THE RISK OF CEREBRAL MICROBLEEDS IN ISCHEMIC STROKE PATIENTS USING ANTIPLATELET THERAPIES

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Received: 16/11/2020
Accepted:14/12/2020

Online ISSN: 2735-3540

ABSTRACT

Background: *Interest in cerebral microbleeds (CMBs) has increased based on advances in magnetic resonance imaging (MRI) technology. Both MRI T2-weighted gradient-echo (GRE) and susceptibility-weighted imaging may be sensitive techniques for the detection of past and more recent brain hemorrhage. The prevalence of CMBs in healthy population ranges 3.7–7.7%, whereas in patients with intracerebral hemorrhage is thought to be around 60%.*

Objective: *To evaluate the prevalence and possible risk of microbleeds among patients with ischemic stroke using antiplatelets (Aps).*

Patients and Methods: *The observational hospital-based cross-sectional analytical study involved 150 consecutive patients with ischemic stroke (recent or old ischemic strokes or both), from inpatients of neurology departments of Ain Shams University Hospital and Agouza Police Hospital for a period of 15 months from April 2018 to June 2019.*

Results: *Cerebral microbleeds were present in 13 patients representing 26% of the no AP group, 16 patients representing 32% of the single AP group and 19 patients representing 38% of the double AP group, there was no statistically significant difference between the three groups of patients. Cerebral microbleeds were present in 60% of patients on double APs and 37.5% of patient on single AP for more than two years, compared to 23.3%and 26.9%for the two groups respectively on APs for less than two years, In the current study we found that the significant risk factor for the presence of CMBs was the duration of APs use. There was no statistically significant difference in the laboratory data (including full lipid profile, HbA1c and platelet count) between the three groups.*

Conclusion: *CMBs are significantly associated with long term use of antiplatelets, so careful clinical and radiological follow up of ischemic stroke patients with CMBs using antiplatelets for risk of future intracranial hemorrhage.*

Keywords: *Cerebral Microbleeds, Ischemic Stroke, Antiplatelet Therapies*

INTRODUCTION:

Stroke is considered to be one of the important global health problems fifteen million individuals worldwide suffer from stroke annually. Of these, five millions die and another five millions are permanently left disabled, placing a burden on family and community. Nowadays, it ranks the second most common cause of mortality in the

world, and remains the most common cause of long-term disability in adults .Although the incidence of stroke is decreasing in many developed countries, largely as a result of better control of high blood pressure, and reduced levels of smoking, the absolute number of strokes continues to increase because of the ageing population[(1)].

In the mid-1990s reports began to appear of small hemorrhagic lesions on magnetic resonance imaging (MRI) studies, Scharf and colleagues described black dots of signal loss on T2-weighted MRI in patients with spontaneous intra cerebral hemorrhage (ICH) and termed these 'hemorrhagic lacunes'[(2)].

Subsequent studies using T2*-weighted gradient-echo (T2*-GRE) MRI, a technique with greater sensitivity to the signal loss from magnetic 'susceptibility' effects of blood breakdown products – detected small round black dots which have become known as 'cerebral micro bleeds' (CMBs)[(3)].

CMBs reflect small areas of hemorrhage, and are common in both ischemic stroke and ICH[(4)].

Antiplatelet medications have proven efficacy for patients at high risk of ischemic cardiovascular or cerebrovascular disease yet, can predispose individuals to ICH. Patients risk stratifying to individually optimize the balance of anti-ischemic to pro-hemorrhagic effects of antithrombotic drugs remains a major goal of cerebrovascular medicine. With the increasing evidence about the close association of CMBs with ICH, there is increasing interest in whether this radiological marker can help to identify patients at high risk of treatment-associated hemorrhagic complications, and hence, directly influence the choice of treatment[(6)].

However, it is unclear whether antithrombotic treatment raises the risk of future ICH among patients with CMBs. In addition, even at baseline the association between the presence of CMBs and previous antithrombotic treatment is controversial; the association between antithrombotic treatment and CMBs was not significant in some studies, while in others it was positive, and in one study there was negative correlation observed[(7)].

