

# The Preventive Role of Vitamin E Against Imatinib Induced Toxicity on Liver of Albino Rats: A Histomorphometric Study

Vitamin E  
Against Imatinib  
Induced Toxicity  
on Liver

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## ABSTRACT

**Objective:** To observe changes in the histology of hepatic tissue of Albino rats exposed to the oral administration of toxic doses of Imatinib and to assess the protective effect of vitamin E.

**Study Design:** Analytical experimental randomized control study.

**Place and Duration of Study:** This study was conducted at the Department of Anatomy, Peshawar Medical College Peshawar from February 2013 to July 2013.

**Materials and Methods:** This study of twenty four male albino rats was conducted at PCSIR lab complex and Peshawar Medical College, Peshawar. Rats were randomly divided into three groups, one control and two experimental groups. Experimental group I were treated with the oral administration of Imatinib for two weeks and experimental group II were treated with the oral administration of same dose of Imatinib with the concomitant administration of vitamin E. Haematoxylin and Eosin used for routine examination Masson Trichrome for hepatocellular necrosis and fibrosis.

**Results:** Scoring system was applied to evaluate the degree of toxic effect of Imatinib on the hepatic tissue of rats. The degree (no change, mild to moderate change and marked change) of hepatocellular necrosis were observed. It is concluded that the most affected rats were those treated with Imatinib i.e. experimental I. Rats in experimental II, which received antioxidant in addition to Imatinib were least affected, thus conforming the protective role of vitamin E.

**Conclusion:** The simultaneous use of antioxidant vitamin E with Imatinib could prevent the hepatic toxicity which includes hepatocellular necrosis.

**Key Words:** Imatinib, Hepatic tissue, Multifocal hepatocellular necrosis, Vitamin E

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## INTRODUCTION

Chemotherapy for cancer defines as the chemical agents use to stop the growth of cancer cell even at sites distant from the origin of primary tumor. However, since these agents do not distinguish between a cancer and a normal cell, they not only eliminate the fast growing cancer cells but also other fast growing normal cells e.g. the hair and blood cells.<sup>1,2</sup>

Imatinib is an anticancerous drug it was initially marketed by Novartis with the trade name of Gleevec. It is a tyrosine - kinase inhibitor that is used in the

treatment of multiple cancers, most notably Philadelphia chromosomes positive (Ph+) chronic myelogenous leukemia (CML) as well as in gastrointestinal tumors.<sup>3</sup>

Hepatic toxicities were seen in the dogs after a two week course of Imatinib, in which mild multifocal hepatocellular necrosis, single cell bile duct necrosis and bile duct hyperplasia. Bile duct hyperplasia remains after the recovery duration of four weeks and that was related with peribiliary fibrosis.<sup>4</sup>

Swelling of hepatocytes, diffuse parenchymal congestion, dilations of central vein and portal tract infiltration were also demonstrated in the patients treated with Imatinib.<sup>5-9</sup> Vitamin E is an important fat soluble natural nutrient . Vitamin E consists of eight forms in which alpha toopherol is the most important natural nutrient in the human body. Vitamin E serves the body as an anti-oxidant and is also used in regulating the gene expression, cell signaling and function immuning.<sup>10</sup>

Antioxidants individually protect normal cells against some of the toxicities produced by the chemotherapeutic agents.<sup>11</sup>In animal studies, various preparations like vitamin E, vitamin C, vitamin B<sub>6</sub> have

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been studied, which combat or reverse the oxidative damage. Now a day, a lot of attention is being paid on the use of natural antioxidants because of their fewer side effects, and easy and cheap availability.<sup>12</sup>

This research project was designed to see the effects of vitamin E, if any, on the histoarchitecture of hepatic tissue of rats subjected to toxic doses of Imatinib for a period that had induced changes otherwise in the hepatocytes.

## MATERIALS AND METHODS

Twenty four male albino rats were obtained from Pharmacy Department of Peshawar University. They were kept in the pharmacy department of PCSIR lab for further experiment. The rest of study was carried out in the Anatomy and Pathology department of Peshawar Medical College. Rats with any disease prior to the onset of experiment, or the ones that developed disease during the study were excluded. Eight weeks old healthy male albino rats of Sprague-Dawley strain weighing 150 to 200 gram were selected for the study. The rats were randomly divided in to three groups; one control and two experimental groups with eight rats in each group. Control group comprised of 8 rats fed on standard diet. Experimental group I comprised of 8 rats fed on standard diet, oral administration of Imatinib solution (50 mg /kg /day) 6 days a week for a period of 2 weeks. Experimental group II comprised of 8 rats fed on standard diet, oral administration of Imatinib solution (50mg/kg/day), vitamin E (500mg/kg/day) 6 days a week for a period of 2 weeks. All three groups of rats were sacrificed after completed 2 weeks to observe any morphological change in the liver due to Imatinib toxicity and possible protective role of Vitamin E. After sacrificed proper abdominal dissection was done abdominal viscera are identify and liver was remove carefully. The liver tissue was processed and then stain with the (a Haematoxalin and eosin for routine examination (b) and Masson Trichrome for demonstration of collagen fibers.

