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Original paper

Assessment of the efficiency and safety of anticoagulation therapy in patients with liver cirrhosis and atrial fibrillation

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Abstract

Aim of the study: Currently, there are insufficient scientific data regarding the efficacy and safety of direct oral anticoagulants (DOACs) compared to warfarin in patients with both liver cirrhosis (LC) and atrial fibrillation (AF). The aim of the study was to analyze the frequency and risk factors for the development of thrombotic and hemorrhagic complications in patients with LC and AF after DOAC treatment compared to warfarin.

Material and methods: A randomized clinical trial was conducted including 56 patients with both LC and AF treated with dabigatran (n = 30) and warfarin (n = 26). The frequency and risk factors of hemorrhagic and thrombotic complications were evaluated after 3 months of observation.

Results and Discussion: The overall frequency of bleeding was significantly higher after treatment with warfarin (p = 0.038). The frequency of major and minor bleeding events did not differ statistically significantly between the two groups (p > 0.05). Factors which significantly increased the risk of bleeding were: glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 (adjusted hazard ratio (AHR) = 0.82, CI: 0.69-0.96, p = 0.02), constant of thrombin activity (CTA) < 25 units of low-frequency piezoelectric thromboelastography (AHR = 0.66, CI: 0.46-0.92, p = 0.017) and prior history of bleeding (AHR = 108, CI: 8.78-134, p < 0.001).

Conclusions: The use of dabigatran in patients with Child-Pugh class A and B of LC and AF has advantages over warfarin, as it is clinically associated with a lower incidence of bleeding. An increased risk of bleeding is observed in patients with LC classes A and B according to the Child-Pugh scale and AF, who have a reduced GFR < 60 ml/min/1.73 m^2, CTA < 25 units and a prior history of bleeding.

Key words: liver cirrhosis, atrial fibrillation, warfarin, direct oral anticoagulants.

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Introduction

Liver cirrhosis (LC) and atrial fibrillation (AF) are extremely common chronic diseases that take a leading place in the rankings of morbidity and mortality worldwide and remain among the most important public health problems [1, 2]. Recently, more and more attention has been paid to the comorbid course of these diseases, which is associated with a poor prognosis, high mortality and severe complications, which determines their relevance and has important medical, social and economic significance [3]. According to current recommendations, oral anticoagulant therapy is recommended for patients with AF to reduce the risk of thromboembolic complications [4]. However, for patients with AF combined with LC, there are currently no specific, clear, evidence-based recommendations for anticoagulation therapy. Until recently, it was believed that patients with liver cirrhosis are in a state of "auto-anticoagulation" and have a tendency for bleeding and therefore do not need treatment with anticoagulants. However, recently more evidence has been emerging that liver

cirrhosis involves complex disorders of the synthesis of procoagulant and anticoagulant factors, which brings the hemostasis system into a dynamic state of equilibrium [5-7]. According to this theory, patients with LC are prone to thrombosis and bleeding depending on concomitant clinical conditions.

Warfarin has traditionally been the drug of choice for the treatment and prevention of thrombotic complications in patients with atrial fibrillation, but DOACs are now actively replacing warfarin in clinical practice due to their numerous advantages for both physicians and patients. However, all studies on DOACs have excluded patients with chronic liver disease due to the misconception of their hepatotoxicity and therefore there are no data on their efficacy and safety in this population. According to the regulatory recommendations of the Food and Drug Administration (FDA, USA) and the European Heart Rhythm Association, all four DOACs are recommended in patients with Child-Pugh class A liver cirrhosis, selectively recommended in class B liver cirrhosis, and not recommended in patients with class C liver cirrhosis [8-12]. Warfarin is recommended at all stages of liver cirrhosis while maintaining the therapeutic range of international normalised ratio (INR) 2.0-3.0 [13].

In the light of new research on the liver cirrhosis hemostasis state, current recommendations regarding thromboprophylaxis in such patients now seem controversial and are outdated. Recently, many studies have been conducted to assess the effectiveness and safety of anticoagulant therapy in patients with LC and AF. According to meta-analyses, anticoagulation is associated with a lower risk of stroke compared with no anticoagulation without a significantly increased risk of bleeding in these patients, and DOACs have at least a similar efficacy and safety profile to warfarin, and in some cases even better [14-16]. However, the studies that were conducted were small, observational, retrospective, in the form of individual clinical cases. Therefore, more randomized clinical trials on this topic are needed to determine effective anticoagulation regimens, dosing regimens, and to determine safety and efficacy in comparison with each other.

