

COMPARISON OF SAFETY AND EFFICACY OF RIVAROXABAN AND ENOXAPARIN FOR TREATMENT OF CANCER ASSOCIATED VENOUS THROMBOEMBOLISM

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Abstract: *The retrospective study was conducted in Nishtar Medical Hospital from January 2022 to January 2023 to compare the safety and efficacy of Rivaroxaban with low molecular weight heparin (LMWH) such as enoxaparin for the treatment of cancer-associated venous thromboembolism (VTE). A total of 250 patients were included in the study. The participants were divided into a control group (who received LMWH (enoxaparin)) and a study group (who received Rivaroxaban). The primary outcome was the occurrence of symptomatic VTE and major bleeding events during the follow-up period. After 3 months, VTE recurred in 1 (1.6%) patient in the Rivaroxaban group and 6 (3.1%) patients in the enoxaparin group. After 3 months, Rivaroxaban had 4 (6.6%), and the enoxaparin group had 5 (2.6%) major bleeding events. During the 3 to 12-month period, there was no significant difference regarding treatment outcomes in groups. Based on the results, we can conclude from this study that Rivaroxaban offers effective therapy for cancer-associated VTE, but its bleeding complications are higher than LMWH.*

Keywords: Malignancy, venous thromboembolism, Rivaroxaban, enoxaparin, anticoagulation

Introduction

Cancer is associated with an increased risk of venous thromboembolism (VTE) (Espitia et al., 2023). Cancer-associated central venous catheterization, invasive techniques, and chemotherapy further elevate this risk. Cancer is also associated with 5 fold higher risk of recurrence of venous thromboembolism compared to normal people (Paul and Cifu, 2019). Cancer-associated VTE recurrence is associated with a 3 times higher risk of mortality (Htut et al., 2022). Thus, current guidelines suggest continuing anticoagulation therapy after the acute phase of treatment until the end of active treatment (Stevens et al., 2021a). Active cancer also increases the risk of bleeding due to anticoagulation therapy. Thus, balancing the risk of anticoagulant-associated bleeding and VTE recurrence complicates treatment in these patients.

An effective anti-coagulant that causes low bleeding is recommended for cancer patients. According to current guidelines, low molecular weight heparin (LMWH) is preferred over direct oral anticoagulants (DOACs) and vitamin K antagonists (Stevens et al., 2021b). CLOT trial reported favorable outcomes of dalteparin compared to warfarin for reducing VTE recurrence; however, the results of the CATCH trial were less definitive (Lee et al., 2015). DOACs and vitamin K antagonists have the same efficacy and

safety for treating VTE without cancer. A study has shown the superiority of DOACs over warfarin for cancer-associated VTE (Elsebaie et al., 2019). Another study reported Rivaroxaban's safety and efficacy for cancer and non-cancer patients (Iorga et al., 2019). A study compared the result of dalteparin and edoxaban for cancer-associated VTE. The results showed that both VTE recurrence rates were similar, though edoxaban had higher bleeding events (Raskob et al., 2017). For further analysis, this study compares the safety and efficacy of Rivaroxaban with LMWH (enoxaparin) for treating.

Methodology

The retrospective study was conducted in Nishtar Medical Hospital from January 2022 to January 2023. The study included patients who had active cancer and associated acute VTE. Patients with chronic illnesses were excluded. A total of 250 patients were included in the study. Informed consent of the participants was taken. Ethical board of the hospital approved the study. The participants were divided into the control group (who received LMWH (enoxaparin)) and the study group (who received rivaroxaban). These patients received anticoagulants for at least 3 months, and outcome events after 3 months and between 3 to 12 months were recorded.

Medical data of the participants, including laboratory, radiology, and pathology examinations, were taken from the hospital's data. The thrombosis risk was assessed by Khorana score, type of cancer, and systematic chemotherapy. Autopsy results, death certificates, and medical records were used to determine the cause of death. The primary outcome was the occurrence of symptomatic VTE and major bleeding events during the follow-up period.

SPSS version 23.0 was used for data analysis. Numerical variables were represented as mean and standard deviation. Student t-test was used for inter-group comparison of numerical variables. Categorical variables were represented as frequency and percentages. The Chi square test was used for inter-group comparison of categorical data. Overall survival in both groups was compared through a log-rank test. Kaplan –Meier analysis was used for estimating differences in primary outcomes. P value <0.05 was considered statistically significant.

Results

Of the 250 patients, 60 were in the study group and 190 in the control group. Regarding baseline data, there was no significant difference between both groups, except for surgery as a provoking factor and female participants, which were more common in the

rivaroxaban group. Pulmonary embolism was most common in both groups. Generally, cancer locations in both groups were similar. The most common cancers were hematological, genitourinary, and pancreatic. Two-thirds of participants were on active chemotherapy when VTE was diagnosed. More than 50% of patients in both groups had stage IV cancer at the time of VTE diagnosis.

