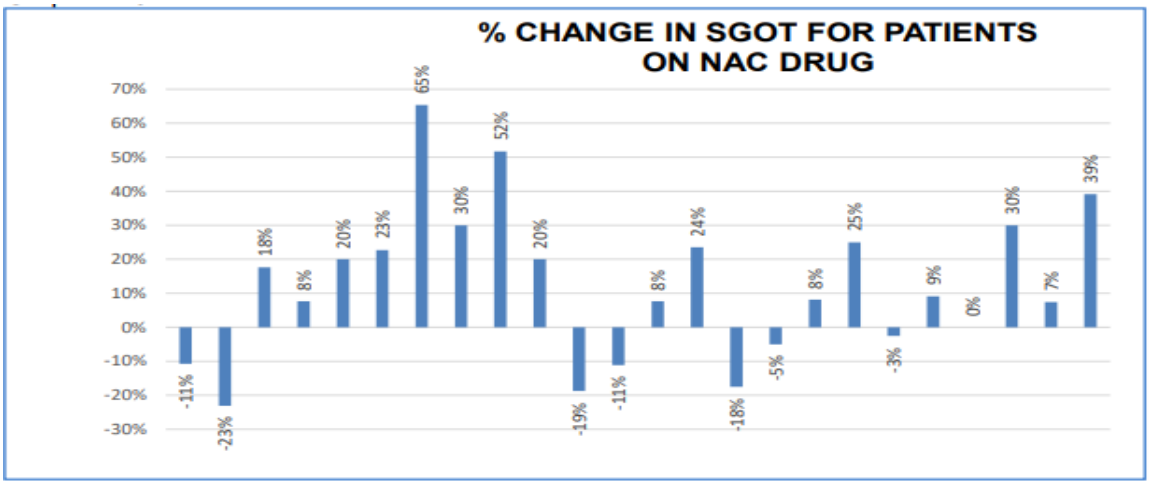
The Patients, under study, not administered NAC drug were 26 in numbers. Their 1st week SGOT & 3rd week SGOT were documented & compared. The value in percentage change varied from 2.27% to as high as 2420.83%. Out of 26 samples, 1 change was in negative (-3.57%), 13 values were under 100%, 10 values were from 100 – 260%, 1 varied to 710% and 2 changed to 2420%.

Graph No 5



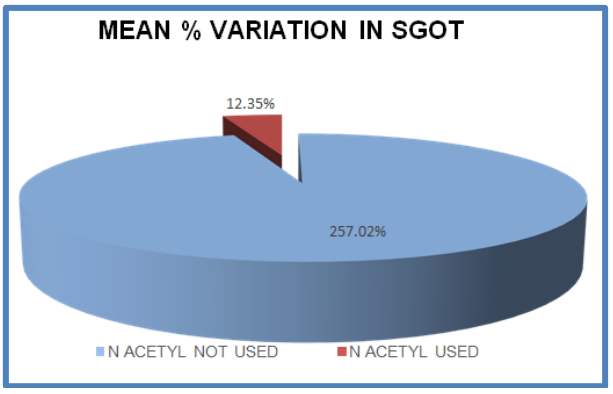
Out of 50 Samples, 24 patients were administered NAC & observed. Their LFT parameter was monitored for 1st week & 3rd week. It was observed that only one patient had no change in the SGOT value in the 1st&3rd week. 7 Patients had their SGPT values decreased by average 11%, 5 Patient's valuesincreased within 10% and remaining 11 Patients had values increased within 70%. Mainly, the values were within Normal range with slight increase in 8 Patients out of24.

