

Clinical Center of Vojvodina, Clinic of Neurology, Novi Sad
University of Novi Sad, Faculty of Medicine Novi Sad

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EFFECT OF ANTICOAGULANT AND ANTIPLATELET THERAPY ON THE OCCURRENCE OF PRIMARY INTRACEREBRAL HEMORRHAGE

UTICAJ ANTIKOAGULANTNE I ANTITROMBOCITNE TERAPIJE NA POJAVU PRIMARNE INTRACEREBRALNE HEMORAGIJE

Aleksandra LUČIĆ PROKIN, Armin PAKOCI, Sanela POPOVIĆ and Arsen UVELIN

Summary

Introduction. The incidence of intracerebral hemorrhage related to oral anticoagulant and antiplatelet therapy has an increasing trend, thus it may be a potential indicator of unfavorable outcome of primary intracerebral hemorrhage. The aim of the study was to determine the effect of these therapies on the occurrence, localization and outcome of primary intracerebral hemorrhage. **Material and Methods.** A retrospective study included 246 patients with first time diagnosed primary intracerebral hemorrhage. Patients were divided into three groups, according to the drugs they have used. The incidence, anatomical distribution of primary intracerebral hemorrhage and survival/mortality rates were observed in all groups. **Results.** Antiplatelet therapy was used by 20.3% of patients, 8.2% received anticoagulant therapy, while the rest of 71.5% did not take these drugs in the pre-morbid period. The most common risk factor was arterial hypertension (97.2%). In all groups, patients had a tendency for supratentorial hematomas. Only alcohol consumption had a significant impact on the localization of hemorrhage ($p < 0,05$). There was no statistically significant difference between groups in National Institutes of Health Stroke Scale score on admission and a modified Rankin Scale Score at discharge. Oral anticoagulant users presented with the highest mortality rate in the first 24 hours (odds ratio - 2.5). Patients in other two groups showed a significantly higher survival rate (odds ratio - 1.5). **Conclusion.** Oral anticoagulant users had significantly higher National Institutes of Health Stroke Scale score on admission with an increased risk for early death. A significantly higher percentage of survival was noted in other two groups. Approximately 2/3 of all patients had poor functional recovery.

Key words: Anticoagulants; Platelet Aggregation Inhibitors; Cerebral Hemorrhage; Incidence; Treatment Outcome; Recovery of Function; Drug-Related Side Effects and Adverse Reactions; Risk Factors

Introduction

Primary intracerebral hemorrhage (pICH) is a non-traumatic hemorrhage in the brain parenchyma and/or chamber system, most commonly from small blood vessels due to chronic hypertension or cerebral amyloid angiopathy [1, 2]. The most common risk

Sažetak

Uvod. Incidencija intracerebralnog krvarenja zbog upotrebe oralne antikoagulantne i antitrombocitne terapije ima tendenciju porasta, te bi ovaj vid terapije mogao da bude potencijalni indikator nepovoljnog ishoda primarne intracerebralne hemoragije. Cilj istraživanja bio je utvrđivanje uticaja antikoagulantne i antitrombocitne terapije na pojavu, lokalizaciju i ishod primarne intracerebralne hemoragije. **Materijal i metode.** Retrospektivno istraživanje obuhvatilo je 246 bolesnika sa prvi put doživljenom primarnom intracerebralnom hemoragijom. Bolesnici su podeljeni u tri grupe u zavisnosti od lekova koje su koristili. Praćene su učestalost pojavljivanja i anatomska distribucija primarne intracerebralne hemoragije, kao i preživljavanje/mortalitet među grupama. **Rezultati.** Antitrombocitnu terapiju koristilo je 20,3% bolesnika, 8,2% njih oralne antikoagulanse, dok ostalih 71,5% nije uzimalo nijedno od navedenog u periodu pre bolesti. Najčešće zastupljeni faktor rizika bila je arterijska hipertenzija (97,2%). Sve tri grupe imale su tendenciju ka supratentorijalnoj lokalizaciji hematoma. Jedino je alkohol imao značajan uticaj na lokalizaciju hemoragije ($p < 0,05$). Nije utvrđena statistički značajna razlika u na Skali moždanog udara Nacionalnog instituta za zdravlje skor za težinu moždanog udara na prijemu i modifikovanom Rankin skor na otpustu između grupa. Korisnici oralnih antikoagulanasa su imali najveći mortalitet u prvih 24 sata (OR = 2,5). Druge dve grupe su zabeležile značajnu sklonost ka preživljavanju (OR = 1,5). **Zaključak.** Korisnici oralne antikoagulantne terapije imaju veći skor moždanog udara na skali moždanog udara Nacionalnog instituta za zdravlje na prijemu i povećan rizik za rani smrtni ishod. Druge dve grupe imaju veću sklonost ka preživljavanju. Oko 2/3 bolesnika imalo je loš funkcionalni oporavak.

