

An institutional-based observational study of the effect of iodinated contrast media used in computed tomography scan on liver function tests in a tertiary care hospital



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ABSTRACT

Background: Iodine-based contrast media are used to obtain contrast-enhanced computed tomography (CECT) images for better visualization of anatomical structures and improved diagnostic accuracy. These contrast agents are water soluble and are primarily eliminated through renal route. Studies on the acute effects of these agents on the hepatic function are very few in literature. This study was conducted to assess the change of serum parameters of hepatic function within 1 week of administration of the contrast agents. **Aims and Objectives:** The aim of the study was to study the acute effect of iodinated contrast media on liver function test. **Materials and Methods:** Patients attending radiology department for CECT, pre-advised by physicians as part of the treatment protocol of their specific indication were invited to participate in the study. Patients of either gender with normal kidney function test were included in the study. The study was a single-arm, observational prospective study designed to evaluate the change in liver function tests in the study participants after administration of iodinated contrast agent for CECT. All patients who participated in the study provided written informed consent (n = 50). Blood sample was obtained for hepatic function tests before administration of the contrast agent and after 3–7 days of CECT. The parameters observed were serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase (ALP), serum bilirubin-total bilirubin, direct bilirubin, indirect bilirubin, serum protein-total protein, serum albumin, and serum globulin. Paired t-test was used to find out the significant differences between the respective blood parameters before and after the CECT. $P < 0.05$ was considered statistically significant. **Results:** The mean hepatic serum parameters before and after the CECT were found to be in the normal range. There was a nearly statistically significant ($P = 0.052$) but clinically insignificant increase in the mean value of ALP after the CECT (3.020 ± 10.739 , 95% confidence interval: $-0.032-6.072$). Similarly, there was a paradoxical decrease in indirect bilirubin after CECT ($P = 0.002$) which, however, was clinically insignificant (-0.0280 ± 0.0607 , 95% confidence interval: $-0.0453- -0.0107$). There was no statistically or clinically significant difference between the before and after test values in all other parameters. **Conclusion:** Iodinated contrast agents used in CECT do not have any clinically significant effects on change in serum hepatic functions within 1 week of administration of the contrast agents. The mild elevation in alkaline phosphatase may be an indication of acute cholestatic effect of the contrast agents on the hepatic parenchyma. Further studies are warranted to decipher the complete and true picture of these agents on hepatic function.

Key words: Alkaline phosphatase; Bilirubin; Contrast-enhanced computed tomography; Contrast media; Liver function tests

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INTRODUCTION

Nowadays, iodinated contrast media are among most commonly used contrast agent in radiology department. It has been in use since the 1950s to facilitate radiographic imaging modalities.¹ Iodinated contrast agents are the contrast agents which contain iodine atoms used for X-ray-based imaging modalities such as computed tomography (CT), although they are also used in fluoroscopy, angiography, venography, and sometimes even plain radiography.² Intravenous route of administration is the most common, but there are many other routes of administration such as gastrointestinal (oral and rectal), cystourethral, vaginal, and interosseous.³ Iodinated contrast media have two major types, that is, water-soluble type and water-insoluble types. Water-soluble types are classified into high osmolality contrast media and low osmolality contrast media.⁴ There is very little literature on the possible effects of the iodinated contrast dyes on the hepatic function. In this research work, we sought to study the effect of such dyes on liver function by comparing the pre-CT and post-CT values of hepatic enzymes, bilirubin, and serum proteins.

Aims and objectives

The aim of the study was to study the effect of iodinated contrast media on liver function test. The parameters of liver function tests that were tested before and after the contrast enhanced CT scan were as follows:

1. Serum glutamic-oxaloacetic transaminase (AST/SGOT)
2. Serum glutamic-pyruvic transaminase (ALT/SGPT)
3. Alkaline phosphatase (ALP)
4. Serum bilirubin-total bilirubin, direct bilirubin, and indirect bilirubin
5. Serum protein-total protein, serum albumin, and serum globulin

MATERIALS AND METHODS

Study design and type

This was an institution-based, single-arm, prospective, observational study.

Study population

Patients attending radiology department for contrast-enhanced (iodinated) CT scan, pre-advised by physicians of various departments of COMJNMH as part of the treatment protocol of their specific indication.

Inclusion criteria

Patients of either gender visiting radiology department who were advised iodinated contrast media enhanced CT scan were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

1. The patients having a history of hypersensitivity reaction to iodinated contrast media.
2. Impaired kidney function.

Sample size

All the patients who came to the radiology department, fulfilling the inclusion criteria and providing voluntary informed consent, were included in the study. The study was conducted from March 2020 to September 2020. A total of 50 patients participated in the study during the said period.