Graph No 6



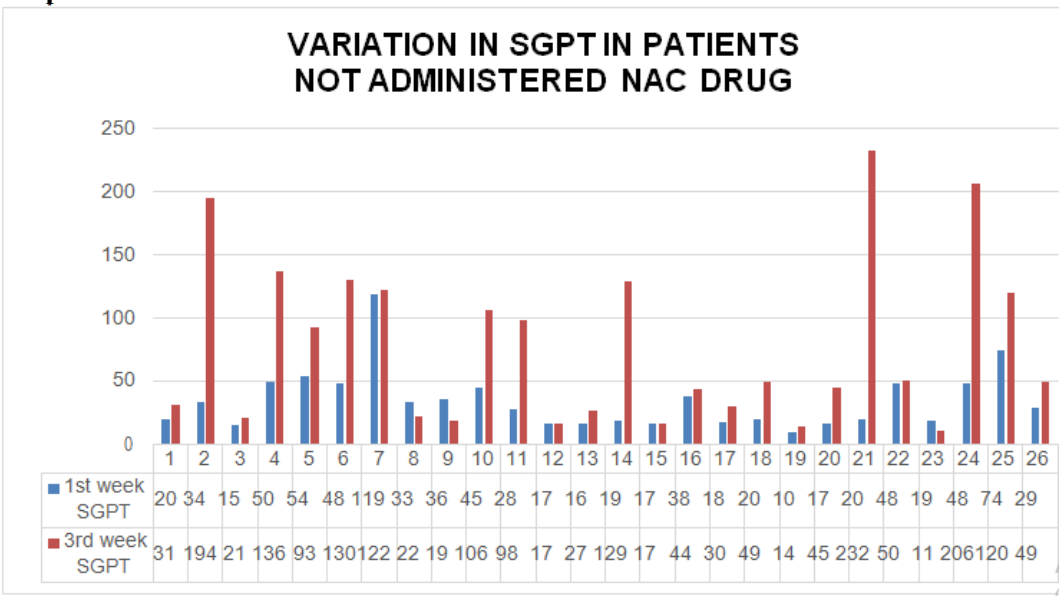
The observation revealed slight change in the values. The value in percentage change varied from -23% to +65%.

Graph No 7



In all the 24 patients, the average SGOT value change is +12.35% (increased) with NAC. Whereas it was 257.02% increase in Patients without NAC drug.

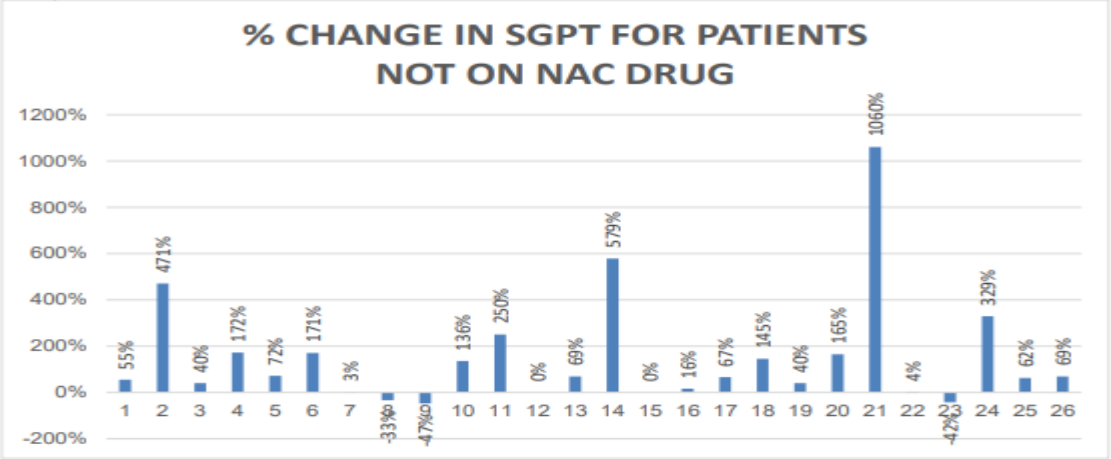
Graph No 8



For 26 patients, NAC was not administered and LFT parameter was monitored for 1st week & 3rd week.