KLjučne reči: antikoagulant; inhibitori agregacije trombocita; intracerebralno krvarenje; incidenca; ishod lečenja; oporavak funkcije; nuspojave i neželjene reakcije izazvane lekovima; faktori rizika

factor (RF) is arterial hypertension (HTA), but oral anticoagulant therapy (OACT), as well as antithrombotic therapy (AT) are also significant RFs [2, 3]. Warfarin, as the most commonly used oral anticoagulant, is considered a significant RF for pICH [2, 4, 5]. The overall risk of stroke in persons using warfarin accounts for 0.3 – 3.7% per year, with an expo-

Abbreviations

pICH	– primary intracerebral hemorrhage
HTA	– arterial hypertension
RF	– risk factor
OACT	– oral anticoagulant therapy
AT	– antithrombotic therapy
ASA	– acetylsalicylic acid
IS	– ischemic stroke
INR	– International Normalized Ratio
NIHSS	– National Institutes of Health Stroke Scale
mRS	– Modified Rankin Score

nential growth rate with age, but the benefit of this drug still significantly outweighs the risk of bleeding [2, 6–11]. The AT comprises acetylsalicylic acid (ASA) and clopidogrel. The benefit of using low-dose ASA (75 – 100 mg) monotherapy by far exceeds the risk of potential adverse effects, while long-term use of high doses (> 175 mg/day and > 1225 mg/week) represents the potential RF for pICH. Although having a different mechanism of action, there was no difference in risk for pICH between patients who used ASA and clopidogrel [12]. The aim of this study was to determine the incidence of pICH in patients who used AT or OACT, anatomical distribution, and pICH outcome among the examined groups.

Material and Methods

A retrospective study included 246 patients with first-time pICH hospitalized at the Emergency Neurology Department of the Emergency Center and the Neurology Clinic of the Clinical Center of Vojvodina in Novi Sad, in the period from January 2014 to December 2015. The following clinical and demographic data were observed: age, sex, RF for pICH (hypertension, hyperlipidemia, alcohol consumption, use of AT and OACT), platelet count, anamnestic data of previous ischemic stroke (IS). The International Normalized Ratio (INR) value was recorded on admission. The normal INR value was < 1.3 for patients without prior use of OACT, while INR values 2 – 3 were taken as physiological for patients using OACT, and according to the recommended therapeutic range.

The initial pICH severity was reported, according to the National Institutes of Health Stroke Scale (NIHSS), a value derived from the clinical neurological examination on admission. The degree of functional dependence and disability was assessed based on the Modified Rankin Score (mRS) at discharge from the hospital. The positive functional outcome was defined by the values of mRS from 0 – 2, while unfavorable values of mRS were from 3 – 5. The patients' survival was monitored for 30 days, and mortality, depending on the time elapsed from admission: in the first 24 hours, from 24h to 7th day, and from 8th to 30th day. Using available neuroradiological examinations, each patient was diagnosed with topographic localization of pICH: lobar, deep cerebral (basal ganglia, thalamus), brainstem or cerebellum.

Patients were divided into three groups: OACT users, AT users, and a group of patients who did not use any of these therapies (group without AT/OACT).

