THE COMPARISON OF EFFECTIVENESS AND SAFETY BETWEEN WARFARIN AND RIVAROXABAN IN HYPERCOAGULATED CENTRAL NERVOUS SYSTEM TUMORS

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ABSTRACT:

Background: Central nervous system (CNS) tumors originate from the brain and spinal cord, and have complications, such as hypercoagulation. The administration of anticoagulants (warfarin and rivaroxaban) has been able to reduce hypercoagulation-related morbidity and mortality, however, the effectiveness and safety of their use has not been well studied.

Objectives: This study aims to compare the effectiveness and safety of anticoagulant drugs between warfarin and rivaroxaban in hypercoagulated CNS tumors.

Methods: This was a randomized clinical trial study, double-blinded, conducted on CNS tumor patients from September-November 2020 at Mohammad Hoesin Hospital. The patients were given warfarin and rivaroxaban for 3 weeks. Coagulation status was measured before and after. Data were analyzed using SPSS ver.24.

Results: The mean age of 20 patients was 42.70+8.14 years and majority were female (80%), with tumor characteristics were primary (80%), single (85%), and located in the brain (95%). In the warfarin group (n=10), there were significant improvements in PT (p 0.008), INR (p 0.013), Fibrinogen (p 0.041), and D-Dimer (p 0.008) value, also the rivaroxaban group (n=10) in PT (p 0.013), APTT (p 0.012), INR (p 0.028), Fibrinogen (p 0.047), D-Dimer (p 0.032), and Anti Fxa (p 0.028). However, there was no significant difference between groups, except when comparing the Anti Fxa delta (p 0.041). There was 1 person with major bleeding using warfarin, and 1 person (excluded) with GIT bleeding using rivaroxaban.

Conclusion: There was a significant improvement of coagulation value in both groups, also side effects were seen as well.

Keyword: *CNS Tumor, Hypercoagulation, Warfarin, Rivaroxaban*

INTRODUCTION

Central nervous system (CNS) tumors are tumors originating from within the brain, spinal cord, meninges, and metastatis. Brain tumors account for about 85-90% of total CNS tumors and have an incidence of 22.36 cases per 100,000 people in 2007-2011, and increase to 23.82 per 100,000 people in 2019. The worldwide incidence rate for malignant brain tumors is 3.4 per 100,000 population, with a mortality of 4.25 per 100,000 population per year.[1-4] The high mortality and morbidity in malignant brain tumors is associated with many complications, such as hypercoagulation, which are marked by impairment in coagulation included PT, APTT, INR, Fibrinogen and D-Dimer values.[2]

Anticoagulation therapy that frequently used in patient with brain tumors with hypercoagulable condition are warfarin and rivaroxaban.[5] Warfarin works by inhibiting the synthesis of vitamin K which is an important component in the formation of clotting factors II, VII, IX and X, as well as regulatory factors protein C, protein S and protein Z.[6] Rivaroxaban, one of the NOAC agent, another anticoagulant drug created to overcome the shortcomings of warfarin, while this agent acts selectively on clotting factor Xa to produce its therapeutic effect.[7]

There are several studies comparing the use of anticoagulant drugs in cancer patients. Fanola et al's study did not show a significant difference in the effectiveness and safety of using edoxaban compared to warfarin.[8] On the contrary, Shah et al's study have shown that, the risk of bleeding was more common with rivaroxaban dan darbigatran than warfarin, however, based on the patient's thromboembolic events, there was a lower incidence of rivaroxaban, darbigatran dan apixaban compared to warfarin.[9]

There are currently no previous studies comparing the efficacy and safety of warfarin with rivaroxaban in hypercoagulable central nervous system tumors in Indonesia. The purpose of this study are to see whether there are differences in the effectiveness of coagulation using blood coagulation parameters such as routine blood, PT, APTT, INR, Fibrinogen, D-Dimer and Anti-Fxa between warfarin and rivaroxaban, in addition, this study also has to assess the safety of the drug in the form of side effects of drug-induced bleeding risk.

This study was approved by ethical committee of Mohammad Hoesin Hospital no 51/ kepkrsmh/ 2020

METHODS

This was a clinical trial study with a double-blind randomized clinical trial (RCT) study design that compared the effectiveness and safety of anticoagulants between warfarin and rivaroxaban in hypercoagulated CNS tumor patients at dr. Mohammad Hoesin Hospital from September to November 2020.

