INTRACEREBRALNO KRVARENJE I PRIMENA RAZLIČITIH VRSTA ANTIKOAGULANASA – KLINIČKA PREZENTACIJA I ISHODI LEČENJA

ORIGINALNI RAD

ORIGINAL ARTICLE

INTRACEREBRAL HEMORRHAGE AND THE USE OF VARIOUS TYPES OF ANTICOAGULANTS – CLINICAL PRESENTATION AND TREATMENT OUTCOMES

Ljubica Dimitrijević[1], Dejan Munjiza[1], Nikola Mitović[2], Marija S. Stanković[2], Biljana Georgievski-Brkić[1,3], Marjana Vukićević[1,3]

[1] Specijalna bolnica za cerebrovaskularne bolesti „Sveti Sava", Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Institut za patološku fiziologiju, Beograd, Srbija

[3] Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Kragujevac, Srbija

[1] *Special Hospital for Cerebrovascular Diseases "Sveti Sava", Belgrade, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Institute of Pathophysiology, Belgrade, Serbia*

[3] *University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia*

SAŽETAK

Uvod: Antikoagulantna terapija igra ključnu ulogu u prevenciji i tretmanu različitih vaskularnih oboljenja, ali istovremeno povećava rizik od hemoragijskih komplikacija, uključujući intracerebralnu hemoragiju (ICH). Cilj ovog rada bio je ispitati ishod pacijenata sa ICH u zavisnosti od prethodne antikoagulantne terapije.

Metode: U pitanju je retrospektivna kohortna studija u koju je od 277 pacijenata sa ICH iz bolničkog registra lečenih od januara do novembra 2024. godine u Specijalnoj bolnici za cerebrovaskularne bolesti „Sveti Sava", uključeno njih 37. Svi pacijenti podeljeni su u dve grupe, na pacijente lečene antagonistima vitamina K (VKA) ili direktnim oralnim antikoagulansima (NOAK). Ishod lečenja pacijenata na otpustu i 90 dana nakon otpusta određivan je na osnovu modifikovane Rankin skale (mRS).

Rezultati: U grupi pacijenata prethodno lečenih VKA srednja vrednost mRS skora na otpustu bila je 4,6, dok je u grupi prethodno lečenih NOAK terapijom ona iznosila 5,1, što je bez statističke značajnosti između grupa ($p = 0,442$). Takođe statistička značajnost nije pronađena ni među mRS 90 dana nakon otpusta ($p = 0,341$). U grupi VKA-ICH srednja vrednost je iznosila 4,3, dok je u drugoj grupi ona iznosila 4,9. U prvoj grupi procenat letalnih ishoda bio je 58%, dok je u drugoj grupi 76%.

Zaključak: Pacijenti sa ICH i prethodnom terapijom VKA u odnosu na pacijente sa prethodnom NOAK terapijom su bez značajnih razlika u ishodu lečenja.

Ključne reči: intracerebralna hemoragija, antagonisti vitamina K, direktni oralni antikoagulansi

ABSTRACT

Introduction: Anticoagulant therapy plays a key role in the prevention and treatment of various vascular diseases, but it simultaneously increases the risk of hemorrhagic complications, including intracerebral hemorrhage (ICH). This study aimed to examine the outcomes of patients with ICH based on prior anticoagulant therapy.

Methods: This was a retrospective cohort study involving 37 out of 277 patients with ICH from the hospital registry treated between January and November 2024 at the Special Hospital for Cerebrovascular Diseases "Sveti Sava". All patients were divided into two groups: those treated with vitamin K antagonists (VKA) or direct oral anticoagulants (NOAC). The treatment outcome of patients at discharge and 90 days after discharge was determined using the modified Rankin Scale (mRS).

Results: In the group of patients previously treated with VKA, the mean mRS score at discharge was 4.6, while in the group previously treated with NOAC therapy, it was 5.1, with no statistically significant difference between the groups ($p = 0.442$). Additionally, no statistical significance was found in the mRS 90 days after discharge ($p = 0.341$). In the VKA-ICH group, the mean value was 4.3, while in the other group, it was 4.9. In the first group, the mortality rate was 58%, while in the second group, it was 76%.

Conclusion: Patients with ICH and prior VKA therapy showed no significant differences in treatment outcomes compared to patients with prior NOAC therapy.