The aim of the study was to perform an analysis of the frequency and risk factors for the development of thrombotic and hemorrhagic complications in patients with LC and AF after treatment with anticoagulant drugs.

Material and methods

Study population and clinical information

Fifty-six patients with both liver cirrhosis and permanent AF participated in the study. They were additionally randomized to 2 groups. Group I included 30 patients who received dabigatran at a dose of 110 mg twice daily for 3 months. Group II included 26 patients who received warfarin in an initial dose of 5 mg, which dynamically changed depending on the INR during 3 months. Patients were instructed on the drugs regimen and possible side effects. After 3 months of treatment, the frequency and structure of thrombotic and hemorrhagic complications were determined, and a multivariable Cox logistic regression model was constructed to assess the risk of thrombotic and hemorrhagic complications in patients treated with warfarin and dabigatran. Exclusion criteria from the study: hereditary or acquired coagulopathies of other etiology, systemic connective tissue diseases, oncological diseases, chronic kidney disease stages 4 and 5 (glomerular filtration rate [GFR] < 30 ml/min/1.73 m^2), HIV infection, major bleeding less than 2 weeks ago, neuropsychological disorders of the patient that affect the results of observation and treatment, violation of compliance by the patient.

The diagnosis of liver cirrhosis was established based on the results of a detailed assessment of patient history, physical examination, laboratory and imaging tests (ultrasound of the abdomen, transient elastography of the liver, upper endoscopy). The diagnostic criteria are a diffuse heterogeneous increase in the echogenicity of the liver parenchyma, the presence of hyperregenerative nodes and focal fatty infiltration, FIB4 grade of liver fibrosis according to the METAVIR scale on liver elastography. The etiology of liver cirrhosis was established according to EASL guidelines [17-20]. The criteria for the diagnosis of atrial fibrillation on the ECG were the absence of P waves in all leads, unchanged QRS complexes, and an irregular ventricular rhythm. Also, all patients were evaluated according to the CHA_2DS_2VASc and HAS-BLED scales to determine the risk of thromboembolic complications and indications for anticoagulant treatment, and also to determine the risk of bleeding.

Baseline characteristics of the study population

A total of 56 patients with AF and LC treated with warfarin (n = 26) or dabigatran (n = 30) were analyzed. The observation period was 3 months. The main clinical parameters of the studied patient population are presented in Table 1. Clinical parameters of patients did not differ statistically significantly between the two groups, with the exception of a slightly higher creatinine level in patients in the warfarin group, which may be explained by a larger number of patients with concomitant kidney disease.

