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Pharmacotherapy prior to and in acute haemorrhagic stroke. The use of pharmacotherapy and drugs-associated outcomes in real-world practice – findings from the Polish Hospital Stroke Registry

Farmakoterapia w okresie poprzedzającym wystąpienie udaru i w ostrym udarze krwotocznym. Zastosowanie oraz wpływ leków na wyniki leczenia udaru krwotocznego mózgu w codziennej praktyce klinicznej – wyniki Szpitalnego Rejestru Udarów Mózgu w Polsce

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Abstract

Background and purpose: Haemorrhagic stroke is associated with substantial mortality and disability, thus prevention and appropriate treatment of acute intracerebral haemorrhage is crucial. We aimed to evaluate the use and the early and late outcomes impact of drugs administered before and in acute haemorrhagic stroke in a real-world practice.

Material and methods: Haemorrhagic stroke patients hospitalized between 1st March 2007 and 29th February 2008 and reported in Polish Hospital Stroke Registry were analysed. Fully anonymous data were collected with standardized, authorized access, web-based questionnaire. Multivariate regression models were used to adjust for case-mix and evaluate the impact of drugs used prior to or in acute haemorrhagic stroke on outcomes. The early outcomes were defined as in-hospital mortality or poor outcome (death or dependency – modified Rankin Scale ≥ 3) at hospital discharge, while late outcomes covered one-year survival.

Streszczenie

Wstęp i cel pracy: Udar krwotoczny jest związany ze znaczną śmiertelnością oraz niepełnosprawnością chorych; wymaga zarówno skutecznej profilaktyki, jak i leczenia ostrej fazy. Celem badania była ocena farmakoterapii stosowanej przed zachorowaniem i w ostrej fazie udaru krwotocznego mózgu, w warunkach codziennej praktyki klinicznej.

Materiał i metody: Analizie poddano grupę chorych hospitalizowanych z powodu udaru krwotocznego mózgu od 1.03.2007 r. do 29.02.2008 r., zgłoszonych do Szpitalnego Rejestru Udarów Mózgu w Polsce. W pełni anonimowe dane gromadzono z wykorzystaniem strukturyzowanego kwestionariusza internetowego z autoryzowanym dostępem. Do oceny wpływu leków stosowanych przed zachorowaniem oraz w ostrej fazie udaru krwotocznego na rokowanie wykorzystano wieloczynnikową analizę regresji z uwzględnieniem wpływu innych czynników rokowniczych. Wczesne wyniki leczenia zdefiniowano jako śmiertelność wewnątrzszpitalną i niekorzystny efekt terapeutyczny (punktacja ≥ 3 w zmody-

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Results: A total of 3111 haemorrhagic stroke patients (mean age: 68.9 years; females: 46.7%) was reported. The analysis of pharmacotherapy showed low preventive use of hypotensive agents in hypertensive patients, high consumption of antibiotics and still overuse of vasoactive or neuroprotective compounds in acute haemorrhagic stroke. Regression models confirmed expected negative impact on stroke outcomes associated with oral anticoagulants but not antiplatelets and inconsistent impact of statins used prior to or in acute haemorrhagic stroke.

Conclusions: Preventive underuse of hypotensive compounds contribute substantially to haemorrhagic stroke risk. The high consumption of antibiotics and neuroprotective or vasoactive compounds in haemorrhagic acute stroke reflect the need to improved quality and evidence-based clinical practice.

Key words: haemorrhagic stroke, pharmacotherapy, antihypertensives, oral anticoagulants, statins.

Wyniki: Analizie poddano dane 3111 osób hospitalizowanych z powodu udaru krwotocznego (średnia wieku: 68,9 roku; kobiety: 46,7%). Analiza farmakoterapii wykazała mały odsetek chorych z nadciśnieniem tętniczym stosujących leki hipotensyjne przed udarem i względnie częste wykorzystanie w leczeniu ostrego udaru krwotocznego antybiotyków oraz leków wazoaktywnych i neuroprotekcyjnych. W modelach wieloczynnikowych potwierdzono niekorzystny wpływ na rokowanie leków przeciwzakrzepowych, ale nie przeciwpłytkowych, i obserwowano przeciwstawny efekt statyn stosowanych przed udarem i w trakcie hospitalizacji.

