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Relationship Between Serum Uric Acid Level And Frequency Of Gastrointestinal Bleeding in Patients Using New Oral Anticoagulants

Yeni Nesil Oral Antikoagülan Kullanan Hastalarda Serum Ürik Asit Düzeyi ile Gastrointestinal Kanama Sıklığı Arasındaki İlişki

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Abstract

Introduction: The primary objective of utilising non-vitamin K antagonist oral anticoagulants is to inhibit the onset of stroke. Gastrointestinal bleeding represents the most prevalent form of bleeding, and bleeding prediction scoring systems have been devised. Nevertheless, none of these scoring systems are specific or sensitive in detecting bleeding risk. Elevated uric acid levels have been demonstrated to impact endothelial function. This study sought to ascertain whether uric acid levels exert an influence on the prediction of gastrointestinal bleeding.

Methods: This retrospective study comprised 501 patients who were undergoing treatment with direct oral anticoagulants. These patients were screened for a history of gastrointestinal bleeding. The serum uric acid levels of the patients were evaluated during their previous outpatient visit. The control group comprised patients treated with direct oral anticoagulants who did not have a history of gastrointestinal bleeding.

Results: A total of 68 patients (13.6%) exhibited evidence of gastrointestinal bleeding, with no discernible difference between the various direct oral anticoagulant types. The mean uric acid level was 7.87 mg/dL in the gastrointestinal bleeding group and 6.30 mg/dL in the control group ($p < 0.001$). A correlation was observed between uric acid level and HAS-BLED score ($r = 0.387$).

Conclusion: The presence of elevated uric acid levels has been correlated with gastrointestinal bleeding in patients on direct oral anticoagulant therapy. In light of the uric acid levels observed in these patients, it is recommended that those deemed to be at elevated risk of bleeding undergo more frequent monitoring.

Keywords: Uric acid, gastrointestinal bleeding, direct oral anticoagulants

Öz

Giriş Yeni nesil oral antikoagülan alan hastalarda ilaç kullanımının primer hedefi hastada inme gelişimini önlemek olup, bu tedavinin en sık görülen komplikasyonu kanamadır. Bu hastalarda görülen kanamalar incelendiğinde gastrointestinal istem kanamaları en fazla görülen kanama türü olup, kanamayı öngörücü skorlama sistemleri geliştirilmiştir. Fakat bu skorlama sistemlerinin hiçbirisi kanama riskini saptamada spesifik ve sensitif değildir. Yüksek ürik asit seviyelerinin endotel disfonksiyonuna neden olduğu gösterilmiştir. Bu çalışmada ürik asit düzeylerinin gastrointestinal kanama tahmini üzerinde bir etkisi olup olmadığı araştırılmıştır.

Yöntemler Bu retrospektif çalışma, yeni nesil oral antikoagülan tedavisi gören 501 hastayı içermektedir. Bu hastalar gastrointestinal kanama öyküsü açısından tarandı. Hastaların serum ürik asit düzeyleri bir önceki poliklinik ziyaretleri sırasında değerlendirildi. Kontrol grubunda ise önceden gastrointestinal kanama geçirmemiş yeni nesil oral antikoagülan kullanan hastalar değerlendirildi.

Bulgular Toplam 68 hastada (%13.6) gastrointestinal kanama bulguları görüldü ve çeşitli direkt oral antikoagülan tipleri arasında belirgin bir fark yoktu. Ortalama ürik asit düzeyi gastrointestinal kanama grubunda 7.87 mg/dL iken kontrol grubunda 6.30 mg/dL idi ($p < 0.001$). Ürik asit düzeyi ile HAS-BLED skoru arasında bir korelasyon gözlendi ($r = 0.387$).

Sonuç Yüksek ürik asit seviyelerinin varlığı, doğrudan oral antikoagülan tedavisi gören hastalarda gastrointestinal kanama ile korele olarak saptanmıştır. Bu hastaların takibinde ürik asit seviyelerinin göz önünde bulundurularak, kanama riskinin yüksek olduğu düşünülen hastaların daha yakından takibinin uygun olduğu kanısındayız.