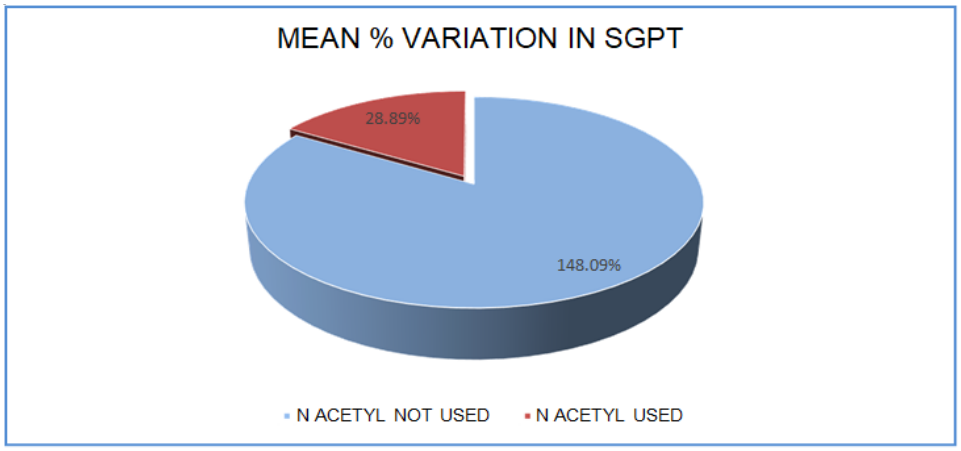
It was observed that only 02 patient had stable SGPT at 17 units, 03 Patient had decreased their SGPT values and remaining 21 Patients had their SGPT increased from 2 units to as high as 212 units. 10 Patients had crossed the Critical Value of their SGPT.

Graph No 9

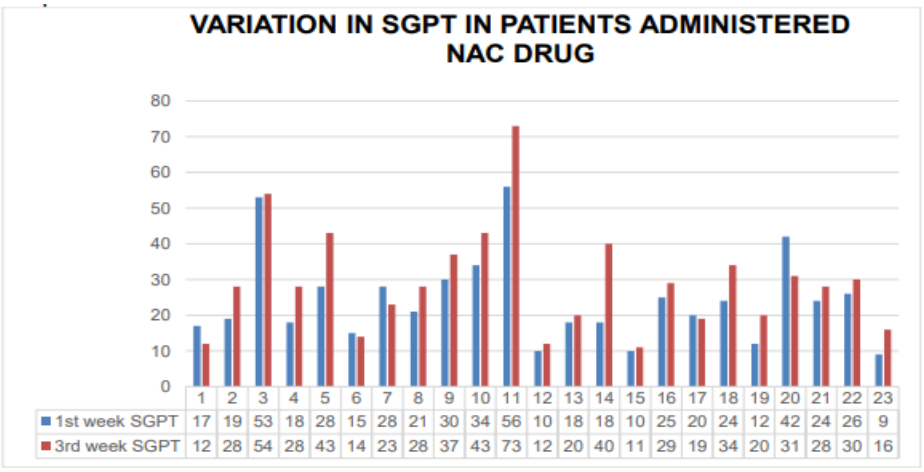


03 Patients had their SGPT decreased in the range of 33% to 47%.
21 Patients had their SGPT Values increased from 2.52% to as high as 1060%.

Graph No 10



Graph No 11



For 24 patients, NAC was administered and LFT parameter was monitored for 1st week & 3rd week. It was observed that 05 Patient had decreased their SGPT values