Wnioski: Zbyt rzadkie wykorzystanie leków hipotensyjnych w kontroli nadciśnienia tętniczego w okresie poprzedzającym hospitalizację istotnie wpływa na ryzyko udaru krwotocznego. Częste stosowanie antybiotyków oraz leków wazoaktywnych i neuroprotekcyjnych wskazuje na potrzebę dalszej poprawy jakości opieki w ostrym udarze krwotocznym.

Słowa kluczowe: udar krwotoczny, farmakoterapia, leki hipotensyjne, leki przeciwzakrzepowe, statyny.

Introduction

Haemorhagic stroke, also named intracerebral haemorrhage (ICH), accounts for 10-15% of strokes, which translates into approximately 2 million new episodes of ICH worldwide each year [1]. It is associated with a 30-day mortality rate that approaches 50%, and only 20% of survivors are functionally independent at 6 months [2]. Haemorrhagic stroke is associated with a recurrence rate of 1-3% per year. Approximately half of the stroke recurrences after haemorrhagic stroke are in the form of another intracranial bleeding, with the other half corresponding to ischaemic stroke. Despite its substantial frequency and its major toll in terms of acute mortality and long-term disability, haemorrhagic stroke has been relatively understudied, especially with regard to treatment and the value of various measures for secondary prevention.

Haemorrhagic strokes are most often due to high blood pressure. Adequate control of blood pressure could prevent the majority of haemorrhagic strokes as untreated or poorly controlled hypertension increases the risk of intracranial haemorrhage by three to fourfold. Another risk factor is diabetes, although it slightly increases the risk of haemorrhagic stroke including intracranial bleeding following thrombolysis in acute ischaemic stroke. Certainly, excessive alcohol consumption increases the risk of haemorrhagic stroke and light to moderate intake was not showed beneficial contrary to ischaemic stroke. Smoking and possibly migraine with aura are also another risk factors [3].

Oral anticoagulants are associated with mean annual rate of haemorrhagic stroke of 0.2% and either more severe stroke or worse prognosis. Anticoagulation resumption after intracranial haemorrhage is a challenge. Current guidelines for patients with a comparatively lower risk of cerebral infarction (eg. atrial fibrillation [AF] without prior ischaemic stroke) and a higher risk of amyloid angiopathy (eg. elderly patients with lobar bleeding) or with very poor overall neurological function recommend consideration of an antiplatelet agent for prevention of ischaemic stroke. While in patients with a very high risk of thromboembolism it may be reasonable to restart warfarin therapy at 7 to 10 days after onset of the haemorrhagic stroke [4]. Antiplatelets for prevention of ischaemic events after ICH are considered safe in general, but caution should be paid to patients with lobar bleeding suspected to be due to cerebral amyloid angiopathy. Statins are effective for prevention of ischaemic events but they seem to increase the risk of lobar ICH recurrence.

Medical therapy of acute haemorrhagic stroke is mainly focused on adjunctive measures to minimize

haematoma enlargement as specific causal treatment is not available. Symptomatic treatment is primarily focused on high blood pressure control, prevention of thromboembolism in high-risk patients and surgical treatment for selected individuals.

We aimed to evaluate the use and the early and late outcomes impact of drugs administered before and in acute haemorrhagic stroke patients reported in the Polish Hospital Stroke Registry and hospitalized in 2007 and 2008.

Material and methods

Data on hospitalized stroke patients reported within third edition of the Polish Hospital Stroke Registry covering time-frame from 1st March 2007 to 29th February 2008 were analysed. All neurological centres in Poland were invited to participate and voluntarily report fully anonymous stroke patients data. Stroke was defined according to WHO definition as a neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours. Haemorrhagic stroke were identified based on ICD-10 classification (I61).