Keywords: intracerebral hemorrhage, vitamin K antagonists, direct oral anticoagulants

Autor za korespondenciju:
Ljubica Dimitrijević
Specijalna bolnica „Sveti Sava"
Nemanjina 2, 11000 Beograd, Srbija
Elektronska adresa: dimitrijeviclj5@gmail.com

Corresponding author:
Ljubica Dimitrijević
Special hospital "Sveti Sava"
2 Nemanjina Street, 11000 Belgrade, Serbia
E-mail: dimitrijeviclj5@gmail.com

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UVOD

Prema poslednjim statističkim podacima, moždani udar je drugi vodeći uzrok smrti i treći vodeći uzrok smrti i invaliditeta zajedno [1]. Hemoragični moždani udar čini oko 20% svih moždanih udara, pri čemu je intracerebralna hemoragija (ICH) najčešći tip [2].

Primena oralne antikoagulantne terapije (OAK) je jedan od faktora rizika za ICH. Stopa propisivanja OAK se povećava, uglavnom zbog sve veće upotrebe u primarnoj i sekundarnoj prevenciji ishemijskog moždanog udara kod pacijenta sa nevalvularnom atrijalnom fibrilacijom (AF) [2].

Stopa smrtnosti pacijenata nakon ICH iznosi oko 40% u roku od jednog meseca i 54% u roku od jedne godine, uprkos napretku u neurointenzivnoj nezi tokom poslednjih nekoliko decenija [2]. Upotreba antikoagulantnih lekova kod ovih pacijenata povezana je sa većom ekspanzijom hematoma, kao i posledičnim povećanim invaliditetom i stopom smrtnosti [3,4].

U prošlosti su se, zbog ograničene dostupnosti, široko koristili antagonisti vitamina K. Međutim, vremenom su se pojavile i alternativne opcije – direktni inhibitori trombina (dabigatran) i inhibitori faktora Xa (apiksaban, edoksaban i rivaroksaban), nazvani oralni antikoagulansi koji nisu antagonisti vitamina K (NOAK) [5].

Poznato je da upotreba VKA usled nevalvularne atrijalne fibrilacije udvostručuje rizik od intrakranijalnog krvarenja, čak i pod optimalnim uslovima lečenja. Pored povećane incidencije, ICH povezan sa VKA (VKA-ICH) povezan je sa većim volumenima hematoma, povećanim mortalitetom i lošim funkcionalnim ishodom. NOAK imaju sličnu efikasnost u prevenciji ishemijskog moždanog udara kod pacijenata sa nevalvularnom atrijalnom fibrilacijom, sa upola manjom incidencijom ICH u poređenju sa warfarinom. Nalazi su kontradiktorni u pogledu ishoda pacijenata sa NOAK-povezanim ICH (NOAK-ICH) u poređenju sa VKA-ICH [6,7]. Iako NOAK nosi znatno manji rizik od ICH, NOAK-ICH postaje pitanje od značajne kliničke važnosti, s obzirom na široku i sve veću stopu propisivanja ovih lekova.

Modifikovana Rankinova skala je efikasna, pouzdana i jednostavna mera funkcionalnog ishoda koja se široko koristi u kliničkim ispitivanjima akutnog moždanog udara [8].

Cilj ovog rada bio je ispitati ishod pacijenata sa ICH u zavisnosti od prethodne antikoagulantne terapije.

METODE

Ovo je retrospektivna kohortna studija u koju je, iz bolničkog registra pacijenata sa ICH lečenih od januara do novembra 2024. godine u Specijalnoj bolnici za cerebrovaskularna oboljenja „Sveti Sava", koji sadrži 277 pacijenata, uključeno njih 37.

INTRODUCTION

According to the latest statistical data, stroke is the second leading cause of death and the third leading cause of death and disability combined [1]. Hemorrhagic stroke accounts for approximately 20% of all strokes, with intracerebral hemorrhage (ICH) being the most common type [2].

The use of oral anticoagulant therapy (OAC) is one of the risk factors for ICH. The prescription rate of OAC is increasing, mainly due to its growing use in the primary and secondary prevention of ischemic stroke in patients with non-valvular atrial fibrillation (AF) [2].