All data were obtained from the medical records, including medical histories and discharge letters. The exclusion criteria were as follows: data and neuroradiological findings on acute and chronic brain injuries and brain bleeding; existence of secondary bleeding in the brain tumor; hemorrhagic transformation of acute IS; presence of an aneurysm or a vascular brain malformation with earlier or existing intracranial bleeding; prehospital use of dual AT; prehospital use of a combination of OACT and AT.

Statistical data processing was done using Microsoft Excel 2007 and the Statistical Package for the Social Sciences. The numerical values were represented by mean values (arithmetic mean) and measure of variability (range of values, standard deviation). Attributive characteristics were represented using frequencies and percentages. A comparison of numerical values between the two groups was carried out using a Student's t-test. The testing of differences in the frequency of the attributes was performed using the χ^2 test. Fisher's Exact test was used in the analysis of the anatomical localization of pICH in all three groups of patients, since there were less than 5 patients for appropriate combination of categories within the analyzed parameters. The p value of < 0.05 was considered statistically significant.

Results

Out of a total of 246 patients, there were 157 (63.8%) males and 89 (36.2%) females. The mean age was 67.9 ± 11.8 years (range, 41 to 95 years). Most patients, 81 (32.9%) had pICH in the 7th decade. The most prevalent RF was HTA, in 97.2% of patients. A statistically significant difference in the prevalence of the previous IS in the AT group was seen in relation to the other two groups ($p < 0.001$). The AT was used by 50 (20.3%) patients, 20 (8.2%) patients were using OACT, while the other 176 (71.5%) did not take any of the aforementioned therapy in the period before pICH. The distribution of patients and RFs among groups is shown in **Table 1**. Compared to the other two groups, the OACT group had a statistically significantly higher INR values ($p < 0.0001$). There was no significant difference in INR between the AT group and the group without OACT/AT (**Table 2**). Patients from all three groups mostly presented with supratentorial localization of pICH (lobar or deep cerebral) ($p > 0.05$). The incidence of lobar localization of pICH was characteristic for the OACT group (60%), while deep cerebral localization was characteristic (50%) for the other two groups.

The analysis of RFs affecting the localization of pICH showed a statistically significant association only in alcohol consumption ($p = 0.03$) as follows: of the 75 patients who consumed alcohol, 44 (58.7%) had a deep cerebral localization of pICH. The effects of RFs on localization of pICH is shown in **Table 3**.

Table 1. Distribution of patients and risk factors among groups
Tabela 1. Raspodela bolesnika i faktora rizika među grupama

	Without OACT AT group/Bez OAKT AT grupa	AT group AT grupa	OACT group OAKT grupa	Total Ukupno	p (statistical significance)/p (statistička značajnost)
<i>Age/Starost</i>					
41-50	20 (95.2%)	1 (4.8%)	0	21 (8.5%)	
51-60	3 (75.6%)	9 (21.9%)	1 (2.5%)	41 (16.7%)	
61-70	58 (71.6%)	15 (18.5%)	8 (9.9%)	81 (32.9%)	
71-80	39 (60.9%)	16 (25%)	9 (14.1%)	64 (26%)	
≥ 81	28 (71.8%)	9 (23.1%)	2 (5.1%)	39 (15.8%)	
<i>Sex/Pol</i>					
Male/Muški	110 (70.1%)	33 (21%)	14 (8.9%)	157 (63.8%)	
Female/Ženski	66 (74.2%)	17 (19.1%)	6 (6.7%)	89 (36.2%)	
<i>Previous IS/Prethodni IMU</i>					
Yes/Da	7 (22.6%)	21 (67.7%)	3 (9.7%)	31 (12.6%)	<0.001
No/Ne	169 (78.6%)	29 (13.5%)	17 (7.9%)	215 (87.4%)	
<i>Arterial hypertension/Arterijska hipertenzija</i>					
Yes/Da	170 (71.1%)	49 (20.5%)	20 (8.4%)	239 (97.2%)	
No/Ne	6 (85.7%)	1 (14.3%)	0	7 (2.8%)	
<i>Alcohol/Alkohol</i>					
Yes/Da	59 (78.7%)	12 (16%)	4 (5.3%)	75 (30.5%)	
No/Ne	117 (68.4%)	38 (22.2%)	16 (9.4%)	171 (69.5%)	
<i>Hyperlipidaemia/Hiperlipidemija</i>					
Yes/Da	58 (61.7%)	28 (29.8%)	8 (8.5%)	94 (38.2%)	
No/Ne	118 (77.6%)	22 (14.5%)	12 (7.9%)	152 (61.8%)	
<i>Platelet count/Broj trombocita</i>					
<140	23 (76.7%)	5 (16.7%)	2 (6.7%)	30 (12.2%)	
140-400	149 (71.6%)	43 (20.7%)	16 (7.7%)	208 (84.5%)	
>400	4 (50%)	2 (25%)	2 (25%)	8 (3.3%)	
<i>INR/INO</i>					
Physiological/Fiziološki	160 (74.4%)	47 (21.9%)	8 (3.7%)	215 (87.3%)	
Pathological/Patološki	16 (51.6)	3 (9.7%)	12(38.7%)	31 (12.7%)	