Data were collected with standardized web-based questionnaire, specially designed to eliminate misreporting and based on Swedish Stroke Registry and WHO *STEPwise approach to Surveillance*. The access to Registry was dedicated to each participating centre and protected from unauthorised use. Data were reported fully anonymously and, additionally, analysed with blinded information on patients allocation to particular stroke centre. To ensure the quality of reported data, randomly selected centres were audited. The following information was reported for all patients: demographics (age, gender), cardiovascular risk factors, modified Rankin Scale (mRS) prior to stroke, time of symptom onset (if unknown, the time patient was last seen without symptoms), clinical status at admission (level of consciousness), hospital management, stroke outcomes (mRS at discharge) and drugs used before stroke, during hospital stay and prescribed on discharge. The manual including all important terms and definitions and easily accessible on the official website of the Registry was provided. The history of cerebrovascular events was defined as documented hospitalisation due to confirmed stroke or transient ischaemic attack (TIA). Hypertension was reported for patients diagnosed before or during index hospitalization (by repeated blood pressure measurements after acute phase, i.e. first seven days); threshold values for hypertension were based on JNC VII report (systolic blood pressure > 140 mm Hg or > 130 mm Hg for diabetic or chronic renal failure patients; diastolic blood pressure > 90 mm Hg or > 80 mm Hg for diabetics or chronic renal failure patients) [5]. Atrial fibrillation encompassed paroxysmal, persistent and permanent arrhythmias. Ischaemic heart disease could have been only reported for patients objectively diagnosed with either interventional or non-interventional methods. The history of myocardial infarction was defined as acute coronary syndrome treated in hospital 30 days before stroke onset. Finally, dyslipidaemias could have been reported only if laboratory tests conducted 3 months preceding stroke onset or during first 24 hours were available for the following: total cholesterol (> 200 mg%) or LDL cholesterol (> 100 mg%) or triglycerides (> 150 mg%) or HDL cholesterol (< 40 mg% for males and < 50 mg% for females). The following drug groups were distinguished: aspirin, other antiplatelets, recombinant tissue plasminogen activator, blood pressure lowering agents, oral anticoagulants, heparins, insulins, oral antidiabetic drugs, vasoactive (i.e. nicergoline, vinpocetine) and neuroprotective (i.e. piracetam) agents, statins, antibiotics. In the third edition of the Polish Hospital Stroke Registry, unique Polish Resident Identification Number (PESEL) was used to track annual survival of stroke patients based on data collected by Department of National Central Evidences run by Ministry of Internal Affairs and Administration.

Statistical analysis

Data were analysed separately for haemorrhagic stroke following ICD-10 classification (I61). Calculations and estimations were conducted for the whole haemorrhagic stroke patients population and appropriate subgroups identified, i.e. target population for studied drugs. Data were presented as numbers and corresponding percentages.

Multivariate regression models were used to adjust for case-mix and evaluate the impact of drugs used prior to or in acute haemorrhagic stroke on outcomes. The early outcomes were defined as in-hospital mortality or poor outcome (death or dependency – mRS ≥ 3) at hospital discharge. The late outcomes covered one-year follow-up and the number of days from stroke onset to death for fatal cases. Logistic regression models and Cox proportional hazard model were applied for early and

late outcomes, respectively. Dedicated models controlled for age, sex, cardiovascular risk factors, disability assessed with mRS prior to stroke, consciousness at admission and treatment centres.

Results

A total number of 123 stroke centres reported data on 3111 haemorrhagic stroke patients in the third edition of the Polish Hospital Stroke Registry. On average, every ninth stroke patient was diagnosed with primary ICH.

Mean age of patients was 68.9 years (95% confidence interval [CI]: 68.4-69.3). For patients with first-ever stroke, mean age was 68.4 (95% CI: 67.9-68.9). Females represented 46.7% of the registered population. Baseline characteristics, including cardiovascular risk factors, is presented in the Table 1. Hypertension was most prevalent cardiovascular risk factor, followed by ischaemic heart disease and diabetes. Less than half of patients presented were alert on admission to hospital. Consciousness disturbances were probably related to prompt medical healthcare seeking as reflected by high percentage of patients admitted within 6 hours from symptom onset.