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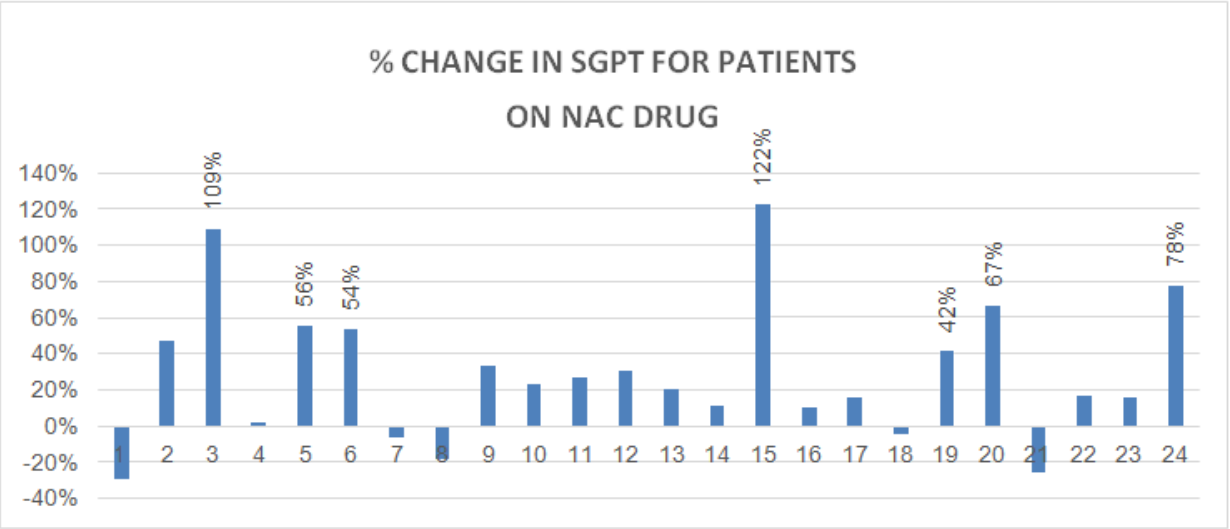
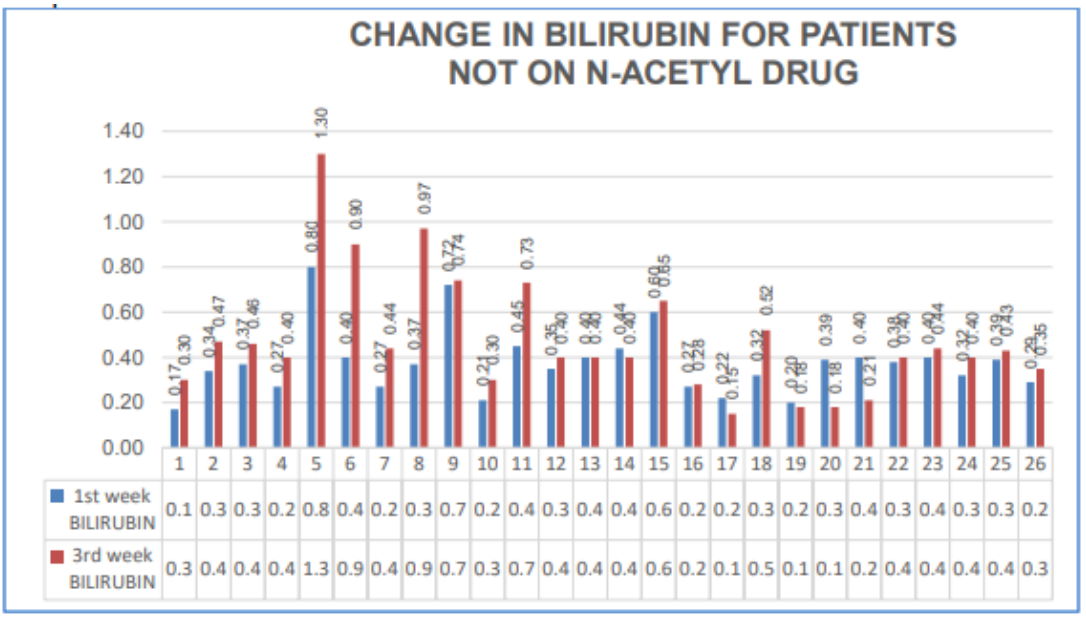
and remaining 19Patients had their SGPT increased from 1 unit to a maximum of 22 units. All the 24 Patients had their SGPT within Normal Range.

Graph No 12



Graph No 13



On comparing the 26 Patients for their 1st week & 3rd week Bilirubin values, it was observed that 01 Patient has stable Bilirubin of 0.40 units. 05 Patients had their Bilirubin decreased and remaining 20 samples had Bilirubinvalues increased in the range of 0.01 to a maximum of 0.60, within Normal range.
Percentage change in Bilirubin values ranges from -54% to 162%.