Anahtar Kelimeler: Ürik asit, gastrointestinal kanama, yeni nesil oral antikoagülan ilaçlar

Foreword

Atrial fibrillation (AF) represents the most prevalent cardiac arrhythmia globally. The prevalence of this condition is estimated to be between 2 and 4% in adults (1). It is recommended that antithrombotic therapy be considered for all patients with atrial fibrillation in order to prevent systemic embolism. In comparison to patients undergoing anticoagulant therapy, the risk of stroke is 2-3 times higher in patients not undergoing anticoagulant therapy (2). Direct oral anticoagulants (DOACs) have been demonstrated to be as effective as warfarin in the prevention of stroke and are associated with a reduced risk of bleeding. The most common type of bleeding in these patients is gastrointestinal bleeding. In order to predict the likelihood of such bleeding, scoring systems have been developed. The HAS-BLED score is the most evidence-based method for assessing the risk of bleeding in these patients. However, no single bleeding scoring system is both specific and sensitive.

Uric acid represents the final product of purine metabolism (3). Uric acid plays a role in scavenging free radicals and has been linked to a pro-oxidant effect in hyperuricemia (4). Endothelial dysfunction plays a role in the development and progression of atherosclerosis, which can result in cardiovascular complications (5). The evidence from experimental studies indicates that hyperuricemia causes endothelial dysfunction (6, 7). The precise role of uric acid in the context of vascular disease remains a topic of contention. The relationship between uric acid levels and the incidence of gastrointestinal bleeding in patients receiving new-generation oral anticoagulants has yet to be investigated. The objective of our study was to investigate whether there is an association between uric acid levels and the occurrence of gastrointestinal bleeding.

Materials and methods

Patients

A total of 501 patients who received DOACs for atrial fibrillation between January 2018 and August 2022 were included in this study. The patients were divided into two groups: the gastrointestinal bleeding group (n = 68) and the control group (n = 433). Patients with haematological disorders, oesophageal varices, cirrhosis, renal insufficiency, rheumatic diseases, use of non-steroidal anti-inflammatory drugs and ACS within the last year were excluded from the study. Laboratory tests, including uric acid, liver and kidney function, haemogram, albumin, and clinical and demographic characteristics, were obtained from the patients' medical records. The study was initiated following the approval of the ethics committee. (Ethics Committee approval number: 2022-78)

Definition of gastrointestinal bleeding bleeding and bleeding scoring systems

Gastrointestinal bleeding can occur at any point along the digestive tract, from the mouth to the rectum. Patients presenting with acute gastrointestinal bleeding often present with melena or haematochezia. Bleeding above the ligament of Treitz is referred to as upper gastrointestinal (GI) bleeding, whereas haematemesis indicates the presence of bleeding in a location proximal to the ligament of Treitz. Haematochezia typically signifies lower GI bleeding, although it may also be indicative of significant upper GI bleeding. It is estimated that 50% of all GI bleeds originate from the upper GI tract, 40% are lower GI bleeds, and 10% are bleeds with an indeterminate focus (8).

HAS-BLED scoring system

A comprehensive assessment of the risk of bleeding is essential prior to the commencement of anticoagulant therapy. A number of bleeding risk scores have been developed that utilise both modifiable and non-modifiable risk factors, and these are generally capable of predicting bleeding events at a moderate level of accuracy. Similarly, as there are scoring systems for the risk of stroke in patients with atrial fibrillation, there are also scoring systems for the risk of bleeding. The HAS-BLED scoring system is recommended for use as it is a more straightforward and reliable method of assessing bleeding risk than other systems, and it has a higher predictive value for intracranial bleeding. The HAS-BLED scoring system comprises six criteria: hypertension, abnormal liver or kidney function, stroke, previous bleeding, unstable INR and drug or alcohol use. In accordance with the HAS-BLED scoring system, a score of ≥3 signifies that the patient is at elevated risk of bleeding. It is therefore advised to exercise greater caution when initiating and monitoring anticoagulant therapy in these individuals (10, 11).

Statistical analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS) 21.0. The Kolmogorov-Smirnov test was employed for the purpose of testing the normality of the data.

Descriptive statistics included the number and percentage of distributions, as well as the mean, standard deviation, or minimum-maximum values. The chi-square test, t-test for independent groups, Mann-Whitney U test and one-way ANOVA analysis were employed. The level of the type 1 error was set at α=0.05.

Results

The mean age of the cohort was 69.5±8.0 years, with 56.7% of patients being female. No statistically significant differences were observed in the mean age of patients included in the study according to gender, heart failure, diabetes mellitus, or vascular disease. A total of 68 patients (13.6%) experienced gastrointestinal bleeding. Of the patients included in the study, 132 (26.3%) were on rivaroxaban, 186 (37.1%) on edoxaban, 143 (28.5%) on apixaban and 40 (8%) on dabigatran (Table 1).