The mean follow-up in the rivaroxaban group was 225 ± 173 days, and in the enoxaparin group was 199 ± 156 days. There was no significant impact of treatment strategy on the rate of recurrence of VTE. After 3 months, VTE recurred in 1 (1.6%) patient in the rivaroxaban group and 6 (3.1%) patients in the enoxaparin group. After 3 months, Rivaroxaban had 4 (6.6%), and the enoxaparin group had 5 (2.6%) major bleeding events. Platelet count during the major bleeding events did not differ in both groups. The Rivaroxaban group had a higher rate of non-major bleeding events (P=0.007). Thus, overall bleeding events were more common in the study group (P=0.027). There was no significant difference in mortality rate between the groups (P=0.14). After 3 months, there were 14 (7.3%) deaths in the enoxaparin group and 3 (5%) in the rivaroxaban group (Table I). During the 3 to 12-month period, there was no significant difference regarding treatment outcomes in both groups (Table II)

Table I 3-Month Treatment Outcomes

	Rivaroxaban group n=60	Enoxaparin group n=190	P value
VTE recurrence	1 (1.6%)	6 (3.1%)	0.15
Major Bleeding event	4 (6.6%)	5 (2.6%)	0.55
Platelet count during bleeding	311.1 ±188.5	165.2 ±67.1	0.20
Non-major bleeding event	5 (8.3%)	1(0.5%)	0.007
Overall bleeding events	9(15%)	6(3.1%)	0.027
All-cause mortality	3 (5%)	14 (7.3%)	0.14

Table II Long-term Treatment Outcomes

	Rivaroxaban group n=60	Enoxaparin group n=190	P value
VTE Recurrence rate	10.2	14.5	0.30
(95 % CI)	(3.6, 22.1)	(7.9, 25.2)	
Major bleeding events	10.2	10.1	0.66
(95% CI)	(3.6, 22.1)	(4.7, 19.1)	
Non-major bleeding events	25.3	11.2	0.25
(95% CI)	(13.9, 42.4)	(5.2, 20.4)	
Overall bleeding events	34.6	20.2	0.63
(95% CI)	(20.7, 53.8)	(12.2, 32.3)	
Mortality rate	53.4	72.5	0.12
(95% CI)	(36.5, 75.3)	(56.1, 92.2)	

Discussion

The current study showed a similar mortality rate with enoxaparin or Rivaroxaban. For cancer-associated

VTE, Rivaroxaban is an effective and safe alternative to LMWH. The current study's findings align with the previous trial conducted by Sabatino et al. (Sabatino et al., 2020). In the current study, the recurrence rate

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of VTE with rivaroxaban was 1.6%, closer to and was reported by a previous study (Mokadem et al., 2021). In a study by Van and Hawe, the recurrence rate of pulmonary embolism and DVT in patients receiving rivaroxaban was 2.1 % (van Hout et al., 2020). In this study, the recurrence rate in the enoxaparin group after 3 months was 3.1%. After a year, the treatment strategy did not impact the recurrence rate. A study showed 3 months VTE recurrence rate of tinzaparin to be 7.1 % (Sidahmed et al., 2020). Notably, VTE propensity differs with cancer stage, type, and treatment. In the current study, after 3 months of rivaroxaban, 6.6% of major bleeding events occurred. During the long term, both groups had no difference. A previous study showed 7.3% major bleeding events and 0.7% non-major events with Rivaroxaban (Pignataro et al., 2017). In the enoxaparin group of the current study, the major bleeding events was 2.6%. A study on the safety of LMWH for cancer patients reported a 5.4% bleeding events (Bates et al., 2018). In another study by Ageno et al., 3 months bleeding events of tinzaparin was 2.7 % (Ageno et al., 2019). A study compared dalteparin to LMWH/edoxaban in cancer patients and found that edoxaban had significantly higher major bleeding events (P=0.04) (Raskob et al., 2018). Results of the studies show that bleeding complications pose an obstacle to managing cancer-associated VTE. Cancer patients are already at increased risk of bleeding due to the nature of the disease. Tissue friability, invasive procedures, thrombocytopenia, and renal and liver disease all increase the risk. After 3 months, the mortality rate with rivaroxaban was 5%, and with enoxaparin was 7.3%. VTE-associated mortality is higher in cancer patients compared to non-cancer patients. No specific anti-coagulant has been proven to reduce mortality rate in such patients. Guidelines recommend continuation of anticoagulant therapy until active malignancy lasts.

There are a few limitations of our study. First, it has a small sample size. Second, it is a retrospective study. Third, there may be selection bias about therapy allocation because of the lack of randomization.

Conclusion

Rivaroxaban offers effective therapy for cancer-associated VTE, but its bleeding complications are higher than LMWH.

Conflict of interest

The authors declared absence of conflict of interest.

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