Graph No 14

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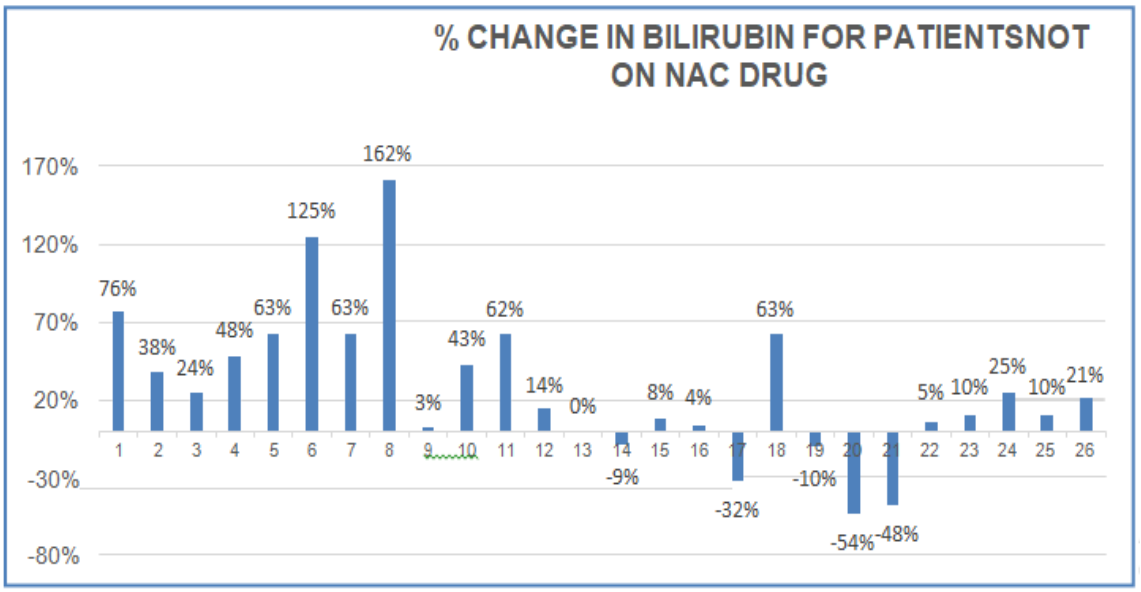
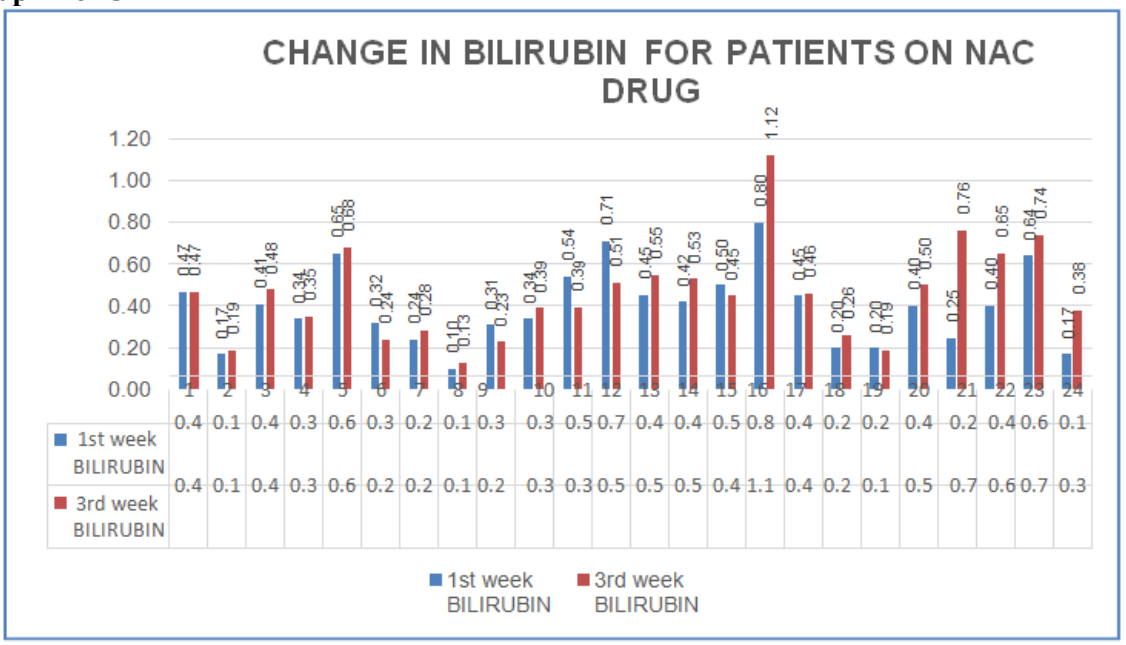
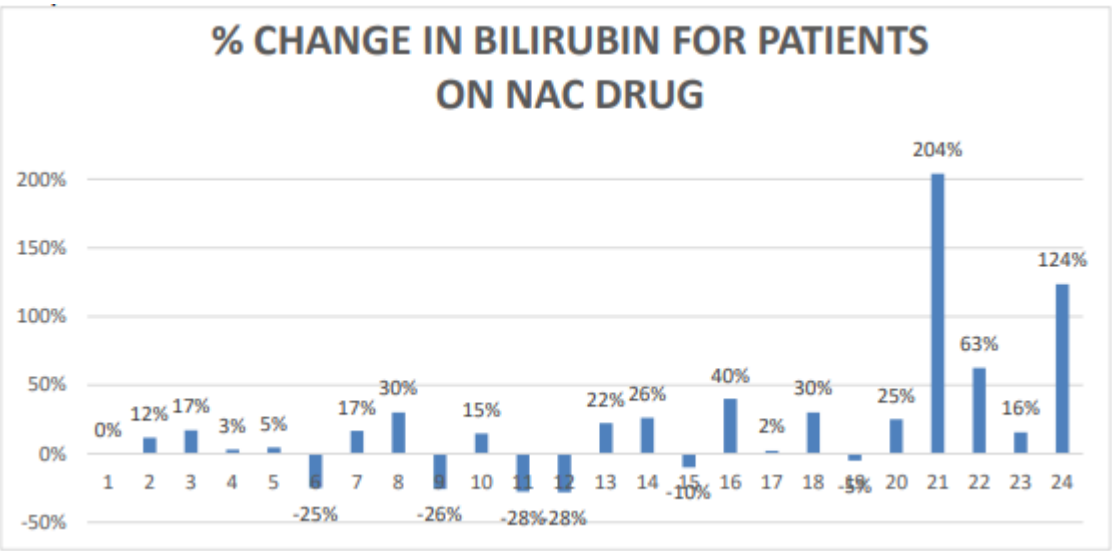