Study period

A study was done for the period of 6 months – March 2020–September 2020. Patients who provided voluntary informed consent underwent blood sampling for hepatic function test before the contrast-enhanced computed tomography (CECT) and after 3–7 days of the CECT procedure.

Study method/procedure

The patients scheduled to undergo contrast CT scan as per advice of the treating physicians were informed about the research work. The patients who were voluntarily interested in participating in the research and provided written informed consent were enrolled in the study. Liver function test as enlisted in the aims and objectives was tested immediately before and repeated within 3–7 days of the CT scan.

Statistical analysis

Data were recorded in pre-prepared case recorded forms and transcribed to Microsoft Excel for analysis and archiving. The continuous data were expressed as mean±standard deviation and categorical data were expressed as frequency and percentage. Paired t-test was used to compare the differences in pre- and post-procedure values of the laboratory parameters. $P < 0.05$ was considered statistically significant.

Novelty of the study

Literature on the effect of contrast agents on hepatic function, though not known to be of great clinical significance, is very limited. Apart from a few case reports where severe toxicity has been reported for unexplained reasons, there is a severe dearth of systematic studies designed specifically to study the possible effect of such agents on hepatic function. We sought to broaden the existing meager information on the subject.

RESULTS

A total of 50 subjects participated in the study over the period of 6 months. Due to corona pandemic and frequent

lockdown, there was decrease in patient return for repeat test so more patient could not be screened. The mean age of the participants was 47.02 ± 15.37 years. The number of male and female participants was 38 and 12, respectively. The study participants underwent the laboratory tests twice, one before CECT and one after 3–7 days of CECT for same liver function test. All patients were found to have normal liver function tests at baseline. The mean of the laboratory values of the liver function test before the administration of contrast agents was obtained (Table 1). Similarly, the mean of the laboratory values of the liver function test after 3–7 days of the administration of the contrast agent was calculated (Table 1). The results of the paired t-test to detect statistically significant difference between the pre- and post-laboratory values of bilirubin, liver enzymes, and serum proteins are shown in Table 1. A statistically significant difference between pre- and post-values of the laboratory parameters was found for indirect bilirubin and alkaline phosphatase (P values – 0.002 and 0.052, respectively). The value of indirect bilirubin decreased by 0.028 ± 0.06 (Figure 1). The value of alkaline phosphatase increased by 3.02 ± 10.74 (Figure 2). No other laboratory parameters showed statistically significant change in mean values between the before and after tests.

DISCUSSION

Iodinated contrast agents are water soluble compounds and are primarily eliminated by the kidney.⁴ The effect of the compounds on hepatic function, as anticipated from their elimination route, is expected to be minimal. Therefore, in literature, the majority of studies have focused on the nephrotoxic effect of the dyes and studies on the hepatotoxic potential of the agents are very less.⁵ However, any water-soluble compound, despite its molecular properties, have the potential to cross cellular membranes and may have a significant effect on alteration of normal physiology.⁶ The transport of water-soluble compounds into the intracellular milieu is concentration dependent as has been observed with highly

ionized molecules like aminoglycosides.⁷ It is also known that the molecular weight and size also determine the transport and diffusion of the molecules inside the cell. In addition, the presence of membrane transporters for intrusion and extrusion of molecules into and out of the cell is ubiquitous in the human body. The multidrug resistance proteins, P-glycoprotein, and myriad set of organic anion and cation transporters are responsible for transport of specific molecules across the cell membrane.⁸⁻¹¹ Moreover, the hydrophilic compounds, once they gain access inside the cell, have the potential to inflict greater damage to the cellular proteins and enzymes because of their greater reactivity.¹² With this background, the effect of iodinated contrast agents on hepatic function assumes clinical importance and needs more studies to establish their safety in the larger population. This is especially true, because the use of contrast-enhanced imaging modalities has shown tremendous increase in frequency in recent past.¹³ In our study, we observed that there is decrease in indirect bilirubin or unconjugated bilirubin level. Although statistically significant ($P < 0.002$), the mean value of the decrease in the level of indirect bilirubin was only 0.028, which in our opinion is not clinically significant to derive any meaningful inference. The effect of the contrast agents (if any) on the decrease in production of erythrocytes, and hence indirect bilirubin, is hard to explain, especially because there was a paradoxical statistically insignificant increase in direct bilirubin. We propose that the any possible explanation for the phenomenon needs further research with long-term monitoring of the hepatic function with the concurrent assessment of thyroid function which may be affected by the iodinated dyes. In our second important observation, we found that there was a statistically significant increase in the serum levels of alkaline phosphatase. A probable explanation of the observation is that there may be development of intrahepatic cholestasis and post-administration of iodinated contrast agent. The wide variation in the increase in alkaline phosphatase level in different patients indicated by a standard deviation of more than 10 suggests that there may be a subset of patients who are predisposed to hepatic impairment following contrast administration. While

