Original Article

# Protective Effect Of Vitamin E On Imatinib Induced Histomorphological Changes In Hepatic Central Vein Dilatation In Albino Rats: Light Microscopic Study

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## Abstract

**Background:** Imatinib, a potent inhibitor of tyrosine kinases that have been approved for the treatment of chronic myeloid leukemia as well as gastrointestinal stromal tumors, is associated with hepatic toxicity including central vein dilatation and portal hypertension. Vitamin E has antioxidant effects and may have a protective effect against this Histomorphological change in hepatic central vein dilatation.

**Aim**: To observe the possible protective effect of vitamin E against imatinib-induced hepatic central vein dilatation in albino rats.

**Study Design:** A cross-sectional study

**Place and duration of study**: Department of Anatomy Peshawar Medical College from 1st Jan 2021 to 31st July 2021.

**Methodology:** One hundred male albino rats of Sprague Dawley strain weighted between 150 -200g were divided into four groups; control, (A) imatinib treated (B), vitamin E treated (C), and combination of both imatinib and vitamin E (D) The drugs were given daily for 4 weeks. Hepatic tissue was fixed overnight in 10% buffered formalin for preservation and processed onto paraffin wax blocks before staining with hematoxylin/eosin as follows: The hepatic central vein caliber was examined under a light microscope using a stage micrometer.

**Results**: The average age of albino rats used in this study was 12 weeks ±2 weeks. Group B rats: In the Imatinib group (group B), 85% of the animals showed marked dilatation in central hepatic veins with a dilation magnitude of 2,500±3002,500±300 micrometers. Results As compared with the control (Group A), central vein changes were accessed in 96.6% of rats on ten protocols treated except the Vitamin E group (Group C, P <0.05). The mean value for dilated diameters was 2,700±1,400 micrometers. Group D tends to have more pronounced hepatocytic necrosis as tested by the percentage of damage area around the central vain than the other four groups (Pooled t =-13.x40, P<0..01)。 In the Combination group (Group D), central vein dilatation was seen in only 20% of rats, which differed significantly from that reported for Imatinib treated animals and had a mean dilation in this group was 1,000±2001,000 \pm 2001,000±200 micrometers, (Table III). These results confirm the protective effect of vitamin E on imatinib-induced hepatic central vein dilatation (% showed an 18% decrease), expressing it as rescue rather than increasing or having a double-edged protection role. These differences were statistically significant (all p-values <0.05 using a series of statistical analyses).

**Conclusion**: Imatinib causes hepatic central vein dilatation in albino rats that is reduced by intake of vitamin E. This suggests that antioxidant therapy might ameliorate hepatic toxicity accompanying imatinib treatment in these patients, opening the way for clinical trials to evaluate this therapeutic possibility.

**Keywords:** Imatinib, Vitamin E, Hepatic toxicity, Albino rats.

## Introduction

Imatinib, a tyrosine kinase inhibitor, is widely accepted for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs). Imatinib acts as an inhibitor of BCR-ABL tyrosine kinase, which is a constitutively active enzyme resulting from the Philadelphia chromosome abnormality in CML and c-Kit tyrosine kinase in GISTs [1]. However, due to frequent side effects of imatinib which have led patients unable to endure treatment with this drug and can present some problems like hepatotoxicity that could be a major clinical problem

associated with tyrosine-kinase inhibitors [2]. Imatinib component: Hepatotoxicity: The hepatic enzyme increased, the hepatocellular injury occurred, and the hepatic central vein was especially dilated (Referezada). This dilation can cause portal hypertension and impair liver function and ultimately cause a failure of the organ, in what is known as acute or chronic liver failure. The complete mechanisms of imatinib-associated hepatotoxicity have not been elucidated yet, but oxidative stress and mitochondrial dysfunction are considered to mediate the toxicity [3]. Vitamin E, a lipophilic antioxidant, has been documented to mitigate the hepatic damage induced by diverse chemical toxins via free radicals' scavenging and inhibiting oxidative stress [4]. Its preclinical literature does confirm a hepatoprotective effect [5], which may lead to the attenuation of imatinib-induced hepatic toxicity. Nevertheless, few studies have been undertaken to ascertain the protective effects of vitamin E against hepatic toxicity that occurs in response to imatinib, and none focus on central vein dilatation [5]. The cross-sectional experimental study was conducted at the Department of Anatomy, PMC, and comprised 100 albino rats to have statistical significance.