The microscopic examination of the liver sections of experimental group revealed several histological changes including, multifocal hepatocellular necrosis, dilatation and congestion of central veins and blood sinusoids were observed. These changes were ameliorated by vitamin E administration. Data analysis was conducted with statistical software SPSS.20. Significance was calculated by using Chi square test and was defined as P value <0.05.

## RESULTS

The current study was conducted to observe the Imatinib induced histomorphological change in the liver of male albino rats and to find out any possible protective role of vitamin E. Animal were grouped in control, experimental group I (treated only with Imatinib

for 2 weeks) and experimental group II (treated with Imatinib and vitamin E for 2 weeks).

A scoring system was applied to evaluate and standardize the degree of toxic effect of Imatinib on the hepatic tissue of experimental animal. Under this scoring system, the degree (no change, mild to moderate change and marked change) of multifocal hepatocellular necrosis was observed. The scores given were: No change (0), mild to moderate change (1) and marked change (2).<sup>13,14</sup>

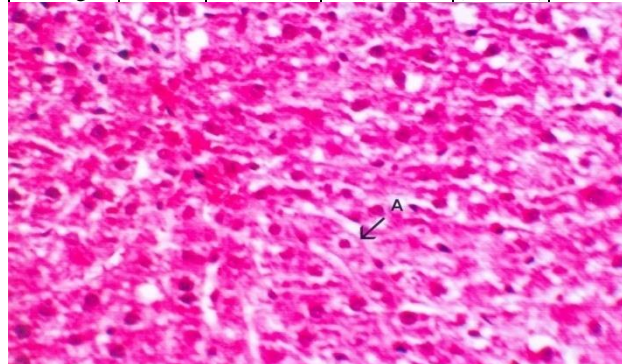
Multifocal hepatocellular necrosis was found to be one of the most common findings seen in the Imatinib induced hepatic toxicities. Based on several observations, 6 animals out of 8 (75%) from experimental II group (Imatinib+Vit E treated) and 2 out of 8 (25%) of experimental group I (Imatinib treated) presented with hepatocellular necrosis of grade 1 (mild to moderate change).

While 1 animal out of 8 (12.5%) of experimental group II (Imatinib+ Vit E treated) did not reveal any hepatocellular necrosis. The degree of severity was, marked grade 2 in 6 animal out of 8 (75%) of experimental group I (Imatinib treated) and 1 animal out of 8 (12.5%) of experimental group II (Imatinib+Vit E treated).

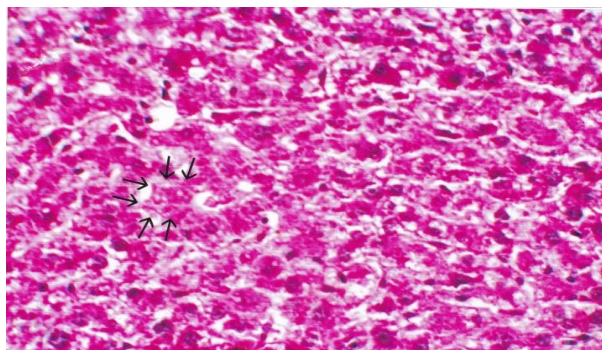
From the aforementioned results regarding the hepatocellular necrosis, it is concluded that the most affected animals were those treated with Imatinib i.e. group I. The animals in experimental group II, which received antioxidant in addition to Imatinib were least effected, thus conforming the protective role of vitamin E. The Chi- square test was applied, and the P value (0.002) was highly significant.

**Table No.1: Degree of multifocal hepatocellular necrosis**

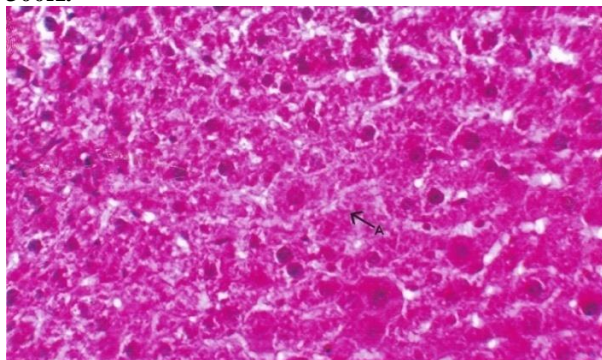
Degree of necrosis	Control Group	Experimental Group I	Experimental Group II	Total	P value
Normal	7 (87%)	-	1 (13%)	8 (33.33%)	0.005
Mild to moderate change	1 (13%)	2 (25%)	6 (75%)	9 (37.5%)	0.024
Marked change	-	6 (75%)	1 (13%)	7 (29.16%)	0.002