Legend/Legenda :*OACT – oral anticoagulant therapy; *OAKT – oralna antikoagulantna terapija; *AT – antiplatelet therapy/antitrombocitna terapija; *IS – ischaemic stroke; *IMU – ishemijski moždani udar; INR – international normalized ratio; INO – internacionalni normalizovani odnos

Table 2. Initial INR values

Tabela 2. Inicijalne vrednosti INO

$\bar{x} \pm SD$	± 0.2	p=0.88	1.09 \pm 0.22	p<0.0001	2.47 \pm 1.27
Range/raspon	0.82-2.75		0.81-2.41		1.03-5.52

Legend/Legenda: INR- international normalized ratio; INO – internacionalni normalizovani odnos

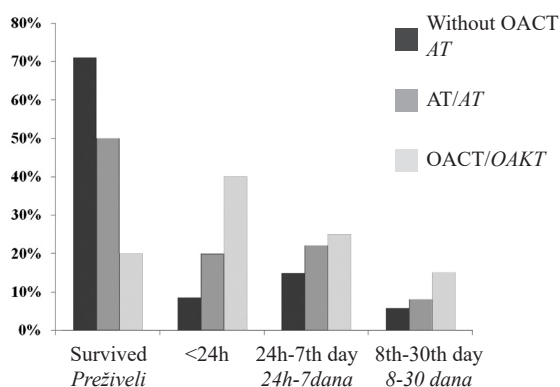
The largest number of patients in the OACT group (40%) had an initially severe clinical picture of pICH (NIHSS 14 – 20), while the other two groups about 30% of patients had a milder clinical picture (NIHSS 0 – 6). An estimated mRS was recorded in 154 (62.6%) patients. In approximately 2/3 of patients in all three groups, pICH had a poor functional outcome (mRS \geq 3). There was no significant difference in the NIHSS on admission and mRS at discharge among the groups (**Table 4**).

The OACT group had the highest mortality rate in the first 24 hours (40%), (OR = 2.5) compared to the other two groups. In the AT group (50%) and in the group without AT/OACT, (71%), a significantly higher survival rate (p < 0.000), OR = 1.5 was established. These results point to a significant early mortality in the OACT group, while the other two groups presented with higher survival rates (**Graph 1**).

Table 3. Risk factors for localization of pICH
Tabela 3. Faktori rizika za lokalizaciju pIKH