The detailed analysis of pharmacotherapy used in patients prior to and in acute haemorrhagic stroke patients for general patients population and subgroups is showed in the Table 2.

Regression models results are presented in Table 3. After adjusting for case-mix we could confirm some

Table 1. Baseline characteristics of haemorrhagic stroke patients reported in third edition of the Polish Hospital Stroke Registry

	N	%
History of stroke	442	14.2
Hypertension	2296	73.8
Atrial fibrillation	357	11.5
Ischaemic heart disease	556	17.9
History of myocardial infarction	138	4.4
Diabetes	447	14.4
Smoking	367	11.8
Alcohol abuse	329	10.6
Dyslipidaemias	420	13.5
Modified Rankin scale prior to stroke		
0	1810	64.4
1	344	12.2
2	216	7.7
3	139	4.5
4	123	4.4
5	179	6.4
Time from onset to admission < 6 h (including missing data or unknown time of onset)	1494	48.0
Consciousness disturbances:		
Alert	1404	45.1
Drowsy	748	24.1
Stupor	352	11.3
Coma	606	19.5

Table 2. Pharmacotherapy prior to stroke and used during hospital stay

Drugs used prior to stroke	N	%
Blood pressure lowering agents in hypertensive patients	1449	63.1
Blood pressure lowering agents in patient with history of stroke	302	68.3
Antiplatelets in patients with history of stroke	112	25.3
Antiplatelets in patients with history of MI or IHD	158	26.4
Anticoagulants in patients with AF	75	21.0
Statins	193	6.2
Statins in patients with history of stroke	34	14.5
Statins in patients with history of MI or IHD	93	15.6
Statins in patients with dyslipidaemias	86	20.5
Vasoactive agents	76	2.4
Neuroprotective agents	114	3.7
Antibiotics	33	1.1
Drugs used during hospital stay	**N**	**%**
Blood pressure lowering agents	2448	78.7
Blood pressure lowering agents in hypertensive patients	2044	89.0
Heparins	54	6.4
Statins	535	17.2
Insulins in diabetic patients	239	53.5
Antibiotics	1404	45.1
Vasoactive agents	284	9.1
Neuroprotective agents	732	23.5

MI – myocardial infarction, IHD – ischaemic heart disease, AF – atrial fibrillation

expected harm resulting from oral anticoagulants use prior to stroke, which was associated with worse early and late survival (in-hospital death: odds ratio [OR] = = 2.83 [95% CI: 1.60-5.02]; one year mortality: OR = 1.84 [95% CI: 1.39-2.44]), but not disability assessed at discharge from hospital. The outcomes associated with statins were inconsistent as these drug used prior to haemorrhagic stroke were observed to increase mortality while administered during hospital stay were of complete opposite effect.

Discussion

Alike for ischaemic stroke, drug utilisation before cerebrovascular accident and in acute haemorrhagic stroke is important in monitoring of the current medical practice. It can also point out pharmacotherapy potential benefit or harm in real-world settings as reported for ischaemic stroke patients [6]. Data from the Polish Hospital Stroke Registry provide a unique opportunity both to evaluate the current practice and to provide evidence on possible drug related benefit in haemorrhagic stroke based on everyday clinical practice data.

The pharmacotherapy practice prior to and in acute haemorrhagic stroke

As hypertension stands for the most important haemorrhagic stroke risk factor, the use of antihypertensive drugs is essential in either primary or secondary prevention. In the INTERSTROKE study, hypertension (defined as blood pressure > 160/90 mm Hg) was more often observed in haemorrhagic then ischaemic stroke patients (83 and 66%, respectively) and authors concluded that almost three quarters of haemorrhagic stroke risk is attributable to high blood pressure [7]. In the Polish Hospital Stroke Registry, antihypertensive drugs were used prior to haemorrhagic stroke on average by two out of three patients with hypertension and substantially less commonly compared to 75% of patients with ischaemic stroke [6]. We lack data on effectiveness of blood pressure control with antihypertensive prior to stroke in the Polish Hospital Stroke Registry. However, it should be stressed that analysis of all three editions of the Polish Hospital Stroke Registry (i.e. 2001-2002, 2004-2005 and 2007-2008 years) showed some negative trends of decreased use of hypotensive agents in haemorrhagic stroke patients with hypertension (compared to first 2001-2002 edition, 15% fewer patients with hypertension in 2007-2008 were treated with blood pressure lowering compounds before haemorrhagic stroke onset; data not presented) and that needs further monitoring.