Table 1: Shows the values of different parameters of Liver function test before and after the CECT scan. The mean difference with confidence interval are also shown along with the P value. A P value < 0.05 was considered statistically significant

Sl. No	LFT parameter	Before CECT	After CECT	Mean difference	95% confidence interval	P-value
01	SGOT	32.02±13.347	32.56±12.051	0.540±3.495	-0.453-1.533	0.280
02	SGPT	27.44±12.274	30.96±21.308	3.520±21.201	-2.505-9.545	0.246
03	ALP	141.64±58.074	144.66±52.698	3.020±10.739	-0.032-6.072	0.052
04	TB	0.548±0.2837	0.530±0.2621	-0.0180±0.0720	-0.0385-.0025	0.083
05	DB	0.286±0.1604	0.296±0.1525	0.0100±0.0580	-0.0065-0.0265	0.229
06	IB	0.262±0.1978	0.234±0.1803	-0.0280±0.0607	-0.0453- -0.0107	0.002
07	TP	7.676±1.0737	7.652 1.0951	-0.0240±0.4438	-0.1501-0.1021	0.704
08	SA	3.950±0.6367	3.892 0.5910	-0.0580±0.3417	-0.1551-0.0391	0.236
09	SG	3.718±0.7482	3.748 0.7500	0.0300±0.3099	-0.0581-0.1181	0.497

Abbreviations: SGOT-Serum glutamatic oxaloacetic transaminase, SGPT-Serum glutamatic pyruvate transaminase, ALP-Alkaline phosphatase, TB-Total bilirubin, DB-Direct bilirubin, IB-Indirect bilirubin, TP-Total protein, SA-Serum albumin, SG-Serum globulin.

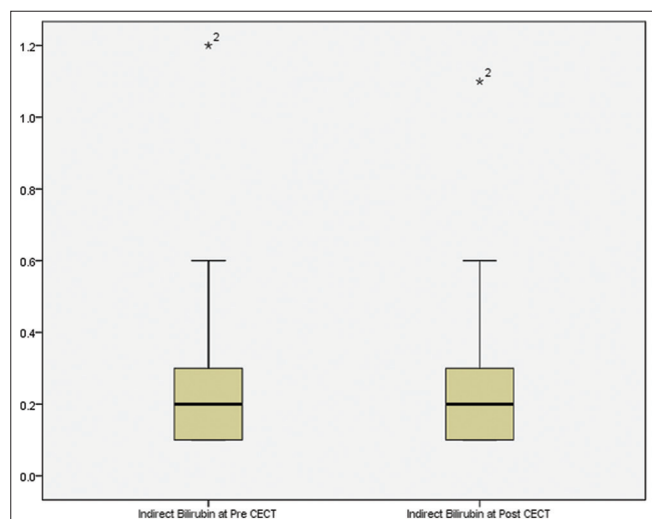


Figure 1: Box-plot showing median and interquartile range of Pre & Post CECT Indirect Bilirubin

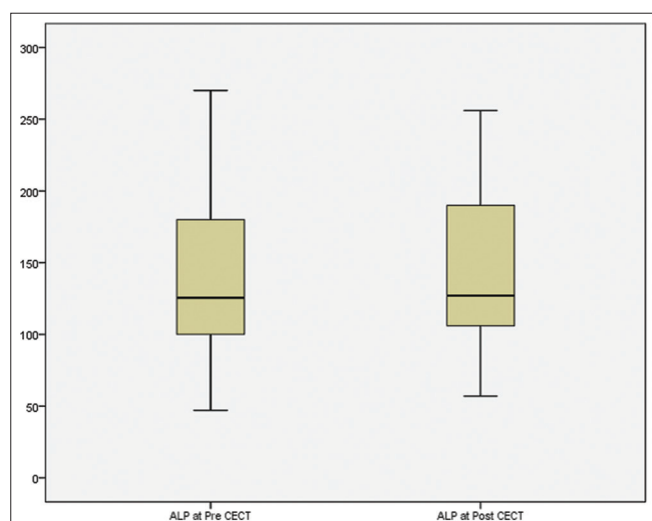


Figure 2: Box-plot showing median and interquartile range of Pre & Post CECT ALP values

the mean increase in alkaline phosphatase of 3 units is not much of a clinical significance, a wider standard deviation justifies the scope of further research to identify the at-risk population. Our study involved assessment of liver function test at a single time point (between 3 and 7 days) which may not have been sufficient to detect the entire spectrum of change in hepatic function with time. Therefore, we suggest that further studies with the assessment of liver function at multiple time points may yield valuable insights.