The inclusion criterias for this study were patients aged > 18 years, diagnosed with CNS tumor with hypercoagulation, evidenced by CT-scan or MRI, had KPS score ≥ 70, did not registered to surgical procedure in the next 3 weeks, using anticoagulant and antiplatelet drugs with conditions free from washout time (2x half life), antiplatelet 7 days and anticoagulant for 3 days, there were no contraindication in taking warfarin or rivaroxaban, and also had signed an informed consent.

Exclusion criterias in this study were patients with poor clinical condition, had contraindications (active bleeding, allergies and pregnancy), with comorbid diseases, had received surgery or chemotherapy or radiotherapy, with creatinine clearance < 30 ml/min or with impaired liver function or had taken P- glycoprotein inhibitor drugs.

Data were recorded, consisted of demographic data, patient and tumor characteristics (KPS score, tumor type, number of tumors, tumor location), as well as hemostasis marker value (PT, APTT, INR, D-Dimer, fibrinogen, Anti Fxa, and routine blood). We also evaluated the side effect with the presence of major and non-major (minor) bleeding. Implementation of the intervention was done by randomization and blinding data.

The warfarin group was given a dose of 2 mg once a day night on an empty stomach (at least 2-3 hours after eating), a placebo drug was given in the morning, the doses used were stable, unless occurred an adverse drug effect. In the Rivaroxaban group, a dose of 15 mg was given twice a day with 12 hour intervals, before meals, with fixated doses during intervention, unless there was an adverse drug effect.

Statistical analysis used SPSS 24.0 for windows. Data were analyzed univariately and bivariately using a significance value of $p < 0.05$. Data normality test was conducted using Shapiro Wilk, effectiveness comparison using Independent T Test/ Mann Whitney, and Paired t test/ Wilcoxon.

RESULTS

A total of 20 subjects were included in this study, with 10 patients using warfarin and 10 others using rivaroxaban. The characteristics of the patients were shown in **Table 1.**

Comparison of the effectiveness of anticoagulant drugs before and after treatment in each group was shown in **Table 2.** Comparison of values before (baseline) and after treatment based on various parameters of coagulation status was shown in **Table 3.**

Table 1. The Characteristics of Patients

Charateristics	Total n(%)	Groups	
		Warfarin n(%)	Rivaroxaban n(%)
Age (years)			
- 19-39	7(35.0)	2(20.0)	5(50.0)
- 40-64	13(65.0)	8(80.0)	5(50.0)
- ≥ 65	(0.0)	0(0.0)	0(0.0)
Gender			
- Male	4(20.0)	2(20.0)	2(20.0)
- Female	16(80.0)	8(80.0)	8(80.0)
Occupations			
- Entrepreneur	2(10.0)	0(0.0)	2(20.0)
- Farmer/Labor	2(10.0)	1(10.0)	1(10.0)
- Housewives	15(75.0)	8(80.0)	7(70.0)
- Retirement/not working	1(5.0)	1(10.0)	0(0.0)
Level of education			
- Elementary school	1(5.0)	1(10.0)	0(0.0)
- Junior high school	1(5.0)	1(10.0)	0(0.0)
- Senior high school	16(80.0)	7(70.0)	9(90.0)
- College	2(10.0)	1(10.0)	1(10.0)
Type of tumor			
- Primary	16(80.0)	9(90.0)	7(70.0)
- Metastasis	4(20.0)	1(10.0)	3(30.0)
Total of tumor			
- Single	17(85.0)	9(90.0)	8(80.0)
- Multiple	3(15.0)	1(10.0)	2(20.0)
Location of tumor			
- Brain	19(95.0)	10(100.0)	9(90.0)
- Spinal cord	1(5.0)	0(0.0)	1(10.0)
Total	**20(100.0)**	**10(100.0)**	**10(100.0)**

Table 2 The Comparison of Hemostasis of Coagulation status Before and After the Intervention

Warfarin			
Values	**Before** Med(min-max)	**After** Med(min-max)	**P Values**
PT	13.1(12.5-13.7)	19.7(12.6-90.0)	0.008[a]
APTT	28.4(22.0-33.5)	31.5(23.2-57.1)	0.173[a]
INR	0.9(0.8-1.0)	1.4(0.8-7.8)	0.013[a]
Fibrinogen	438.5(337.0-695.0)	370.0(253.0-493.0)	0.041[a]
D-Dimer	0.6(0.2-2.4)	0.2(0.2-1.5)	0.008[a]
Anti Fxa	10.0(4.0-17.0)	11.0(6.0-18.0)	0.644[a]