Majority of hypertensive patients were treated with blood pressure lowering compounds during hospitalization. As blood pressure tends to fluctuate in acute stroke and blood pressure lowering agents are not recommended below 180/105 mm Hg, the assessment of antihypertensive agents is limited. Although the hypertension contributes more to the risk of haemorrhagic then ischaemic stroke, the use of blood pressure lowering agents was very similar – three out of four stroke patients were prescribed blood pressure lowering drugs and that rate increased to 90% for individuals with hypertension. Guidelines recommend that all ischaemic and haemorrhagic stroke patients regardless of blood pressure value should be offered antihypertensive drugs. As the secondary stroke prevention should be established during hospital stay and hardly ever hypotensive treatment needs late start (i.e. after discharge), one can argue there is still

Table 3. The statistically significant findings of multivariate regression modelling on the drugs associated with early and late haemorrhagic stroke outcome

Drugs associated with in-hospital mortality:	***p*-value**	**OR**	**95% CI**
Oral anticoagulants prior to stroke	< 0.001	2.832	1.603-5.017
Statins prior to stroke	0.001	2.128	1.335-3.384
Statins in hospital	< 0.001	0.292	0.207-0.406
Antibiotics in hospital	0.001	1.674	1.354-2.074
Drugs associated with functional outcome at discharge:			
Antibiotics in hospital	< 0.001	3.599	3.331-3.891
Drugs associated with one-year survival:			
Oral anticoagulants prior to stroke	< 0.001	1.841	1.390-2.436

OR – odds ratio, CI – confidence interval

room to improve secondary prevention with blood pressure lowering agents also in haemorrhagic stroke.

Oral anticoagulants are associated with risk of bleeding, including severe intracranial episodes. During 1990s the incidence of anticoagulant-associated ICH quintupled in United States and the majority of this change was attributed to increased warfarin use [8]. In our study, 21% of AF patients prior to haemorrhagic stroke were reported oral anticoagulants users (twice more often than AF patients hospitalized with ischaemic stroke) [6]. The corresponding values in other studies were similar and ranged from 18.3 to 23.4% [9,10].

Antiplatelets before haemorrhagic stroke onset were used only by quarter of patients with history of myocardial infarction or ischaemic heart disease and slightly more often in patients with secondary stroke. Moreover the antiplatelets were generally twice less often used for haemorrhagic stroke patients with history of cardiovascular disease compared with ischaemic stroke patients [6].

Statins were used only for 15% of patients with history of stroke or myocardial infarction and ischaemic heart disease. Alike antiplatelets, that is generally also twice less often compared with ischaemic stroke patients with history of cardiovascular event [6]. Use of statin was more driven by dyslipidaemia then cardiovascular diseases and did not reflect clinical guidelines.

Insulins were more often used in haemorrhagic than ischaemic stroke patients [6]. That can result from more severe stroke and the need to monitor glycaemia with insulin rather oral hypoglycaemic agents.

Antibiotics usage reflects the risk of infectious complications and indirectly also indicates the quality of acute stroke care. Almost half of haemorrhagic stroke patients in the Polish Hospital Stroke Registry were treated with antibiotics in hospital and that is high compared with results of the systematic review of 87 studies involving 137 817 patients, which estimated the overall pooled infection rate complicating acute stroke at 30% or 45% for all trials or intensive care unit studies, respectively [11].