Graph No 15



Of the 24 sample Patients, 01 Patient had stable Bilirubin on NAC Drugs. 06 Patients had decrease in value of Bilirubin where as 17 Patient has slight increase in their Bilirubin values. The maximum increase is 0.51 units.

Graph No 16



The Mean variation in percentage value for Bilirubin is remarkably lower in the Patient administered NAC drug. 21.97% for Patient on NAC drug v/s 27.52% for Patients not on NAC Drug.

Discussion

Standard anti-tuberculosis drug (ATD) regimens that comprise the hepatotoxic chemicals isoniazid, rifampicin, and pyrazinamide are known to have the undesirable consequence of hepatotoxicity, which occurs often and has the potential to be very severe. The incidence of ATD-induced liver damage that has been documented in various research ranges anywhere from 2% all the way up to 28% of the time. This might be because to the features of the patient, the treatment regimen that was being utilised, or the cutoff point for liver function tests that was being used to identify hepatotoxicity. The definitions of ATD-induced liver injury that are most commonly used rely on serum alanine aminotransferase activities (ALT) that are greater than 5 times the upper limit of normal (ULN) and bilirubin concentrations that are greater than 2 times the ULN without symptoms, or ALT levels that are greater than 3 times the ULN with clinical symptoms of hepatotoxicity [11-13].