The possible association between the exposure to antithrombotic drug and the presence of CMBs is potentially confounded by the indications for which the drugs are prescribed: as CMBs may be related to the presence of cardiovascular and cerebrovascular diseases in general, antithrombotic drugs may be more often prescribed to patients with an increased risk of developing CMBs unrelated to the use of antithrombotic agents[(8)].

Because ischemic cerebrovascular disease patients are frequently treated with antiplatelet agents, the investigation of the effects of antiplatelet use on the development of cerebral microbleeds in these patients is very important. However, the association between antiplatelet use and the presence of cerebral microbleeds remains controversial[(9)].

AIM OF THE WORK:

The primary objective of this study was to evaluate the prevalence and possible risk of microbleeds among patients with ischemic stroke using APs.

PATIENTS AND METHODS:

The observational hospital-based cross-sectional analytical study involved 150 consecutive patients with ischemic stroke (recent or old ischemic strokes or both), from inpatients of neurology departments of Ain Shams University Hospital and Agouza Police Hospital of 15 months duration from April 2018 to June 2019.

The study divided into three groups: The first group included 50 patients not

receiving any antiplatelet agents: No AP Group. The second group included 50 patients receiving aspirin only: Single AP Group. The third group included 50 patients receiving double antiplatelet: Double AP Group.

Inclusion Criteria: Age: 45-70 years, both sexes were included in the study and patients with recent or old ischemic strokes or both.

Exclusion Criteria: Patients with comorbid CNS diseases other than ischemic stroke, to avoid overlapping of these disorders with the CMBs lesions, patients with ICH or history of ICH, patients with bleeding tendency due to hematological disorder and patients on anticoagulation therapy.

All patients were subjected to the following assessment procedures:

Clinical evaluation: Complete medical history of risk factors, history of treatment with antiplatelet drugs prior to the onset of stroke and detailed neurological examination and National Institute of Health Stroke Scale (NIHSS) score for assessment of severity of stroke on admission.

Laboratory investigations: CBC, INR, bleeding profile, urea, creatinine, other labs for risk factors related to stroke as lipid profile, HBA1C and uric acid.

Imaging investigations: Carotid duplex was done for estimation of degree of stenosis of the extracranial carotid system, echocardiography was done for estimation of left atrial diameter and ejection fraction and an MRI of the brain according to stroke protocol including diffusion weighted images (DWI), FLAIR, T2*-weighted images for CMBs detection and MRA. Studies were performed using Siemens 1.5 T scanner.

MRI criteria of cerebral microbleeds:

Microbleeds (MBs) were defined as homogeneous, rounded hypointense lesions of <5 mm in diameter located in the brain parenchyma on the gradient-echo images.

Symmetric signal loss or hypointensity in the globuspallidum, most likely calcification, was ruled out.

Flow void artifacts of the pial blood vessel based on morphology and correlation with FLAIR and T2-weighted were not regarded as MBs.

Similarly, hypointensities in any areas of cortex near the inner skull table, which were considered to be signal averaging from adjacent bone, were ignored.

Microbleeds were classified as absent (grade "0"), mild (grade "1"; total number of microbleeds, one to two), moderate (grade "2"; total number of microbleeds, three to 10), and severe (grade "3"; total number of microbleeds, >10) according to the grading scale presented by **Lee and colleagues.[(9)].**

The location of the CMBs was classified by cerebral region as strictly lobar (lobar CMBs: patients with≥1 CMBs restricted to a lobar location) and deep (deep CMBs: patients with≥1 CMBs in a deep or infratentorial location with or without concomitant lobar CMBs)**[(10)].**

Leukoaraiosis was graded using the scoring system presented by **Fazekas et al.[(11)]** as follows: grade "0", absent, grade "1", punctuate white matter hyper intensities, grade "2", early confluent white matter hyper intensities, grade "3", confluent white matter hyper intensities.

Ethical Considerations: Written consent from each patient or relatives from the research study and ethical approval was obtained from the ethical committee of faculty of medicine Ain Shams University prior to data collection.