An animal study on the effect of contrast dyes on hepatic function by Miller et al., is a relevant and interesting comparison to our own study.¹⁴ Results for ALT were measured before and after administration in sham and exposed samples. The ALT for exposure with contrast infusion was significantly elevated relative to shams ($P < 0.05$). For AST, the enzyme activity was significantly increased for

both contrast infusion and bolus, and the after exposure results were significantly elevated above the before exposure results for the contrast bolus. The enzyme results showed enzyme release indicative of liver cell injury. However, the study differed from our study in two respects. First, it was a pre-clinical study, and second, it used ultrasound to image the liver following lipoidal suspension contrast.

We describe a clinical case report where derangement of hepatic enzymes was observed following a cerebral angiogram study with iohexol (3 mL/kg) in a previously healthy 10-year-old boy with diagnosis of cerebral arteriovenous malformation. Development of vomiting and abdominal pain on the 4th post-procedure day prompted the clinicians to assess liver function tests which showed marked elevation of transaminases. The case was complicated with oliguria and hypertension. The patient recovered with dialysis and supportive treatment for 13 days. This report brings to the fore, the hepatic complications that may develop due to low non-ionic contrast media.¹⁵ A similar case report of severe liver injury following the injection of non-ionic contrast medium in a 49-year-old woman with endometrial cancer was reported by Morita et al., in 2001. In this case, the hepatic injury progressed into a fulminant hepatitis-like picture requiring repeated plasmapheresis and hemodialysis.¹⁶ The reporting of such cases in the history of medical literature clearly indicates that there is a possibility of hepatic injury with administration of radiocontrast agent which has a wide spectrum of presentation varying from mild asymptomatic hepatic enzyme elevation to fulminant hepatic failure. Although we did not observe any significant change in SGPT and SGOT level in our study, probably because of no injurious effect on liver cells, the existence of evidence in literature warrants the conduct of further studies, so that the true and complete picture of the hepatotoxic effect of the iodinated contrast agents can be elucidated.

Limitations of the study

The study was conducted on a small sample size. The liver function tests were assessed at a single time point after the administration of contrast agents. Therefore, the temporal variation in the liver function tests after the contrast CT scan could not be assessed. Further studies with a large sample size at multiple time points will yield a better understanding of the study outcomes.

CONCLUSION

Iodinated contrast agents administered intravenously for contrast-enhanced imaging with CT scan may have an acute cholestatic effect on the hepatic parenchyma. Further studies are warranted to decipher the complete and true picture of these agents on hepatic function.

- Iodinated contrast agents have the potential to cause hepatic injury in patients undergoing contrast-enhanced CT scan.
- Very few studies are available in literature where the hepatotoxic effect of these agents has been studied.
- We observed the pre- and post-hepatic function laboratory values in 50 such patients. The post-hepatic function test was done between 3 and 7 days.
- Our study sought to analyze the acute effects of the iodinated contrast agents on the hepatic function of the patients undergoing contrast-enhanced CT scan.
- There was a significant increase in the laboratory value of alkaline phosphatase in the study cohort.
- There was a statistically significant but insignificant decrease in the laboratory value of indirect bilirubin.
- The other hepatic function parameters of direct bilirubin, SGPT, SGOT, and serum proteins did not show any significant change.
- The increase in alkaline phosphatase may be due to intrahepatic cholestasis following the administration of iodinated contrast agents.
- Further studies are required to elicit the entire spectrum of hepatic effects of the administration of iodinated dyes on such patients.

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KM- Concept and design of the study; **SK**- Recruitment of study participants, data collection, and prepared first draft of manuscript; **SNA**- Interpreted the results, reviewed the literature, and manuscript preparation; **KM, SK, RS, and SNA**- Concept, coordination, statistical analysis, and interpretation; and **KM and RS**- Preparation of manuscript and revision of the manuscript

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