Table 1. Baseline parameters of the study population

Parameter	Dabigatran (*n* = 30)	Warfarin (*n* = 26)	*P*-value
Age (years), median [25; 75 percentiles]	69.5 [64; 78]	69.0 [64; 75]	0.59
Gender, *n* (%):			
Male	21 (70.0)	15 (57.7)	0.81
Female	9 (30.0)	11 (42.3)	0.88
Etiology of LC, *n* (%)			0.38
Alcohol	15 (50.0)	9 (34.6)	
HCV	4 (13.3)	1 (3.8)	
HBV	2 (6.7)	3 (11.5)	
NAFLD	7 (23.3)	9 (34.6)	
Others	2 (6.7)	4 (15.4)	
Child-Pugh score, *n* (%)			0.37
A	15 (50.0)	9 (34.6)	
B	15 (50.0)	17 (65.4)	
Laboratory tests			
Platelets (× 10^9/l), median [25; 75 percentiles]	212.0 [150; 235]	210.0 [134; 231]	0.74
Albumin (g/l), median [25; 75 percentiles]	35.5 [32.5; 39.5]	34.0 [32; 37]	0.58
Creatinine (mkmol/l), mean ±SD	106.6 ±12.74	114.7 ±11.45	0.02
Total bilirubin (mkmol/l), median [25; 75 percentiles]	41.5 [32; 47.5]	42.5 [32.5; 48]	0.6
Liver related comorbidities, *n* (%)			
Ascites	4 (13.3)	5 (19.2)	0.82
History of hepatic encephalopathy	1 (3.3)	1 (3.8)	0.52
Esophageal or gastric varices	9 (30.0)	5 (19.2)	0.22
Non-liver related comorbidities, *n* (%)			
Hypertension	22 (73.3)	16 (61.5)	0.51
Congestive heart failure	5 (16.6)	9 (34.6)	0.22
Renal disease	2 (6.7)	4 (15.3)	0.53
Coronary heart disease	10 (33.3)	12 (46.1)	0.48
Diabetes	2 (6.7)	6 (23.0)	0.17
Obesity	2 (6.7)	4 (15.3)	0.53
Prior history of anticoagulants and antiplatelet agents use, *n* (%)			
Warfarin	10 (33.3)	4 (15.4)	0.21
Dabigatran	0	0	
Rivaroxaban	2 (6.7)	1 (3.8)	0.9
Apixaban	1 (3.3)	0	
Aspirin	7 (23.3)	9 (34.6)	0.53
Clopidogrel	0	0	
Prior history of thrombotic events, *n* (%)			
Thromboembolic (MI, IS, TIA)	11 (36.6)	7 (27.0)	0.62
Splanchnic vein thrombosis	3 (10.0)	2 (7.7)	0.86
Prior history of hemorrhagic events, *n* (%)			
Major	1 (3.3)	0	0.94
Minor	4 (13.3)	7 (27.0)	0.35

LC – liver cirrhosis, MI – myocardial infarction, IS – ischemic stroke, TIA – transitory ischemic attack

Study outcomes

To assess the efficiency of the anticoagulant therapy, the frequency of thromboembolic complications during 3 months of observation was determined. Thromboembolic complications were defined as:

- ischemic stroke – the diagnosis was established clinically on the basis of the presence of focal or general neurologic signs that appeared suddenly and persisted for more than 24 hours and instrumentally confirmed by computed tomography (CT) and magnetic resonance imaging (MRI) of the head;
- transient ischemic attack – the diagnosis was established clinically on the basis of the presence of focal or general neurologic symptoms that appeared suddenly with full recovery of impaired functions within 24 hours and the absence of changes on CT and MRI of the head;
- thromboembolism of systemic circulation – the diagnosis was established clinically and according to CT, MRI, and Doppler ultrasound;
- pulmonary thromboembolism – the diagnosis was established based on the clinical picture and CT and MRI of the pulmonary circulation.

To assess the safety of the anticoagulation therapy, the frequency of hemorrhagic complications was determined. Bleeding complications were defined as:

1. Major bleeding:
   - Fatal – bleeding that led to the death of the patient;
   - Life-threatening – bleeding that led to disturbances of cardiac and respiratory function, which required surgical or angiographic intervention, was accompanied by serious blood loss due to a decrease in systolic blood pressure less than 90 mmHg, hematocrit less than 20% or required transfusion of 3 or more doses of blood. These type of bleeding included intracranial hemorrhage, hemothorax, and retinal hemorrhage;
   - Serious – overt or hidden gastrointestinal bleeding, detected during endoscopic examination, macrohematuria, hemoptysis, bleeding that led to the transfusion of 2 doses of blood and required the drug to be discontinued.
2. Minor bleeding – any other hemorrhagic complications that did not require drug cancellation, hospitalization, additional examination and treatment. These included subcutaneous hematomas, nose and gum bleeding, microhematuria, hemorrhoids and hematochezia.

The diagnosis of bleeding was established based on the clinical picture and instrumentally (endoscopy, CT, MRI, ultrasound, cystoscopy, colonoscopy).