The mortality rate after ICH is around 40% within one month and 54% within one year, despite advances in neurocritical care over the past few decades [2]. The use of anticoagulant medications in these patients is associated with greater hematoma expansion, and consequently with increased disability and mortality rates [3,4]. Due to limited availability, vitamin K antagonists (VKAs) were widely used in the past. However, over time, alternative options emerged - direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban), collectively known as non-vitamin K oral anticoagulants (NOACs) [5]. It is well known that VKA use in the context of non-valvular atrial fibrillation doubles the risk of intracranial hemorrhage, even under optimal treatment conditions. In addition to the increased incidence, VKA-associated ICH (VKA-ICH) is linked to larger hematoma volumes, higher mortality, and poorer functional outcomes. NOACs offer similar efficacy in preventing ischemic stroke in patients with non-valvular atrial fibrillation, with approximately half the incidence of ICH compared to warfarin. However, findings remain contradictory regarding outcomes in patients with NOAC-related ICH (NOAC-ICH) compared to those with VKA-ICH [6,7]. Although NOACs carry a significantly lower risk of ICH, NOAC-ICH is becoming a matter of notable clinical importance due to the widespread and growing prescription of these drugs.

The modified Rankin Scale is an effective, reliable, and simple measure of functional outcome that is widely used in clinical trials of acute stroke [8].

This study aimed to evaluate the outcomes of patients with ICH depending on their prior anticoagulant therapy.

METHODS

This is a retrospective cohort study that included 37 patients from the hospital registry of patients with intracerebral hemorrhage (ICH) treated between January and November 2024 at the Special Hospital for Cerebrovascular Diseases "Sveti Sava," which contains a total of 277 patients.

Unapred definisani kriterijumi za isključenje bili su: ICH koji nije povezan sa antikoagulantnom terapijom, subduralno i subarahnoidalno krvarenje, kao i ICH povezan sa vaskularnim malformacijama, primarnim tumorima mozga, metastazama, septičkim embolijama i hemoragijskom transformacijom ishemijskog moždanog udara.

Prikupljeni su podaci o godinama starosti, polu, anamnestički podaci o prethodno lečenoj hipertenziji i dijabetesu, lekovima pre hospitalizacije (uključujući vrstu antikoagulantne terapije) i laboratorijskim podacima pri prijemu.

Svim pacijentima po dolasku u prijemnu ambulantu učinjen je CT endokranijuma, sa CT angiografijom glave i vrata.

Svi pacijenti podeljeni su u dve grupe na osnovu vrste antikoagulantne terapije - na pacijente lečene antagonistima vitamina K (VKA) I pacijente lečene direktnim oralnim antikoagulansima (NOAK).

Članovi tima za moždani udar ocenjivali su ishod lečenja pacijenata na otpustu i nakon 90 dana od otpusta na osnovu modifikovane Rankin skale (mRS), kao i bolnički mortalitet.

U zavisnosti od tipa varijabli i normalnosti raspodele, deskripcija podataka je prikazana kao n (%), aritmetička sredina±standardna devijacija (as±sd) ili medijana (min-max). Za poređenje razlika između grupa sa podacima koji su imali normalnu raspodelu je korišćen Studentov t-test, dok je za podatke koji nisu imali normalnu raspodelu primenjen Mann-Whitney U test. Kategorijske varijable analizirane su pomoću hi-kvadrat testa ili Fisher-ovog egzaktnog testa, u zavisnosti od očekivanih frekvencija u tabelama kontingencije. Nivo statističke značajnosti je postavljen na $p < 0,05$. Za ispitivanje zavisnosti između promenljivih korišćen je Spearmanov test korelacije rangova. Sve statističke analize su sprovedene korišćenjem softvera GraphPad Prism 8.

REZULTATI

Od 277 pacijenata sa netraumatskom ICH lečenih u Specijalnoj bolnici za cerebrovaskularne bolesti „Sveti Sava" od januara do novembra 2024. godine, u istraživanje je uključeno njih 37, a nakon primene kriterijuma za isključenje iz istraživanja. Zatim su na osnovu vrste antikoagulantne terapije pacijenti podeljeni na one koji su prethodno lečeni antagonistima vitamina K (VKA-ICH) ili direktnim oralnim antikoagulansima (NOAK-ICH). U grupi pacijenata lečenih VKA bilo je 20 pacijenata (54%), a u grupi lečenih NOAK je bilo 17 (46%) (Slika 1).

U grupi VKA-ICH je 11 pacijenata muškog (55%) i 9 pacijentkinja ženskog pola (45%) prosečne starosti 76,3 godina, dok je u grupi NOAK-ICH 6 pacijenta muš-

Predefined exclusion criteria were: ICH not associated with anticoagulant therapy, subdural and subarachnoid hemorrhage, as well as ICH related to vascular malformations, primary brain tumors, metastases, septic embolisms, and hemorrhagic transformation of ischemic stroke.