Finally, the vasoactive (i.e. nicergoline, vinpocetine) and neuroprotective (i.e. piracetam) compounds, which have not been shown effective in randomised controlled trials, are still often used in Polish haemorrhagic stroke patients but less often compared to ischaemic stroke [6]. Although alike for ischaemic stroke, these drugs are less and less popular in following edition of the Polish Hospital Stroke Registry (data not presented; in first 2001-2002 edition of the Registry the corresponding rates were 16.3 and 56.3% for vasoactive and neuroprotective drugs, respectively), they are still fairly common. As a kind of negative indicator, the use of vasoactive and neuroprotective agents can reflect the dissemination of evidence-based clinical practice in either haemorrhagic and ischaemic stroke. It should be stressed that these drugs alike for ischaemic stroke were used rarely prior to haemorrhagic stroke and much more often during hospital stay, thus hospital management resulted in increased use of these drugs and therefore should be further monitored and improved.

The impact of drugs used before cerebrovascular accident or in acute haemorrhagic stroke on patients prognosis

Unlike ischaemic stroke, blood pressure lowering drugs used either prior to or during acute haemorrhagic stroke did not affect the outcome of haemorrhagic stroke patients and this is new finding as hardly ever studied.

The harmful impact of oral anticoagulants used prior to hemorrhagic stroke on short and long-term mortality observed in our study confirmed other findings. The increased odds of early death and long term mortality associated with pretreatment with oral anticoagulants ranged from 1.5 to 3.2 [9,10,12,13]. In the study by Stead *et al*., reversal of increased INR to normal with either fresh frozen plasma, vitamin K, activated factor VIIa or platelets did not influence mortality or functional outcome. Probably warfarin's effect on ICH mortality is mediated by increased risk of in-hospital haematoma expansion as warfarin did not increase ICH volume at admission [14].

We observed no impact of pretreatment with antiplatelets on prognosis in haemorrhagic stroke, most probably because of low doses of aspirin used regularly in cardiovascular prevention in Poland. Relevant publications are inconclusive. Some studies, especially those reporting high mean dose of aspirin used, found increased risk of early mortality of haemorrhagic stroke patients [13,15-18]. Another studies, including analysis of randomized trials, did not find any harmful impact of antiplatelets used prior to haemorrhagic stroke [19, 20]. Finally, systematic review of 25 studies (including 15 unpublished trials) also showed inconsistent results [21]. Antiplatelets in uni- and multivariate analysis were associated with increased mortality, but not poor functional outcome.

Unlike to ischaemic stroke, statins used prior to haemorrhagic stroke were associated with higher in-hospital mortality in our study. Only a few studies have

addressed the pretreatment with statins and haemorrhagic stroke outcomes. Most of the publications showed no relation between statins used prior to stroke and mortality or functional outcome [22-24]. Other, more recent, studies showed even some benefit produced by pretreatment with statins in haemorrhagic stroke, thus our study findings should be interpreted with caution and do not support the avoiding of statins due to intracranial bleeding risk [25-28]. Statins used during hospital treatment were associated with opposite outcomes compared with statins used prior to stroke. The data on statins benefits in haemorrhagic stroke are lacking. In SPARCL (*Stroke Prevention by Aggressive Reduction in Cholesterol Levels*) study, atorvastatin used in non-cardioembolic stroke patients reduced the risk of recurrent stroke and TIA but increased slightly the risk of intracranial bleeding, although increased fatalities were not observed [29,30]. Patients more likely to suffer intracranial bleeding while treated with statins in secondary prevention were males, with history of intracranial bleeding and concomitant hypertension.

Our study has a number of limitations, some of them were already mentioned [6]. Main limitation is voluntarily reported, not fully representative, sample of registered patients and limited scope of collected data. Nevertheless, it is so far the largest study on real world everyday stroke care in Poland.

Conclusions

The preventive use of blood pressure lowering agents in haemorrhagic stroke is inadequate and needs to be monitored and improved. Underuse of hypotensive compounds contribute substantially to haemorrhagic stroke risk. The benefits of statins in haemorrhagic stroke is less evident compared to ischaemic stroke. The high consumption of antibiotics and neuroprotective or vasoactive compounds in heamorhagic acute stroke reflect the need to improved quality and evidence based clinical practice.

Disclosure

Authors report no conflict of interest.

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