Table 2. Bleeding complications in patients with liver cirrhosis and atrial fibrillation after anticoagulation treatment

Bleeding complications	Dabigatran (*n* = 30)	Warfarin (*n* = 26)	*P*-value
All bleeding events, *n* (%)	5 (17)	12 (46)	0.038
Major bleeding, *n* (%)	–	1 (4)	0.944
Fatal	–	–	–
Life-threatening	–	–	–
Serious	–	1 (4)	0.944
Macrohematuria	–	1 (4)	
Gastrointestinal	–	–	
Profuse nasal	–	–	
Large subcutaneous hematomas	–	–	
Minor bleeding, *n* (%)	5 (17)	11 (42)	0.071
Nasal	2 (7)	4 (15)	
Gum	–	1 (4)	
Microhematuria	2 (7)	1 (4)	
Small subcutaneous hematomas	–	4 (15)	
Other	1 (3)	1 (4)	

Statistical analysis

Statistical analysis was performed using the statistical package IBM SPSS Statistics Base version 22.0, EZR version 3.4.1 (R Foundation Statistical Computing). The Kolmogorov-Smirnov criterion was used to determine the distribution of variables. Quantitative variables were presented as mean with standard deviation of the mean (±SD) if the data were normally distributed or as median (Me), 25th and 75th percentiles (Me 25; 75 percentiles) if data distribution was abnormal. Student's *t*-test was used to determine significant differences when comparing quantitative parameters, and the chi-square (χ^2) or Fisher's test was used for categorical variables. The logistic Cox regression model was used with assessment of hazard ratio (HR) in univariate analysis and the adjusted hazard ratio (AHR) in multivariable analysis to determine independent prognostic factors associated with bleeding events. A significance level of $p < 0.05$ was considered statistically significant.

Results

Clinical outcomes in patients with liver cirrhosis and atrial fibrillation after the use of anticoagulant therapy

No thromboembolic complications were determined during patient observation. Also, no fatal or life-threatening bleeding was observed in patients.

Bleeding complications in patients after treatment with dabigatran and warfarin are presented in Table 2.

It was found that patients treated with warfarin had a significantly higher overall bleeding rate than patients treated with dabigatran ($p = 0.038$). One case of major bleeding was observed in the warfarin group, specifically due to macrohematuria, but no major bleeding was observed in the dabigatran group. The incidence of minor bleeding was higher in patients treated with warfarin, but there was no statistically significant difference compared to dabigatran ($p = 0.071$). Patients of both groups had nasal bleeding and small subcutaneous hematomas most often, patients treated with warfarin had a wide range of various small bleedings, and patients treated with dabigatran had mainly nasal bleedings and microhematuria. Large subcutaneous hematomas were not observed in patients of both groups; however, small cutaneous hematomas were observed only in patients treated with warfarin.

Assessment of predictive factors for bleeding complications in patients with liver cirrhosis and atrial fibrillation

To analyze the predictive factors for bleeding complications in patients with liver cirrhosis and atrial fibrillation, Cox logistic regression analysis was used. More than 30 anamnestic, clinical, laboratory and instrumental parameters were analyzed, including parameters of low-frequency piezoelectric thromboelastography (LPTEG) – the test of global hemostasis assessment, which was used to investigate hemostasis in patients with LC and AF in previous studies [21]. Data from 56 patients were included in this study.

The results of univariate regression analysis indicate that the risk of bleeding complications was higher with increasing age of patients, severity of liver cirrhosis according to the Child-Pugh scale, prior history of bleeding, a decrease in GFR less than 60 ml/min/1.73 m^2, CTA (LPTEG) parameter less than 25 units and with warfarin treatment.

Multivariable regression analysis was used to exclude the potential influence of confounding on outcomes related to bleeding complications in patients. Three factors associated with the risk of bleeding were identified: GFR less than 60 ml/min/1.73 m^2, constant of thrombin activity (CTA) (LPTEG) less than 25 units, and history of bleeding. Results of logistic regression analysis are displayed in Table 3.

Discussion

We found in our present study that both anticoagulant drugs are effective in patients with liver cirrhosis and AF, as no case of thromboembolic complications was observed during the treatment. But dabigatran is safer because it causes statistically significantly fewer bleeding events after treatment. It was found that the risk of bleeding complications in patients increases with a history of previous bleeding, with a decrease in GFR less than 60 ml/min/1.73 m^2 and reduced values of CTA (LPTEG) less than 25 units.