Data were collected on age, sex, medical history of previously treated hypertension and diabetes, medications used before hospitalization (including type of anticoagulant therapy), and laboratory findings at admission.

Upon arrival at the emergency department, all patients underwent a non-contrast cranial CT scan, followed by head and neck CT angiography.

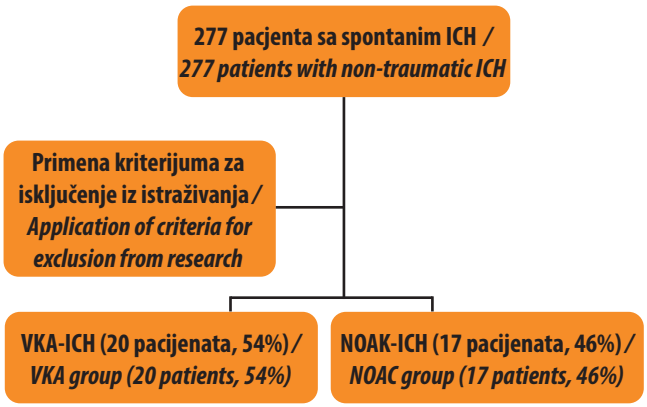
Patients were divided into two groups based on the type of anticoagulant therapy – those treated with vitamin K antagonists (VKAs) and those treated with direct oral anticoagulants (NOACs).

Stroke team members assessed patient outcomes at discharge and 90 days post-discharge using the modified Rankin Scale (mRS) and in-hospital mortality.

Data were described as n (%), mean ± standard deviation (as±sd), or median (min–max) depending on the type of variables and distribution normality. The student's t-test was used for normally distributed data to compare differences between groups, and the Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed using the chi-square test or Fisher's exact test, depending on expected frequencies in contingency tables. A p-value < 0.05 was considered statistically significant. Spearman's rank correlation test was used to examine correlations between variables. All statistical analyses were performed using GraphPad Prism 8 software.

RESULTS

Out of 277 patients with non-traumatic intracerebral hemorrhage (ICH) treated at the Special Hospital for Cerebrovascular Diseases "Sveti Sava" from January to



Slika 1. Distribucija pacijenata sa ICH po grupama

Picture 1. Distribution of patients with ICH by group

kog pola (35%), odnosno 11 ženskog (65%), prosečne starosti 78,1 godina (Tabela 1).

Nisu pronađene statistički značajne razlike između grupa u anamnestičkim podacima vezanim za prethodno lečenu hipertenziju (p = 1,000) i dijabetes melitus (p = 0,159) (Tabela 1).

Među pristiglim rezultatima laboratorijskih analiza izdvojeni su markeri inflamacije kao mogući prediktori lošeg funkcionalnog ishoda pacijenata sa ICH. Nije bilo statistički značajnih razlika između grupa u vrednostima CRP (p = 0,704), limfocita (p = 0,482) i NLR (p = 0,104). Međutim, u NOAK-ICH grupi pacijenata srednje vrednosti leukocita (p = 0,034) i neutrofila (p = 0,030) bile su statistički veće (Tabela 2). U našem radu dokazana je statistički značajna pozitivna povezanost NLR i mRS na otpustu (p = 0,002), kao i 90 dana nakon otpusta (p = 0,001) (Tabela 3).

U VKA-ICH grupi pacijenata srednja vrednost mRS skora na otpustu iznosila je 4,6, dok je u NOAK-ICH grupi 5,1, što je bez statističke značajnosti između grupa (p = 0,442). U grupi VKA-ICH srednja vrednost mRS 90

November 2024, a total of 37 patients were included in the study after applying the exclusion criteria. Based on the type of anticoagulant therapy, patients were divided into those previously treated with vitamin K antagonists (VKA-ICH) and those treated with direct oral anticoagulants (NOAC-ICH). The VKA group included 20 patients (54%), while the NOAC group included 17 patients (46%) (Figure 1).

In the VKA-ICH group, there were 11 male patients (55%) and 9 female patients (45%) with an average age of 76.3 years. In the NOAC-ICH group, there were 6 male patients (35%) and 11 female patients (65%) with an average age of 78.1 years (Table 1).