	Lobar <i>Lobarna</i>	Deep cerebral <i>Duboka cerebralna</i>	Cerebellum <i>Mali mozak</i>	Brainstem <i>Moždano stablo</i>	p (statistical significance)/p <i>(statistička značajnost)</i>
Age/Starost					
41-50	7 (33.3%)	9 (42.8%)	3 (14.3%)	2 (9.6%)	
51-60	18 (44%)	16 (39%)	5 (12.1%)	2 (4.9%)	
61-70	38 (46.9%)	35 (43.2%)	3 (3.7%)	5 (6.2%)	
71-80	28 (43.7%)	31 (48.4%)	2 (3.1%)	3 (4.6%)	
≥81	16 (41%)	22 (56.4%)	1 (2.6%)	0	
Sex/Pol					
Male/Muški	65 (41.4%)	77 (49%)	9 (5.7%)	6 (3.8%)	
Female/Ženski	42 (47.1%)	36 (40.4%)	5 (5.6%)	6 (6.7%)	
Previous IS/Prethodni IMU					
Yes/Da	14 (45.2%)	15 (48.3%)	1 (3.2%)	1 (3.2%)	
No/Ne	93 (43.2%)	98 (45.6%)	13 (6%)	11 (5.1%)	
Arterial Hypertension/Arterijska hipertenzija					
Yes/Da	105 (44%)	110 (46%)	13 (5.4%)	11 (4.6%)	
No/Ne	3 (42.8%)	3 (42.8%)	1 (14.3%)	0	
Alcohol/Alkohol					
Yes/Da	27 (36%)	44 (58.7%)	3 (4%)	1 (1.3%)	p=0.03
No/Ne	81 (47.4%)	68 (39.7%)	11 (6.4%)	11 (6.4%)	
Hyperlipidaemia/Hiperlipidemija					
Yes/Da	37 (39.3%)	48 (51%)	6 (6.4%)	3 (3.2%)	
No/Ne	69 (45.4%)	66 (43.4%)	8 (5.3%)	9 (5.9%)	
Platelet count/Broj trombocita					
< 140	12 (40%)	15 (50%)	3 (10%)	0	
140-400	92 (44.2%)	94 (45.2%)	11 (5.3%)	11 (5.3%)	
>400	4 (50%)	3 (37.5%)	0	1 (12.5%)	
INR/INO					
Physiological/Fiziološki	88 (40.9%)	103 (47.9%)	13 (6%)	11 (5.1%)	
Pathological/Patološki	17 (54.8%)	11 (35.5%)	2 (6.4%)	1 (3.2%)	

Legend/Legenda : *IS – ischaemic stroke; *IMU – ishemijski moždani udar; INR – international normalized ratio; INO – internacionalni normalizovani odnos; pICH – primary Intracranial Hemorrhage; pJKH – primarna intreakranijalna hemoragija



Graph 1. Analysis of survival in a one month period
Grafikon 1. Analiza preživljavanja u periodu od mesec dana
Legenda: AT – antitrombocitna terapija, OAKT – oralna antikoagulaciona terapija

Discussion

Our research confirmed that pICH is most frequent in males in the 7th decade of life with HTA as the dominant RF, which is in accordance with the known epidemiological data [2, 13–19]. It is believed that the susceptible hyaline degeneration and fibrinoid necrosis of the walls of small arteries and arterioles make HTA the main cause of pICH [20]. The previous IS treated with antithrombotic therapy represents a significant RF for pICH, as confirmed by the Seçil et al. [14]. The same authors established a significantly higher incidence of IS as a RF in the OACT group in regard to the group without OACT/AT, which is not the case in our study [14]. An acceptable explanation is based on the widespread use of AT in the prophylaxis of ischemic complications after IS in relation to OACT, in our area. The avail-

Table 4. Stroke severity on admission (NIHSS score) and functional outcome at discharge (mRS score)
Tabela 4. Težina moždanog udara na prijemu (SMUNIZ skor) i funkcionalni oporavak na otpustu (mRS skor)

Group/Grupa	NIHSS score/ SMUNIZ skor				p=0.27	mRS score/mRS skor		p=0.85
	0-6	7-13	14-20	≥ 21		0-2	3-5	
OACT/OAKT	1 (5%)	4 (20%)	8 (40%)	7 (35%)		1 (25%)	3 (75%)	
AT/AT	13 (26%)	12 (24%)	12 (24%)	13 (25%)		6 (24%)	19 (76%)	
Without OAKT/AT Bez OAKT/ATT	49 (27.8%)	43 (24.4%)	47 (26.7%)	37 (21%)		37 (29.6%)	88 (70.4%)	