Table 1. Demographic characteristics of the patients

		n	%
Sex	Women Men	284 217	56,7 43,3
Age	18-65 65-75 >75	128 235 138	25,5 46,9 27,5
DOACs	Rivaroxaban Edoxaban Apixaban Dabigatran	132 186 143 40	26,3 37,1 28,5 8
GI bleeding	Yes No	68 433	13,6 86,4
HF	Yes No	150 351	29,9 70,1
HT	Yes No	401 100	80 20
DM	Yes No	197 304	39,3 60,7
Strok	Yes No	60 441	12 88
Vascular disease	Yes No	313 188	62,5 37,5

DM; Diabetes mellitus; GI: Gastrointestinal; HF: Heart failure; HT: Hypertension; DOACs: Direct oral anticogulants

No statistically significant difference was observed in the mean CHA_2DS_2-VASc and HAS-BLED scores among the DOACs groups (Table 2). A comparison of the groups in terms of HAS-BLED score revealed no significant difference between the dabigatran and rivaroxaban groups (p=0.1). However, a statistically significant difference was observed when dabigatran was compared with edoxaban (p<0.01).

Table 2. CHA_2DS_2-VASc and HAS-BLED scores of the DOACs groups

DOACs	CHA_2DS_2-VASc	HAS-BLED
Rivaroxaban	3,91	2,37
Edoxaban	4,15	2,54
Apixaban	4,13	2,55
Dabigatran	3,82	2,02
Total	4,05	2,46

DOACs: Direct oral anticogulants

The median uric acid level was 5.61 mg/dL, which is above the normal reference value of <5.6 mg/dL. The mean uric acid levels were 6.85±2.37 mg/dl in men and 6.25±2.24 mg/dl in women, demonstrating a statistically significant difference (p<0.005). The mean uric acid level was 7.87 mg/dL in patients with GI bleeding and 6.87 mg/dL in those without, yielding a statistically significant difference between the two groups (p < 0.001). The uric acid/albumin ratio was 2.27 in patients with gastrointestinal bleeding and 1.67 in patients without gastrointestinal bleeding, yielding a statistically significant result (p < 0.001).

An evaluation of the DOACs groups revealed no significant differences with regard to gastrointestinal bleeding (Table 3).

Table 3. Association between DOACs groups and gastrointestinal bleeding

DOACs	GI bleeding (n, %)	Without GI bleeding (n, %)	χ2	p
Rivaroxaban	21 (30,9)	111 (25,6)	7,84	0,058
Edoxaban	21 (30,9)	165 (38,1)		
Apixaban	25 (36,7)	118 (27,3)		
Dabigatran	1 (1,5)	39 (9)		
Total	68 (100)	433 (100)		

DOACs: Direct oral anticogulants

A correlation was observed between the HAS-BLED score and the incidence of GI bleeding in the patients included in the study (k:0.387, p<0.001). A positive correlation was observed between uric acid levels and the HAS-BLED score in this patient cohort (k: 0.197, p < 0.001) (Table 4).

Table 4. Correlation between CHA_2DS_2-VASc and HAS-BLED scores and uric acid level

	correlation coefficient	p
CHA_2DS_2-VASc score and uric acid level	0,178	<0,001
HAS-BLED score and uric acid level	0,197	<0,001

Discussion

The use of vitamin K antagonists has been demonstrated to be an effective method for the prevention of stroke in patients diagnosed with atrial fibrillation. However, due to the narrow therapeutic window of vitamin K antagonists and the inter-individual variability observed among patients, lifelong monitoring of coagulation is necessary. Maintaining the INR within the therapeutic range is challenging, which diminishes the potential benefit of vitamin K antagonist treatment and increases the risk of stroke (12). DOACs represent a promising alternative for this patient group. As the use of these drugs increases, so too does the importance of monitoring for and managing the side effects associated with these drugs.

In a retrospective study of 501 patients with non-valvular atrial fibrillation on DOACs, a significant association was identified between elevated uric acid levels and gastrointestinal bleeding (p < 0.001). In this patient cohort, independent predictors of GI bleeding were identified as the CHA_2DS_2-VASc score, HAS-BLED score, uric acid level and uric acid to albumin ratio. Prior research has demonstrated that the CHA2DS2-VASc score is an effective predictor of ischemic stroke, with an increased risk of bleeding observed with elevated scores (13). The mean CHA_2DS_2-VASc score was 4.05, with no significant difference in CHA_2DS_2-VASc score between the DOACs groups (p=0.43). In alignment with the aforementioned findings, our results demonstrated a statistically significant correlation between a high CHA_2DS_2-VASc score and an increased risk of GI bleeding (correlation coefficient: 0.089, p < 0.05).