No statistically significant differences were found between the groups in terms of medical history regarding previously treated hypertension (p = 1.000) and diabetes mellitus (p = 0.159) (Table 1).

Among the available laboratory results, inflammation markers were analyzed as potential predictors of poor functional outcome in patients with ICH. No statistically significant differences were found between

Tabela 1. Sociodemografski i anamnestički podaci pacijenata sa ICH u zavisnosti od grupe, bez statistički značajne razlike

Table 1. Sociodemographic and anamnestic data of patients with ICH depending on the group, with no statistically significant difference

Varijable / *Variables*	*VKA-ICH*	*NOAK-ICH*	p-vrednost / *p-value*
Starost, as ± sd / *Age, as ± sd*	76.3 ± 7.5	78.1 ± 8.3	0.490
Pol M/Ž / *Gender M/F*	11/9	6/11	0.231
Prethodno lečena hipertenzija, n (%) / *Previously treated hypertension, n (%)*	18 (90%)	16 (94%)	1.000
Prethodno lečen dijabetes mellitus, n (%) / *Previously diabetes mellitus, n (%)*	1 (5%)	4 (23.5%)	0.159

Tabela 2. Uporedni prikaz laboratorijskih markera inflamacije između grupa. Vrednosti leukocita i neutrofila bile su statistički značajno veće u grupi pacijenata NOAK-ICH

Table 2. Comparative presentation of laboratory markers of inflammation between groups. The values of leukocytes and neutrophils were statistically significantly higher in the NOAK-ICH patient group

Varijable / *Variables*	*VKA-ICH*	*NOAK-ICH*	*p-value*
CRP (mg/L), median (range) / *CRP (mg/L), median (range)*	3.9 (0.6–54.2)	2.9 (1.1–186.0)	0.704
Leukociti (10^9/L), mean ± sd / *Leukocytes (10^9/L), mean ± sd*	10.2 ± 3.7	12.9 ± 3.6	0.034*
Neutrofili (10^9/L), mean ± sd / *Neutrophils (10^9/L), mean ± sd*	8.2 ± 3.6	10.9 ± 3.7	0.030*
Limfociti (10^9/L), median (range) / *Lymphocytes (10^9/L), median (range)*	1.1 (0.2–3.3)	0.8 (0.4–2.7)	0.482
NLR, median (range) / *NLR, median (range)*	7.2 (1.9–44.5)	14.1 (1.6–32.3)	0.104

Tabela 3. Povezanost odnosa neutrofili/limfociti (NLR) sa funkcionalnim ishodom pacijenta sa ICH na otpustu i 90 dana nakon otpusta

Table 3. Association between neutrophil-to-lymphocyte ratio (NLR) and functional outcome in patients with ICH at discharge and 90 days post-discharge

	mRS na otpustu / *mRS on discharge*	mRS nakon 90 dana / *mRS after 90 days*
NLR	*rs* = 0.50 *p* = 0.002	*rs* = 0.56 *p* = 0.001

the groups in CRP levels (p = 0.704), lymphocyte count (p = 0.482), or neutrophil-to-lymphocyte ratio (NLR) (p = 0.104). However, the NOAC-ICH group had significantly higher mean leukocyte counts (p = 0.034) and neutrophil counts (p = 0.030) (Table 2).

Our study showed a statistically significant positive correlation between NLR and mRS at discharge (p = 0.002) as well as 90 days after discharge (p = 0.001) (Table 3).

Tabela 4. Ishod pacijenata sa ICH u zavisnosti od vrste prethodne antikoagulantne terapije, bez statističke značajnosti

Table 4. Patient outcomes with ICH based on the type of prior anticoagulant therapy, without statistical significance

Varijable / *Variables*	*VKA-ICH*	*NOAK-ICH*	p-vrednost / *p-value*
mRS, median (range) / *mRS, median (range)*	6 (1–6) mean (4.6)	6 (1–6) mean (5.1)	0.442
mRS nakon 90 dana, median (range) / *mRS after 90 days, median (range)*	6 (1–6) mean (4.3)	6 (1–6) mean (4.9)	0.341
Letalni ishod n (%) / *Fatal outcome n (%)*	11 (58%)	13 (76%)	0.238

dana nakon otpusta iznosila je 4,3, dok je u drugoj grupi ona iznosila 4,9, takođe bez statističke značajnosti između grupa (p = 0,341). U prvoj grupi bilo je 11 letalnih ishoda (58%), dok je u drugoj grupi bilo 13 letalnih ishoda (76%), bez statističke značajnosti (p = 0,238) (Tabela 4).