**Figure No.1: Photomicrograph of 5 μm thick section of rat liver from control group showing cords of intact hepatocytes (A) H&E staining, 600 X.**



**Figure No.2: Photomicrograph of 5 μm thick section of rat liver from experimental group II showing multifocal hepatocellular necrosis of mild to moderate degree (multiple arrows) H&E stain, 300X.**



**Figure No.3: Photomicrograph of 5 μm thick section of rat liver from experimental group I showing hepatocellular necrosis of marked degree (A) H&Estain,900 X.**

## DISCUSSION

In developing countries like Pakistan humans are suffering from different types of cancers. It continues to represent the largest cause of mortality in the world and claims over 6 million lives every year.<sup>15</sup> Chemotherapy is one of the conservative treatments of this harmful disease. It is not found to be safe because of the side effects of the drugs on the healthy tissue. The liver being the first organ to be exposed to these therapeutic agents tends to be transformed and clean these agents, and while doing so, it is susceptible to the toxic effects of these agents. These drugs therefore, even introduced within the therapeutic ranges, may injure the organ. Among these chemotherapeutic agents, Imatinib mesylate is the only effective and approved systemic agent for the treatment of patient with advanced gastrointestinal tumors and chronic myeloid leukemia. To reduce the adverse effects of Imatinib during the chemotherapy co administration of antioxidant such as vitamin E have been proved to be beneficial, although very limited studies have been conducted in this regard. The present study was conducted to evaluate the toxic effects of Imatinib on hepatic tissues of albino rats and to observe the protective role of vitamin E, against

Imatinib induced histological changes in the rat's hepatic tissues. For this purpose 24 male albino rats were selected. Rats were randomly divided into a control, and two experimental groups, receiving Imatinib only (group I) and Imatinib simultaneously with vitamin E (group II) respectively.

In the present study multifocal hepatocellular necrosis was found to be one of the most common findings in the hepatic tissue of rats of both experimental groups. Based on several observations, the degree of hepatocellular necrosis was mild to moderate in 75% of group C animals, moreover, 75% of group B animals have also shown changes though the degree of change in this group was marked hepatocellular necrosis.

Therefore our findings are in accord with the result of a study conducted by Monovaet al<sup>4</sup> who recorded hepatic toxicities in animals after two weeks course of Imatinib which includes hepatocellular necrosis.

The results of present study also corresponds to a recent case report which was presented by Tonyali et al<sup>16</sup> about a patient of gastrointestinal tumor who was treated with Imatinib, and developed hepatotoxicity and histological changes consist of inflammation and multifocal necrosis right after six month of treatment with Imatinib.

The results of current studies are also in agreement with a study conducted by Guilhot<sup>17</sup>, which revealed that Imatinib treatment is toxic in the patients of chronic myeloid leukemia and causes acute liver failure and histopathological findings demonstrating cytolytic hepatitis with necrosis, and portal and lobular inflammation.

The present study is also being supported by another study conducted by a Kong et al<sup>18</sup>, according to whom during adjuvant Imatinib treatment in a patient with Gastrointestinal tumor hepatotoxicity was observed in about 2–5% of patients receiving Imatinib. Histological changes described in some of these cases consist of inflammation, fatty degeneration and necrosis of the liver.<sup>19</sup>

This study is in the conformity with the study done by Talpaz et al<sup>20</sup>, who found four out of 50 CML patients who were treated with the Imatinib, their liver biopsy revealed focal necrosis of hepatocytes and mild infiltration of hepatocytes around the necrosis.

At the same time our study is in agreement with the study done by Kedaret al.<sup>21</sup> They reported that alpha tocopheryl Succinate alone and with dietary micro-nutrients can be very useful as an supplement to cancer therapy by increasing tumor response and possibly decreasing some of the toxicities of cancer chemotherapy to normal cells.

Our study is also in agreement with the several clinical studies conducted by Siejaet al<sup>22</sup>, Pace et al<sup>23</sup>, Conklin et al<sup>24</sup>, Branda et al<sup>25</sup>, Bairati et al<sup>26</sup> and Ferreira et al<sup>27</sup> who have reported that supplemental anti-oxidants with

dietary nutrients were very useful in decreasing the side effects of chemotherapy in cancerous patient.

## CONCLUSION

The simultaneous use of antioxidant vitamin E could prevent the hepatic toxicity which includes multifocal hepatocellular necrosis.

### Author's Contribution:

Concept & Design of Study: Nighat Ara  
 Drafting: Farooq Khan, Noman Ullah Wazir  
 Data Analysis: Fahad Ullah, Ambereen Hamayun, Riffat Shameem  
 Revisiting Critically: Nighat Ara  
 Final Approval of version: Nighat Ara

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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