The HAS-BLED score is a straightforward and pragmatic scoring system for evaluating the individual risk of bleeding in patients with atrial fibrillation (AF). It is currently recommended for use in clinical practice. In a study by Lip and colleagues, it was demonstrated that the risk of gastrointestinal bleeding was elevated in patients with a HAS-BLED score of 3 or above. Furthermore, the use of DOACs was shown to be more effective than warfarin in reducing the risk of bleeding (14).

The results of our study demonstrated a statistically significant correlation between the HAS-BLED score and GI bleeding, with a correlation coefficient of 0.387 and a p-value less than 0.001. No significant difference was observed between the HAS-BLED scores of the NOAC groups. Nevertheless, a distinction was observed between the dabigatran cohort and the remaining three DOACs groups. No significant difference was observed between the HAS-BLED scores of patients in the dabigatran group and those in the rivaroxaban group (p=0.1). However, a notable discrepancy was evident when dabigatran was compared with edoxaban and apixaban (p=0.01). The discrepancy in the HAS-BLED score for dabigatran may be attributed to the relatively limited number of patients who were administered this medication. A review of the literature revealed that the use of dabigatran 150 mg, edoxaban 60 mg and rivaroxaban 20 mg was associated with an elevated risk of gastrointestinal bleeding. Among the DOACs groups, rivaroxaban was associated with the highest incidence of gastrointestinal bleeding, while edoxaban and dabigatran exhibited comparable rates of this adverse event. Apixaban demonstrated the lowest incidence of gastrointestinal bleeding among the DOACs. In the ROCKET AF trial, the incidence of major GI bleeding was 3.2% in the rivaroxaban group and 2.2% in the warfarin group (15). The incidence of GI bleeding observed in our study was comparable to that reported in the ROCKET AF study. The incidence of GI bleeding among patients treated with rivaroxaban was comparable to that observed in other DOACs groups. This may be attributed to the absence of a notable discrepancy between the CHA_2DS_2-VASc and HAS-BLED scores of the DOACs cohorts. In the ARISTOTLE trial, apixaban was demonstrated to reduce the incidence of bleeding by 27% in comparison to warfarin (p < 0.001) (16). In the RE-LY trial, dabigatran was observed to be associated with a higher incidence of GI bleeding compared to warfarin (p=0.001) (17). The ENGAGE AF-TIMI study demonstrated that rivaroxaban was associated with a higher incidence of GI bleeding compared to warfarin (18). A prospective study comparing DOACs head-to-head in terms of bleeding has yet to be performed. However, a meta-analysis has indicated that apixaban may be associated with a lower incidence of GI bleeding than dabigatran and rivaroxaban (19). A breakdown of the DOACs groups used by patients who experienced GI bleeding in the study revealed that 30.9% were on rivaroxaban, 30.9% on edoxaban, 36.5% on apixaban and 1.5% on dabigatran. No significant difference was identified between the DOACs groups in the development of GI bleeding (p=0.058). The disparate number of patients in the DOACs groups and the absence of patients on warfarin may have exerted an influence on the results.

In particular, the limited number of patients on dabigatran does not allow for an adequate assessment of the propensity for GI bleeding in the DOACs groups. In their study, Jansen et al. demonstrated that elevated levels of uric acid, a natural antioxidant and anti-inflammatory agent, are associated with an increased risk of GI bleeding (20). Similarly, an association between elevated uric acid levels and GI bleeding was identified in patients with colonic diverticula (21). The relationship between elevated uric acid levels and bleeding in patients using DOACs has yet to be investigated. The present study yielded statistically significant results with regard to the correlation between elevated uric acid levels and GI bleeding, a finding that is consistent with the existing literature ($p < 0.001$).

It has been demonstrated that hypoalbuminaemia is linked to complicated GI bleeding (22). The uric acid to albumin ratio has been demonstrated to predict contrast-induced nephropathy and is associated with the prevalence of coronary and peripheral arterial disease. In their study, Ozgur et al. demonstrated that the uric acid to albumin ratio was associated with acute renal failure and mortality. In the present study, a significantly higher uric acid-to-albumin ratio was observed in patients with GI bleeding compared to those without ($p < 0.001$).

In conclusion, our findings suggest that elevated uric acid levels may serve as a predictor of GI bleeding in patients undergoing treatment with DOACs. It may be advisable to subject high-risk patients to closer monitoring, with uric acid levels included in the follow-up protocol.

Limitation Although we found significance in the correlation analysis between elevated uric acid and gastrointestinal bleeding, we think that the fact that we did not perform regression analysis is a limitation of our study.

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