DISKUSIJA

Od uvođenja NOAC-a, više studija analiziralo je razlike između VKA-ICH i NOAC-ICH sa heterogenim rezultatima.

Koristeći se podacima iz Riksstroke i Švedskog registra, u studiji sa 2483 pacijenata nije pronađena značajna razlika u smrtnosti i funkcionalnom ishodu nakon 90 dana između NOAC-ICH i VKA-ICH, što je u korelaciji sa našom studijom [9].

Slični rezultati dobijeni su retrospektivnom opservacionom studijom u koju je uključeno 182 pacijenta; zaključeno je da je mortalitet podjednako visok kod pacijenata sa NOAC-ICH u odnosu na pacijente na drugim oralnim antikoagulansima [10].

Meta-analiza koja je uključivala sedam opservacionih studija pokazala je da je NOAC-ICH bio povezan sa manjim početnim volumenom hematoma i težinom moždanog udara (NIHSS) pri prijemu. VKA-ICH i NOAC-ICH imali su sličan funkcionalni ishod pri otpustu i nakon tromesečnog praćenja [11].

Naše istraživanje je u korelaciji sa meta-analizom Boulouis G. i saradnika, u koju je uključeno 12 studija i 3875 pacijenata. Nisu pronađene razlike između pacijenata sa NOAC-ICH i VKA-ICH u pogledu ukupnog mortaliteta pri otpustu, nepovoljnog funkcionalnog ishoda pri otpustu, kao i nakon tri meseca od otpusta [7].

Međunarodna multicentrična analiza upoređivala je mortalitet, funkcionalni ishod, ali i volumen intrakranijalnog krvarenja i ekspanziju hematoma između NOAK-ICH i VKA-ICH. Početni volumen ICH, ekspanzija hematoma, mortalitet nakon 90 dana i funkcionalni ishod bili su slični u obe grupe ispitanika [12].

Jedna retrospektivna studija bavila se sličnom temom. Naime, Malgorzata Miller i saradnici, analizira-

In the VKA-ICH group, the mean mRS score at discharge was 4.6, while in the NOAC-ICH group it was 5.1, with no statistically significant difference between the groups (p = 0.442). Ninety days after discharge, the mean mRS score was 4.3 in the VKA-ICH group and 4.9 in the NOAC-ICH group, also without statistical significance (p = 0.341). There were 11 deaths (58%) in the VKA-ICH group and 13 deaths (76%) in the NOAC-ICH group, again without statistical significance (p = 0.238) (Table 4).

DISCUSSION

Since the introduction of NOACs, several studies have analyzed the differences between VKA-ICH and NOAC-ICH with heterogeneous results.

A study involving 2,483 patients, using data from Riksstroke and the Swedish Stroke Register, found no significant difference in mortality or functional outcome after 90 days between NOAC-ICH and VKA-ICH, which correlates with our study findings [9].

Similar results were obtained in a retrospective observational study that included 182 patients; it concluded that mortality was equally high in patients with NOAC-ICH compared to those on other oral anticoagulants [10].

A meta-analysis including seven observational studies showed that NOAC-ICH was associated with a smaller initial hematoma volume and lower stroke severity (NIHSS) at admission. VKA-ICH and NOAC-ICH had similar functional outcomes at discharge and after a three-month follow-up [11].

Our research aligns with a meta-analysis by Boulouis G. and colleagues, which included 12 studies and 3,875 patients. The differences between NOAC-ICH and VKA-ICH patients were not found regarding overall mortality at discharge, poor functional outcomes at discharge, or three months post-discharge [7].

An international multicenter analysis compared mortality, functional outcome, ICH volume, and hematoma expansion between NOAC-ICH and VKA-ICH. Initial ICH volume, hematoma expansion, 90-day mor-

jući 102 pacijenta sa ICH koji su primali antikoagulantnu terapiju, pokazali su da upotreba NOAK nije bila povezana sa lošijim funkcionalnim ishodom nakon ICH [13].