Statistical Methods:

Statistical analysis was done using IBM SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA). Numerical data were

expressed as mean, standard deviation, and range as appropriate. Qualitative data were expressed as frequency and percentage. Pearson's Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. Quantitative data were tested for normality using Kolmogorov-Smirnov test and Shapiro-Wilk test. For normally distributed quantitative data, comparison between 3 groups was done using analysis of variance test (ANOVA)then post-Hoc "Tukey HSD test" was used for pair-wise comparison. While for not normally distributed quantitative data, comparison between 3 groups was done using Kruskal-Wallis test (non-parametric ANOVA) then post-Hoc test was used for pair-wise comparison based on Kruskal-Wallis distribution. All tests were two-tailed. A p-value < 0.05 was considered significant.

RESULTS

Table (1): Baseline characteristics of the three studied groups

	No AP G n=50	Single AP G n=50	Double AP G n=50	p value
Age (years)	58.9±5.9	62.2±5.6	62.9±5.6	0.001
Sex				
Male	31 (62.0%)	32 (64.0%)	32 (64.0%)	0.972
Female	19 (38.0%)	18 (36.0%)	18 (36.0%)	
Smoking	10 (20.0%)	10 (20.0%)	11 (22.0%)	0.960
DM	23 (46.0%)	25 (50.0%)	25 (50.0%)	0.899
Hypertension	32 (64.0%)	36 (72.0%)	35 (70.0%)	0.668
IHD	0 (0.0%)	31 (62.0%)	35 (70.0%)	< 0.001

Data are expressed as mean ± SD, or number (%)
DM: Diabetes mellitus, IHD: ischemic heart disease

The No AP group was significantly younger than the Single AP groups (p=0.012), and Double AP group (p=0.002). Ischemic heart disease was more commonly encountered in patients under antiplatelet therapy compared to those in the No AP group (p < 0.001). Other demographic characteristics of the three groups are listed in (table 1).

Table (2): Past history of cerebrovascular affection, National Institutes of Health Stroke Scale scores and echocardiography findings of the three studied groups

	No AP G n=50	Single AP G n=50	Double AP G n=50	p value
TIA	10 (20.0%)	23 (46.0%)	23 (46.0%)	0.008
Stroke	0 (0.0%)	11 (22.0%)	8 (16.0%)	0.003
NIHSS	8.7±5.5	12.0±5.7	12.3±5.1	0.002
Ejection fraction (%)	60.6±5.6	58.9±7.5	55.1±6.8	<0.001
Left atrial diameter (mm)	37.9±4.1	39.2±5.3	38.9±3.8	0.350

Data are expressed as number (%), TIA: transient ischemic attacks
NIHSS: National Institutes of Health Stroke Scale, Data are expressed as mean ± SD

No AP group less frequently reported past history of transient ischemic attacks or strokes. The National Institutes of Health Stroke Scale (NIHSS) scores were significantly lower in the No AP group compared to Single AP group (p=0.013) and Double AP group (p=0.004), while the latter groups were comparable in the NIHSS (p =

1.000). Ejection fraction was significantly lower in the Double AP group compared to the No AP group (p< 0.001), and the Single AP group (p = 0.014) (Table 2).

Table (3): Frequency, sites, and severity of cerebral microbleeds detected in the three studied groups

	No AP G n=50	**Single AP G n=50**	**Double AP G n=50**	**p value**
Cerebral microbleeds	13 (26.0%)	16 (32.0%)	19 (38.0%)	0.437
Deep	9 (18.0%)	15 (30.0%)	15 (30.0%)	0.287
Lobar	7 (14.0%)	13 (26.0%)	15 (30.0%)	0.144
Infra-tentorial	0 (0.0%)	2 (4.0%)	4 (8.0%)	0.166
CMBs Severity				*
G1 absent	37 (74.0%)	34 (68.0%)	31 (62.0%)	
G2 Mild	9 (18.0%)	10 (20.0%)	9 (18.0%)	
G3 Moderate	4 (8.0%)	5 (10.0%)	8 (16.0%)	
G4 Severe	0 (0.0%)	1 (2.0%)	2 (4.0%)	

Data are expressed as number (%), * No p value due to the small number of cases in subgroups, A patient may have CMBs in more than one site, CMBs: Cerebral microbleeds

Cerebral microbleeds were detected in the three groups with comparable frequency (p = 0.437). Deep CMBs was more common in no AP and Single AP groups. No infratentorial CMBs was found in the No AP group. However, there was no significant difference between the three groups in the site of CMBs. The severity grade of CMBs appears to be comparable between the three groups, but statistical analysis was invalid owing to the small number of cases in some subgroups (Table 3).