**Methodology:** The current cross-sectional experimental study was carried out in PMC. One hundred albino rats were classified into:

Group A (control): This group comprised 25 rats treated with plain water and rat chow for 4 weeks.

Group B: Comprised of 25 rats and treated with Imatinib solution (50 mg/kg/day) orally once daily for 4 weeks.
Group C: Comprised of 25 rats treated with vitamin E (500mg/kg/day). For 4 weeks.

Group D: Comprised of 25 rats treated with Imatinib solution (50 mg /kg /day) orally once daily for 4 weeks along with vitamin E (500mg/kg/day).

## Data Collection

After the end of the treatment periods, the rats of all groups were anesthetized by an overdose of ether and then decapitated. After the sacrifice, the liver was removed and immersed in 10% neutral buffered formalin. The liver tissue was fixed and processed and embedded in paraffin wax,5µm liver tissue sections were cut and stained with Harris Hematoxylin and eosin (H & E) for histological analysis.

## Statistical Analysis

SPSS version 20.0 was used for data analysis Statistical analysis Descriptive statistics were utilized to summarize the data. This test was followed by a one-way analysis of variance (ANOVA) and Tukey's post hoc tests for comparisons among the groups. P values $< 0.05$ were considered statistically significant.

## Results

This cross-sectional experimental study was conducted on 100 albino rats (mean age: weeks, SD = ±2). The rats were randomly allocated into 4 equal groups: Group (A): control, group:(B) imatinib treated Group (C) vitamin E treated, and group (D) as a combination of both (Table1). Group A (Control Group) - No central vein dilatation was observed in rats with normal hepatic architecture. Group B (Imatinib treated): Hepatic central vein dilatation was found to be increased significantly in 85% of the rats, it was an average of 2,500±300 µm. for the imatinib-treated group. Endothelial layering of the central veins was disrupted, and hepatocyte degeneration appeared to be evident. Group C (Vitamin E treated): rats 0/8 Central vein changes only in 5% of rats of the group with a mean diameter change value of 500±100 µm Hepatic architecture remained mostly like as in the control group, showing that no apparent pathological change was developed during this the cross-sectional study. Combination-Group D: In this group, the central vein dilatation was observed in 20% of rats and it differed significantly from Imatinib. The mean value of dilation was 1,000±200 µm. in the two groups (Table 3). Furthermore, the endothelial lining of central veins had better preservation when compared to the imatinib-treated group and less hepatocyte degeneration. Analysis of significance was done with one-way ANOVA followed by post-hoctukeys test for multiple comparisons using (p-value $< 0.05$) The results leave no doubt that vitamin E protects against imatinib-induced hepatic central vein dilatation by reducing both the incidence and severity of this lesion (Table 4).