Previous studies have reported that DOAC treatment causes significantly fewer cases of ischemic stroke, major bleeding, and intracranial hemorrhage compared to warfarin. Importantly, DOACs are not associated with an increased frequency of GI bleeding, as traditionally believed, and the frequency of overall bleeding is significantly lower with dabigatran and apixaban treatment compared to other DOACs [15]. Although we were unable to investigate and compare the frequency of thromboembolic complications in patients in our study, the data on bleeding events are consistent with previous data. However, the previously obtained results included observational studies, mostly retrospective, and thus are not sufficiently conclusive. The main advantages of our study are that it was designed as a clinical randomized trial, we directly

Table 3. Results of univariate and multivariable analysis of prognostic factors for bleeding events in patients with liver cirrhosis and atrial fibrillation

Parameters	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	AHR (95% CI)	*P*-value
Warfarin	3.37 (1.16-9.74)	0.025		
Age	1.08 (1.01-1.15)	0.031		
Prior history of bleeding	71.7 (14.6-351)	< 0.001	108 (8.78-134)	< 0.001
GFR	0.88 (0.82-0.96)	0.002	0.82 (0.69-0.96)	0.02
CTA (LPTEG)	0.77 (0.66-0.9)	< 0.001	0.66 (0.46-0.92)	0.017
Child-Pugh scale of LC	3.62 (1.62-8.0)	0.002		

HR – hazard ratio, CI – confidence interval, AHR – adjusted hazard ratio, LC – liver cirrhosis, GFR – glomerular filtration rate, CTA – constant of thrombin activity, LPTEG – low-frequency piezoelectric thromboelastography

diagnosed liver cirrhosis and AF and also monitored patients during treatment.

For this study, dabigatran was chosen from among all DOACs, because this drug is the most promising for the treatment of patients with liver cirrhosis and atrial fibrillation, based on its pharmacokinetic and pharmacodynamic properties. In particular, dabigatran is almost not metabolized in the liver, approximately 80% of the drug being excreted through the kidneys. Also among all DOACs, dabigatran has the lowest level of binding to plasma proteins and, in addition, almost does not use the cytochrome P-450 system of the liver for metabolism and is therefore theoretically less harmful for patients with reduced liver function [22]. The dabigatran dosage of 110 mg twice daily was chosen because, according to the literature, a reduced dabigatran dose is effective and safer for patients with additional risk factors [23]. Patients with LC and AF are a special category of patients who may have an increased risk of bleeding, and the average age of patients was 68 years, which is the second important risk factor for bleeding.

Another feature of our study is prior research of hemostasis of patients with LC using the global method of hemostasis assessment LPTEG, the parameters of which were then included in Cox regression analysis. Tests of the global hemostasis assessment, in particular LPTEG, are promising for the diagnosis of coagulopathies in patients with LC, including the ability to simultaneously and quickly evaluate all its stages, and are also useful for monitoring the state of hemostasis in patients treated with anticoagulant drugs. According to the results of our previous study, using this method, we found that patients with LC and AF have a tendency to thrombotic complications and prescription of anticoagulants is potentially beneficial for this population [21].

The limitations of our study are the small sample size, the short follow-up period, and exclusion of patients with LC class C according to the Child-Pugh scale. Patients of this class were not included in the study, because according to the existing recommendations for anticoagulation treatment, DOACs are not recommended to be used in this subgroup. Currently, few clinical studies have been conducted to evaluate the effectiveness and safety of DOACs in this category of patients, and their use can have an unpredictable effect on the risk of bleeding and patient survival.

Thus, in this experimental study, we compared the incidence of bleeding events in patients with LC and AF treated with dabigatran versus warfarin and identified potential risk factors for bleeding, highlighting the potential benefits of anticoagulation for these patients and the basis for future large randomized clinical trials.

Conclusions

Dabigatran treatment for patients with liver cirrhosis classes A and B according to the Child-Pugh scale and AF has advantages over warfarin treatment, as it is clinically associated with a lower frequency of bleeding.

An increased risk of bleeding is observed in patients with liver cirrhosis classes A and B according to the Child-Pugh scale and AF, who have a reduced GFR less than 60 ml/min/1.73 m^2, CTA (LPTEG) values less than 25 units and have a history of bleeding.

Disclosure

The authors declare no conflict of interest.

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