Rivaroxaban			
Values	**Before Med(min-max)**	**After Med(min-max)**	**P Values**
PT	13.3(11.6-14.4)	16.3(12.7-26.0)	0.013[a]
APTT	26.8(26.0-34.5)	30.8(26.1-49.0)	0.012[a]
INR	0.9(0.8-1.0)	1.1(0.8-1.9)	0.028[a]
Fibrinogen	455.5(303.0-555.0)	331.5(238.0-706.0)	0.047[a]
D-Dimer	1.3(0.5-3.8)	0.7(0.2-1.5)	0.032[a]
Anti Fxa	10.5(4.0-20.0)	19.0(5.0-77.0)	0.028[a]

[a]Wilcoxon test

Table 3 The Comparison of Hemostasis of Coagulation status Before (Baseline) and After the Intervention

Baseline	**Groups**		**P Values**
	Warfarin Med(min-max)	**Rivaroxaban Med(min-max)**	
PT	13.1(12.5-13.7)	13.3(11.6-14,4)	0.570[a]
APTT	28.4(22.0-33.5)	26.8(26.0-34.5)	0.650[a]
INR	0.9(0.8-1.0)	0.9(0.8-1.0)	0.789[a]
Fibrinogen	438.5(337.0-695.0)	455.5(303,0-555.0)	0.970[a]
D-Dimer	0.6(0.2-2.4)	1.3(0,5-3.8)	0.112[a]
Anti Fxa	10.0(4.0-17.0)	10.5(4,0-20.0)	0.790[a]
After the Intervention	**Groups**		**P Values**
	Warfarin Med(min-max)	**Rivaroxaban Med(min-max)**	
PT	19.7(12.6-90.0)	16.3(12.7-26.0)	0.199[a]
APTT	31.5(23.2-57.1)	30.8(26.1-49.0)	0.821[a]
INR	1.4(0.8-7.8)	1.1(0.8-1.9)	0.364[a]
Fibrinogen	370.0(253.0-493.0)	331.5(238.0-706.0)	0.496[a]
D-Dimer	0.2(0.2-1.5)	0.7(0.2-1.5)	0.058[a]
Anti Fxa	11.0(6.0-18.0)	19.0(5.0-77.0)	0.063[a]

[a]Mann-whitney test

Comparison of the safety of anticoagulant drugs was shown in **Table 4.** In this comparison, 21 study subjects were analyzed (1 patient was excluded due to death during the study, but the cause of death was not related to the intervention).

Table 4 The Comparison of Safety of Anticoagulant drugs

Side Effects	Groups		Total n(%)	P Values
	Warfarin n(%)	Rivaroxaban n(%)		
Major bleeding				0.476[a]
- Yes	1(10.0)	0(0.0)	1(4.8)	
- No	9(90.0)	11(100.0)	20(95.2)	
Non major Bleeding				0.524[a]
- Yes	0(0.0)	1(9.1)	1(4.8)	
- No	10(100.0)	10(90.9)	20(95.2)	
Intracranial Bleeding				0.476[a]
- Yes	1(10.0)	0(0.0)	1(4.8)	
- No	9(90.0)	11(100.0)	20(95.2)	

[a]Fischer exact test

DISCUSSION

The mean age of the patients in this study was 42.70±8.14 years with the most aged 40-64 years (65%). In line with this study, Diansari et al, stated that the mean age was 48.58±12.38 with the majority age range being 40-59 years (56.5%) in brain tumor patients with hypercoagulation. Along with increasing age, there was an increase in procoagulant activity.[10] The majority of patients in this study were female (80%) compared to male (20%). The incidence of non-malignant brain tumors was up to 2 fold higher in women than malignant brain tumors.[11]

We found that the most characteristics of tumors were primary tumor (80%), single tumors (85%), and located in the brain (95%). Based on epidemiological data, we found that primary brain tumors had a higher incidence of 14.17 per 100,000 population and for malignant brain tumors 7.25 per 100,000 population in the United States.[5,12] ABTA revealed that the range of 10-20% brain tumors metastases were single tumors and ±80% were multiple tumors. Brain tumors covered about 85-90% and spinal cord around 10-15%.[6] Diansari et al., eported as many as 90.4% of CNS tumors with hypercoagulation were in the brain.[10]

Patients with tumors experienced changes in the homeostatic mechanisms of coagulation and fibrinolysis, leading to hypercoagulation. Tissue factor (TF) or thromboplastin was a powerful procoagulant that was important in coagulation mechanisms. Endothelial damage caused TF to be exposed to the bloodstream, which ultimately binded and activated factor VII, and converted Factor X to Xa, resulting in

thrombin formation (fibrin deposition and platelet activation). These tumor cells were capable of producing factors associated with the activation of the coagulation cascade, including VEGF, tissue-type plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1).[13] TF was implicated in various oncogenic processes, including angiogenesis, cell migration, invasion and tumor cell proliferation which would certainly had an impact on the development and growth of brain tumors.[14] There was evidence that certain cancers were more likely to be thrombotic, and this can be influenced by many things including the severity of the disease, bedrest, and also treatment intervention.[15] Thus, patients suffered from hypercoagulable brain tumors required anticoagulant therapy to prevent further complications include the direct occurrence of VTE and the progression state of the tumor itself. This study involved the use of warfarin and rivaroxaban as anticoagulant agents in hypercoagulable brain tumor patients and evauated the effectiveness and safety of the drugs.