The clinical manifestations of ATD-induced liver damage might range from asymptomatic elevations in blood transaminases to acute hepatitis and even catastrophic liver failure in extreme cases. Due to the significant morbidity and mortality associated with ATD-induced severe liver impairment, anti-TB medication may need to be discontinued or altered, which will result in a decrease in the effectiveness of tuberculosis treatment. Stopping first-line therapy medicines or failing to comply to treatment schedules may lead to treatment failure, relapse, and drug resistance, all of which can drastically diminish the amount of tuberculosis that is under control.

It is difficult to comprehend the pathophysiology that underlies the ATD-induced liver damage. Direct toxicity of the primary chemical or its metabolites is the major cause, although an immunologically mediated reaction may also play a role [14]. Direct toxicity of the primary compound or its metabolites is the primary cause. When a diagnosis of hepatotoxicity has been made, all ATDs are temporarily removed from the patient's system, and a process called sequential re-challenge of the medicines that were implicated is implemented in order to determine which drug was responsible for the hepatotoxicity. This might be an endeavour that takes a lot of time on the part of the patient as well as the carer. There is currently no hepatoprotective medication that has been shown beyond a reasonable doubt to be efficacious in reducing the hepatotoxicity caused by ATD [15]. It will be necessary to develop new treatments in order to lessen the frequency and severity of ATD-induced hepatotoxicity.

The Mean SGOT variation was observed from 40.23 to 123.65 from the 1st week to 3rd week, Mean SGPT from 34.31 to 77.38 and Mean Bilirubin variation was from 0.37 to 0.48. As per the study, to study the hepato-protective effect of N-acetyl cystein on liver injury induced by anti TB drugs 24 patients were administered NAC drug. It was observed & documented that Mean SGOT variation from the 1st week to the 3rd week, the change was from 26.92 to 29.92, Mean SGPT variation was

from 23.67 to 29.0 and the Mean Bilirubin variation observed was from 0.40 to 0.46.
A similar finding was made by Mumtaz et al. [16], who conducted a prospective trial with historical controls. They found that administration of NAC produces a decrease in NAI-ALF mortality, and that its usage is safe. In addition, some earlier studies conducted on adults as well as children suggested that NAC could be used safely with only a few minor adverse effects. The majority of these adverse effects were either self-limiting or were eliminated through the administration of antihistamine drugs or through a reduction in the infusion rate. The administration of NAC was associated with an increased transplant-free survival rate and shorter hospital stays in retrospective studies conducted on children patients diagnosed with NAI-ALF. [17] In addition, individuals in this research who had drug-induced ALF (ATT induced) demonstrated a superior prognosis in comparison to patients whose ALF was caused by other causes. Monitoring of liver function tests (LFT) was used by Baniasadi et al. to demonstrate that NAC had a protective effect against the hepatotoxicity caused by antituberculosis drugs. [18]
In this study the percentage change is very visible on comparison of the use of NAC drug vis-à- vis NAC drug not administered. The percentage change of SGOT was 111.15% in NAC used patients (p-value 0.0036) & 307.36% in patient not given NAC drug (p-value 0.0009). SGPT percentage change was 122.51% (p-value 0.0005) as compared to 225.56% for Patient not on NAC drug (p-value 0.0009) and Bilirubin percentage change was 115.30% for patient on NAC drug (p-value 0.0050) & 127.31% for patient not onNAC drugs (p-value 0.0301). Nabi T et al were also found similar results.[19]

Conclusion

Isoniazid, rifampicin, and pyrazinamide, the first-line antituberculosis (anti-TB) drugs are associated with hepatotoxicity. Patients treated with antituberculosis drugs may experience hepatotoxicity ranging from simple hepatic enzyme elevations to severe clinical hepatitis. According to our study results, it could be concluded that NAC acts as an effective antioxidant in the prevention of ATT-induced hepatotoxicity. Administration of NAC produced a significant hepatoprotective effect and effectively reduced lipid peroxidation.

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