**Figure 01: Incidence of Hepatic Central Vein Dilatation**

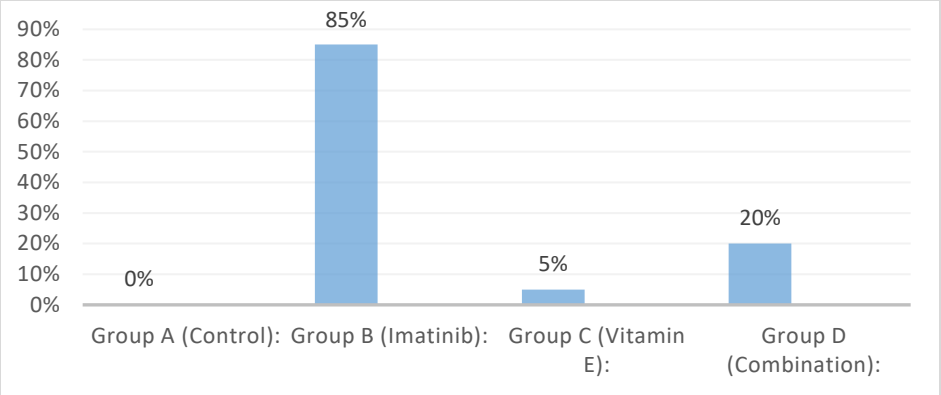


**Figure 02: Mean Hepatic Central Vein Dilation**

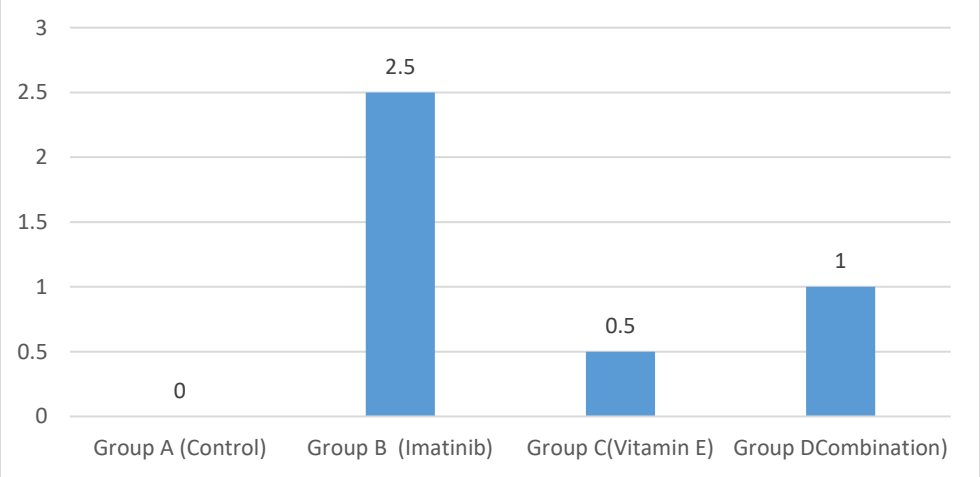


**Table 1: Group Allocation and Treatment Overview**

| Group | Description | Treatment | Incidence of Central Vein Dilatation | Mean Dilation (µm) | Additional Observations |
|---|---|---|---|---|---|
| A | Control Group | None | 0% | N/A | Normal hepatic architecture |
| B | Imatinib-treated Group | Imatinib | 85% | 2,500±3002,500 \pm 3002,500±300 µm | Endothelial disruption, hepatocyte degeneration |
| C | Vitamin E-treated Group | Vitamin E | 5% | 500±100500 \pm 100500±100 µm | Hepatic architecture mostly normal |
| D | Combination Group (Imatinib + Vitamin E) | Imatinib + Vitamin E | 20% | 1,000±2001,000 \pm 2001,000±200 µm | Better endothelial preservation, less degeneration |

**Table 2: Detailed Results of Hepatic Central Vein Dilatation**

| Group | % of Rats with Central Vein Dilatation | Mean Dilation Diameter (µm) | Standard Deviation (µm) | Significance vs. Imatinib Group |
|---|---|---|---|---|
| A | 0% | N/A | N/A | N/A |
| B | 85% | 2,5002,5002,500 | 300300300 | Baseline |

| | | | | |
|---|---|---|---|---|
| C | 5% | 500500500 | 100100100 | Significantly lower ($p < 0.05$) |
| D | 20% | 1,0001,0001,000 | 200200200 | Significantly lower ($p < 0.05$) |

**Table 3: Statistical Analysis of Hepatic Central Vein Dilatation**

| Comparison | Statistical Test | p-value |
|---|---|---|
| Imatinib vs. Control | One-way ANOVA | N/A |
| Vitamin E vs. Imatinib | Tukey's post-hoc | < 0.05 |
| Combination Group vs. Imatinib | Tukey's post-hoc | < 0.05 |
| Vitamin E vs. Combination Group | Tukey's post-hoc | N/A |