U pojedinim kliničkim istraživanjima, praćenjem radioloških parametara, primećeno je da pacijenti sa ICH prethodno lečeni NOAK terapijom imaju manji volumen i ekspanziju hematoma, što je ranije viđeno i na životinjskim modelima, a što se delimično može objasniti različitim farmakološkim svojstvima između ovih klasa antikoagulanata [14]. Na taj način se mogu objasniti rezultati narednih istraživanja koji nisu u saglasnosti sa našom studijom.

Kineska multicentrična klinička studija pokazala je da je ICH kod pacijenata prethodno lečenih inhibitorima faktora Xa bio povezan sa većom smrtnošću u poređenju sa pacijentima bez oralne antikoagulantne terapije, dok su pacijenti na inhibitorima faktora Xa imali bolje ishode od onih sa ICH povezanim sa varfarinom [3].

Studijom koja je ispitivala 161 pacijenta sa ICH, dobijena je medijana mRS skora tri meseca nakon hospitalizacije - u grupi pacijenata NOAK-ICH iznosila je 3, dok u grupi VKA-ICH ona iznosi 4, što predstavlja statistički značajnu razliku i nije u saglasnosti sa rezultatima naše studije [14].

Istom temom bavili su se i drugi autori. Istraživanjem, u koje je uvršćeno 196 pacijenata, zaključeno je da pacijenti sa NOAC-ICH imaju lakši neurološki deficit u poređenju sa VKA-ICH [15].

Upalni mehanizmi igraju važnu ulogu u intrakranijalnom krvarenju i povezani su sa razvojem pneumonije povezane sa moždanim udarom – *stroke-associated pneumonia* (SAP). Odnos neutrofila i limfocita (NLR) je pokazan kao najbolji prediktor za pojavu SAP i loš ishod pri otpustu pacijenata sa ICH, što je u korelaciji sa našim rezultatima. U ovom radu statistički značajno veće vrednosti leukocita i neutrofila bile su u grupi NOAK – ICH, to može objasniti nešto lošiji ishod pacijenata u toj grupi, bez statističke značajnosti [16,17].

S obzirom na heterogene rezultate ovih istraživanja, ukazuje se potreba za daljim prospektivnim, multicentričnim studijama kako bi se omogućila detaljnija analiza po tipovima antikoagulansa, praćenje radioloških parametara i uticaj antidota na ishod ovih pacijenata.

ZAKLJUČAK

Pacijenti sa netraumatskom ICH i prethodnom terapijom VKA, u odnosu na pacijente sa prethodnom NOAK terapijom, su bez značajnih razlika u ishodu lečenja.

Sukob interesa: Nije prijavljen.

tality, and functional outcomes were similar in both groups [12].

A retrospective study conducted by Malgorzata Miller and colleagues, analyzing 102 patients with ICH on anticoagulant therapy, showed that NOAC use was not associated with worse functional outcomes after ICH [13].

In certain clinical studies, radiological parameters showed that patients with ICH previously treated with NOACs had smaller hematoma volume and expansion-this was also observed in animal models - which could be partly explained by the different pharmacological properties of these anticoagulant classes [14]. These findings might account for the results of subsequent studies that differ from ours.

A Chinese multicenter clinical study showed that ICH in patients previously treated with factor Xa inhibitors was associated with higher mortality compared to patients not on oral anticoagulants. However, patients on factor Xa inhibitors had better outcomes than those with warfarin-associated ICH [3].

A study involving 161 patients with ICH found that the median mRS score three months after hospitalization was 3 in the NOAC-ICH group, compared to 4 in the VKA-ICH group. This difference is statistically significant and conflicts with the results of our study [14].

Other authors have addressed this topic as well. A study of 196 patients concluded that patients with NOAC-ICH had milder neurological deficits than those with VKA-ICH [15].

Inflammatory mechanisms play an essential role in intracranial hemorrhage and are associated with the development of stroke-associated pneumonia (SAP). The neutrophil-to-lymphocyte ratio (NLR) best predicts SAP and poor discharge outcomes in ICH patients, which correlates with our findings. In this study, significantly higher leukocyte and neutrophil values were observed in the NOAC-ICH group, which may explain the slightly worse outcomes in that group, though without statistical significance [16,17].

Given the heterogeneous results of these studies, further prospective, multicenter studies are needed to allow for more detailed analysis by anticoagulant type, radiological parameter monitoring, and the impact of reversal agents on patient outcome.

CONCLUSION

Patients with non-traumatic ICH previously treated with VKAs, compared to those previously treated with NOACs, showed no significant differences in treatment outcomes.

Conflict of interest: None declared.

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