Based on PT parameters, in the warfarin group, the median value increased significantly after 3 weeks of observation. Similar to the rivaroxaban group, there was an increase in the PT value, however, when compared between two groups the lengthening of PT time was longer in the warfarin than the rivaroxaban group, although it was not statistically proven.

Increasing of PT value more than normal in both group was consistent with the theory that warfarin through its anticoagulant mechanism affected vitamin K-dependent clotting factors (II, VII, IX, and X) and anticoagulants proteins C and S. Warfarin interfered with clotting activation by blocking the required oxidation-reduction cycle of vitamin K. For the carboxylation of clotting factors, reduced active vitamin K would make these clotting factors inactive and unable to contribute to the clotting cascade pathway.[7] Prothrombin time (PT) was a coagulation parameter used to assess in extrinsic and common pathways cascade that would detect deficiency of factor II, V, VII, X and fibrinogen levels. Vitamin K was an important component of factors II, VII, IX and X so that the consumption of warfarin (vitamin K antagonist) would reduce these factors and prolong the value of PT.[15] Rivaroxaban as DOACs that worked specifically on Factor Xa also still had an effect on elongation value of PT.[16] The study by Tajiri et al., comparing the use of warfarin and rivaroxaban in patients with non-valvular AF was in line with this current study, in which there was no significant difference between the two groups in PT-INR and APTT scores, although this values increased slightly more in the warfarin rather than the rivaroxaban group.[17]

Based on the APTT parameters, there was an increase of median value in the warfarin group but not significant, as for the group rivaroxaban also experienced an increased but significantly proven. Although the difference between the two groups was not significant, there was a greater increase in APTT values in the warfarin group than in the rivaroxaban group. APTT or activated thromboplastin time was a parameter used to measure the activity of the intrinsic pathway of the blood clotting cascade, which precisely measured the function of all clotting factors except factor VII and factor XIII.[18] In contrast to warfarin, Douxfils et al., showed that the use of rivaroxaban affected APTT values although not significantly.[19] These results were in agreement with the current study, which showed the increase in APTT values was greater in the warfarin than in the rivaroxaban group, although not significant.

Based on INR parameters, we found a significantly increase in the warfarin group, as well as in rivaroxaban, but when we compared between two groups the INR value increase was greater in warfarin than rivaroxaban although not significant. INR was the ratio of PT patients to PT controls so that despited having different reagents from various countries, it was hoped that the INR could be a more accurate comparison.[20] In this study, an increase in the average INR value indicated the effectiveness of anticoagulant drugs, especially warfarin. In contrast to warfarin, which experienced a large increase, in the rivaroxaban group this increase was not too large. This might be due to the pharmacodynamic activity of rivaroxaban as an anticoagulant that acted directly on factor X.

Based on fibrinogen parameters, in the warfarin group we found a significant decrease, as well as in the rivaroxaban group there was also a significant decrease. In contrast to the previous parameter where warfarin was superior, in this parameter rivaroxaban was superior in reducing the fibrinogen value, but the change in this value was not significant. Study by Hillarp et al., on the effect of rivaroxaban (15 mg 2 times daily for 3 weeks) showed a significant increase in PT, increase in APTT with a slight decrease in fibrinogen. Rivaroxaban acted directly on factor Xa, but also involved in the activity of factor-Xa associated with the clotting system which was part of the prothrombinase complex. Therefore, rivaroxaban had the potential to efficiently down-regulate the coagulation process so that it affected other coagulation parameters, such as PT, APTT, PiCT, fibrinogen, and in particular on Factor-Xa.[21]

Based on the D-Dimer parameter, there was a significant decrease in both groups, however, when compared between groups this difference was not significant. Li-Saw Hee et al., reported that 61 patients with AF showed a decrease in fibrinogen (p 0.023)

and D-Dimer (p 0.006) significantly after taking full-dose warfarin (INR 2-3) for 6 weeks, however, taking warfarin 2 mg once daily for 6 weeks did not show significant changes in any parameters.[22] D Dimer was the end product of fibrin degradation process by plasmin where the process and thrombus degradation must be in balance in order to achieve the function of clotting and tissue repair. The decrease in D Dimer levels was proportional to the fibrin degradation process, which meant that anticoagulant treatment would improve D Dimer level dan reduced the incidence of hypercoagulability.