Legend/Legenda: *OACT - oral anticoagulant therapy; *OAKT- oralna antikoagulantna terapija; *AT - antiplatelet therapy/antitrombocitna terapija; *p - statistical significance/statistička značajnost; *NIHSS – The National Institutes of Health Stroke Scale/SMUNIZ – skala moždanog udara Nacionalnog instituta za zdravlje; *mRS – modified Rankin Scale/modifikovana Rankinova skala

able literature data indicate that the initial INR value greater than 4.0 represents a significant RF for pICH [21]. Our research did not show a significant influence of INR on the occurrence of pICH. However, if groups with pathological values of INR (> 3.0) are observed, about 40% of them were from the OACT group, and 50% were from the group without AT/OACT. In the second case, we assume that some other factors could have been important, perhaps liver dysfunction.

Lobar localization was a characteristic of pICH [22], and it was confirmed by our research. The most common was the supratentorial localization, which was most frequent in the OACT group (60%), while deep cerebral (50%) was mostly found in the AT group and the group without AT/OACT. The potential explanation lies in the following: cerebral amyloid angiopathy represents the pathohistological basis of the lobar pICH, while vasculopathy of deep perforated arteries is a characteristic of the deep cerebral localization [23, 24]. It is assumed that there are different sensitivities of these two in the AT and OACT group [25]. It is also unavoidable that HTA primarily increases the risk of the non-lobar pICH, while warfarin is a RF predominantly for lobar pICH [14].

Several studies have shown the cause-effect relationship between alcohol consumption and lobar localization of pICH [26–28], while there are also opposite views [29]. Our results indicate a more significant incidence of deep cerebral pICH in alcoholics. Our hypothesis implies selective effects of alcohol on individual brain structures, in this case deep cerebral.

The constant increase rates and an aging population with a higher prevalence of hypertension and cerebral amyloid angiopathy, with a widespread use of AT and OACT, have an impact on the clinical picture and mortality [30, 31]. In our study, most patients in the OACT group (40%), had a more severe clinical picture, with NIHSS 14–20, unlike the other two groups, which had a milder clinical picture (NIHSS 0–6). However, no significant difference was noted. Similarly, other authors have confirmed the dominance of NIHSS 7–18 in all groups of patients [17, 32].

It is known that pICH has poor functional recovery; a very small number of patients recover without severe residual disability, and only 20% have a good functional outcome observed in a six-month period [11, 32]. More than 2/3 of patients in this study, in all three

observed groups, had mRS ≥ 3, that is a poor functional recovery at discharge.

Different factors cause these devastating results. Early mortality in the first 24 hours is associated with the OACT group, which is affected by greater hematoma volumes, multiplicity, and their expansion in the first hours of illness [11]. Some authors report a 2.5 times higher relative risk of early mortality in the AT group than in patients who did not use AT, explaining it by possible early expansion of hematoma and association with other RFs, primarily age, diabetes, and previous IS [33]. Our results point to higher prevalence of survival in the AT group and the group without AT/OACT. This may be explained by the following hypothesis: the use of AT leads to delaying the onset of edema and the expected “mass” effect of hematoma, which prolongs the time of action in the “therapeutic window” in which antiedematous measures may have a positive effect [17].

The benefits of OACT and AT are well known in many primary and secondary indications. Considering that new oral anticoagulants are used in the daily clinical practice [34], warfarin may not be the most commonly used oral anticoagulant any longer. However, intracranial bleeding associated with the use of OACT remains a significant clinical problem. The review of the current therapy, warning patients about an increased risk of bleeding, and prevention of proven RFs for pICH, must be an imperative in everyday clinical practice. This would contribute to further evaluation of the mechanisms of intracerebral hemorrhage and determination of the prognosis.

Knowledge on the following facts could have made our research more complex: the length and dosage of AT and OACT may have an impact on the localization, size and volume of pICH; Glasgow coma scale and Intracerebral hemorrhage score on admission are the best predictors of pICH outcome.

Conclusion

Patients using antithrombotic therapy who had a previous ischemic stroke are at a higher risk for primary intracerebral hemorrhage. Alcohol consumption often leads to a deep cerebral localization, while use of warfarin is associated with early mortality of patients with primary intracerebral hemorrhage.

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