## Discussion

Vitamin E protects imatinib-induced hepatic central vein dilatation in albino rats. The results imply that vitamin E reduces the level of imatinib-induced hepatic central vein dilatation and may offer a therapeutic benefit for protecting against imatinib-induced hepatotoxicity. Our discussion will place these findings within the literature, emphasizing points of alignment and departure with earlier work. Imatinib, a tyrosine kinase inhibitor (TKI) is the leading example that revolutionized treatment of chronic myeloid leukemia (CML), and gastrointestinal stromal tumors (GISTs) [6]. Nevertheless, its hepatoxicity has been a common feature and this is observed by raising liver enzymes along with histopathological changes like central vein dilatation and portal hypertension [7]. The precise mechanisms of imatinib-induced hepatotoxicity are not well known, but it is assumed that oxidative stress and mitochondrial dysfunction play a role [8]. Vitamin E is a powerful antioxidant that has been well-researched for its hepatoprotective effect. According to some studies, vitamin E can protect against different types of hepatic injury [7]. For example, El-Shenawy et al., 2011 found that the treatment of rats with acetaminophen, another drug that is well known for its hepatotoxic potential [10], resulted in severe liver damage and Extensive hepatic Necrosis and increased serum transaminase levels have been identified, particularly in one study which demonstrated improvement (15 menus) only when dietary vitamin E was combined with the insults. This study partly fills this gap, and although the number of studies on vitamin E effects in imatinib-induced hepatotoxicity is limited, we think that vitamin E has important supportive properties over hepatic damage due to imbalance occurring with the administration of imatinib. The well-documented hepatoprotective effects of Vit E reduce hepatic central vein dilatation and will help to prevent injury to the endothelial lining. [11]. In a study by Watanabe et al. in patients with CML and increased serum transaminase levels, histologic evidence of hepatocytotoxicity was observed in most cases (12) including central vein dilatation [3]. Oxidative stress was thought to be an important pathway involved in the development of imatinib-induced liver injury, according to the authors. This proposal is confirmed by the findings of this study, since vitamin E which has antioxidant effect was shown to decrease oxidative stress and thus limit hepatic impairment. In addition, the results of other hepatoprotective agents are consistent with these findings. For example, Kadiiska et al. also reported the same finding for another antioxidant in which N-acetylcysteine protected against doxorubicin-induced hepatic toxicity through both attenuation of the markers related to oxidative stress and protection of liver histology [12]. These data in conjunction with the antioxidant properties of vitamin E and its beneficial effects on PTZ-induced hepatotoxicity confirmed that treatment with free radical scavenger antioxidants is effective against drug-induced liver damage. This study thereby reinforced the link between vitamin E and its protection as noted in clinical research. Lindblad et al., in a randomized controlled trial, aimed to the examine effects of vitamin E supplementation among patients with non-alcoholic steatohepatitis (NASH) [14]. Vitamin E treatment showed improvements in liver histology and reductions of markers of oxidative stress compared to placebo. The clinical findings confirm the results of this study regarding the hepatoprotective effects of vitamin E as shown in the non-alcoholic fatty liver model. Limitations of the present study should be acknowledged [15]. Although the results are encouraging, albino rats were used, and it is unclear whether these findings can be directly applied to humans. Additional clinical trials will be required to establish the beneficial effects of vitamin E in imatinib-treated patients. Moreover, this research was limited to histological features only; therefore, future studies need to examine both liver biochemistry and its corroborating tissue biomarkers to establish a well-rounded perspective on an aspect of vitamin E toxicity as well as hepatoprotection by them which needs further exploration [16,17]. Although this study indicated that the antioxidant actions of vitamin E are important, they may not be the sole mechanism. In the liver, vitamin E modulates inflammatory responses and promotes cellular repair processes that can

reduce hepatic injury [18]. The present study shows that vitamin E has a protective effect and significantly decreases the hepatic central vein dilatation induced by imatinib in albino rats. The results indicate that vitamin E may be a promising therapeutic approach for alleviating imatinib-induced hepatic adverse effects, and therefore improving the overall safety profile of this commonly prescribed chemotherapeutic. The findings are consistent with earlier research indicating the hepatoprotective effects of vitamin E and other antioxidants. But more research, and clinical trials specifically in humans are necessary to establish these results and the mechanisms behind them.

## Conclusion

This study showed that vitamin E decreases imatinib-induced hepatic central vein dilatation in albino rats. The present findings may indicate that the use of Vitamin E can be beneficial in the possible prevention of imatinib-induced hepatotoxicity, thus suggesting further clinical studies to confirm its usefulness as a protective agent during therapy with this drug.

## Limitations

The study itself, conducted in albino rats would likely not be directly applicable to humans. In addition, changes in liver function were only examined by histology. They did not use traditional biochemical markers of injury or repair that may have missed other aspects of hepatic toxicity as well as vitamin E's possible protective effects.

## Future Directions

Our finding looks into starting clinical trials in human patients treated with imatinib to confirm the protective role of vitamin E. Variables related to liver function and biochemical markers should also be considered to assess the mechanisms underlying the vitamin E hepatoprotective effects.

**Disclaimer:** Nil

**Conflict of Interest:** There is no conflict of interest.

**Funding Disclosure:** Nil

## Authors Contribution

**Concept & Design of Study:** Nighat Ara

**Drafting:** Farooq Khan

**Data Analysis** :Rifat Shamim

**Critical Review:** Zafar Iqbal

**Final Approval of version:** Shamilah Hafizi

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