Based on the Anti Fxa parameters, the warfarin group increased and also in the rivaroxaban group. There was a significant difference in the value (delta) of rivaroxaban and warfarin. Many studies showed a concentration-based correlation between rivaroxaban and Anti-Fxa activity. When rivaroxaban calibration was used, Anti Fxa testing can facilitated quantitative measurement of rivaroxaban concentrations, in other words, increasing concentrations of rivaroxaban consumption would increase Anti Fxa concentrations.[23] Macedo et al., reported an increase in Factor-Xa as much as 55% above 1 iu /ml, 9% between 0.6-1 iu/ml and 36% below 0.6 iu/ml. These results indicated a greater increase in Factor-Xa in the group given rivaroxaban-heparin within 24 hours.[24]

Based on several relevant previous studies, the examination of Factor Xa inhibitors and PT prolongation were closely correlated with plasma concentrations of rivaroxaban. Anti-Fxa examination played a role in direct inhibition of Factor Xa and thrombin. Based on previous studies, in vitro chromogenic assays, showed that rivaroxaban prolonged PT and APTT values. The effect of rivaroxaban on APTT is weak, because there was a tendency for the direct inhibitor FxA to have more effect on PT than APTT.[24]

Based on the side effects, we found 1 patient suffered from gastrointestinal bleeding from the rivaroxaban group on day 4 of treatment, we also found 1 patient in warfarin group experienced IVH (intraventriculer haemorrhage) on day 4 after the intervention. Manifestation of black stool occurred on day 4 of therapy, this might be due to the effect of anticoagulant drugs, and the interactions with levetiracetam, and the use of dexamethasone which previously could trigger stress ulcers can be a triggering factor for gastrointestinal bleeding.[25] A case report by Song et al., DVT patients with various abnormalities in coagulation parameters (PT, APTT, D-Dimer) who took rivaroxaban 20 mg once a day, showed gastrointestinal bleeding characterized by black stool after 1 week of therapy and decrease of D-Dimer.[16] The incidence of IVH in warfarin group was evidenced by CT scan, and surely after that the patient got treatment and was currently in good condition. The incidence was

associated with a long half-life of warfarin (approximately 60 hours), presumably there was an accumulated effects that caused bleeding.

In line with the current study, a propensity matching cohort analysis study conducted by Jeong et al., showed that major bleeding events were more common in the warfarin group than rivaroxaban, but this difference was not significantly different. Major bleeding was found in 38 people (4.7%) with warfarin and 14 (1.7%) with rivaroxaban. Gastrointestinal bleeding including mucosal bleeding was found in 19 people (2.3%) with warfarin and 13 people (1.6%) with rivaroxaban.[26]

We also found the incidence of died in rivaroxaban group. The symptomps occurred when he took the drugs on day 7th. We were informed from another hospital that this patient had experienced a gradual loss of consciousness with a previous complaint of headache. He was treated for 2 days and had CT Scan that explained there was no visible signs of bleeding. The cause of death was thought to be increased intracranial pressure due to the space-compressing effect of the tumor, resulting in herniation, which had been radiologically proven, other possibilities were include metabolic abnormalities.

This study has limitations which were minimal sample size, short duration of monitoring for drugs use and effects. Although, significant improvements of PT and D-Dimer values were found in the warfarin group and significant improvements of PT values in the rivaroxaban group, but not all the parameters had changed, which made it would be possible for other parameters to experience significant changes after therapy if the sample size was enlarged. In addition, this study was not able to monitor the long-term effects of drug use and the short duration of bleeding monitoring made the evaluation of bleeding less stringent.

CONCLUSION

The use of anticoagulant drugs was effective in reducing the incidence of hypercoagulability in CNS tumor patients with hypercoagulability. The administration of warfarin was significantly effective in improving the coagulation status based on PT, INR, Fibrinogen and D Dimer examinations. Meanwhile, the effects of rivaroxaban was significantly seen in the examination of PT, APTT, INR, D Dimer, Fibrinogen and Anti Fxa. There was no difference in the efficacy of warfarin compared to rivaroxaban on all coagulation parameters, except for a significant difference in the value of delta Anti Fxa which was greater in the rivaroxaban group than warfarin. In addition, there was no difference of safety between warfarin and rivaroxaban.

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