Table (4): Frequency of cerebral microbleeds in relation to duration and type of antiplatelet therapy

	CMBs	**No CMBs**	**p value**
No AP	13 (26.0%)	37 (74.0%)	0.046
Single ≤ 2yrs	7 (26.9%)	19 (73.1%)	
Single > 2yrs	9 (37.5%)	15 (62.5%)	
Double ≤ 2yrs	7 (23.3%)	23 (76.7%)	
Double > 2yrs	12 (60.0%)	8 (40.0%)	

Data are expressed as number (%), CMB: Cerebral microbleeds

Using double antiplatelet for more than two years was associated with CMBs in 60% of cases. This was significantly higher in comparison to absence of APs, single use for any duration of use of double APs for 2 years or less (Table 4).

DISCUSSION:

Antiplatelet medications have proven efficacy for patients at high risk of ischemic cardiovascular or cerebrovascular disease, but can predispose individuals to ICH. With the increasing evidence about the close association of CMBs with ICH, there is increasing interest in whether this radiological marker can help to identify patients at high risk of treatment associated hemorrhagic complications and, hence, directly influence the choice of treatment[6].

The primary objective of this study was to evaluate the prevalence and possible risk of cerebral microbleeds among patients with ischemic stroke using antiplatelet drugs.

The objective was accomplished through a hospital-based study comparing the data of 3 groups of patients with acute ischemic stroke, a group of patients who had no antiplatelet drugs, a second group of patients who had single antiplatelet drug, and a third group with double antiplatelet drugs.

This study was conducted on 150 patients who were admitted to Agouza Police Hospital with a diagnosis of ischemic stroke performing MRI including gradient-echo (T2*) weighted.

In the current study, cerebral microbleeds were present in 48 patients representing 33% of the study groups (26% of no AP group, 32% of single AP group and 38% of double AP group). The prevalence of CMBs in patients with ischemic stroke is approximately 20-30% **(12).** The prevalence of CMBs in Egyptian patients in the previous studies was 40.7% **(13).**

On the other hand, a higher prevalence rate was reported by **Zhang and colleagues(14)**, as CMBs were detected in 41.2% of patients included in their study, and 40% **(15)**.

Also a higher prevalence rate (50%) was found in a study done by **Lei and colleagues (16)**among patients with acute ischemic stroke. The difference in this prevalence is attributed to the use of susceptibility-weighted magnetic resonance imaging in the detection of CMBs which is highly sensitive than T2*-weighted MR images used in our study.

The prevalence of CMBs in patients with ischemic stroke varies greatly in different studies ranging from 18% to 78%**(15, 17).**

The wide range of reported CMBs prevalence reflects the characteristics of the sample, such as age, stroke history and subtype, comorbidities and genetic susceptibility, variations in methodology, as well as differences in MR acquisition parameters (e.g. slice thickness, interslice gap and field strength) **(18).**

In the current study patients with APs were older than those without APs ($p < 0.001$). Age was an important predictor of CMBs due to vascular changes (either hypertensive or amyloid) are progressive with aging. So prevention strategies for both hypertensive and amyloid angiopathy should start early in life and may be aided by noninvasive imaging biomarkers that indicate early disease, such as CMBs.

In the current study, history of smoking, diabetes and hypertension was insignificant between the three groups of patients ($p = 0.960$, 0.899 and 0.688 respectively), while the history of IHD was significantly different between the three groups of patients ($p = 0.001$).

In the current study, cerebral microbleeds were detected in the three groups with comparable frequency ($p = 0.437$), there was no significant difference between the three groups in the site of CMBs. This was also consistent with the results of the study done by **Kim and colleagues(19).**

However aspirin use could be more associated with lobar CMBs than deep or infratentorial CMBs**(26).** However, in our study, no significant association existed in lobar and deep CMBs, and this lack of relationship might have resulted from a different target population from previous studies and the relatively low number of subjects with strictly lobar CMBs.

In the current study, it was found that using double APs for more than two years was associated with CMBs in 60% of cases. This was significantly higher in comparison to absence of APs, single use for any duration of use of double APs for 2 years or less. Using single AP for more than two years was associated with CMBs in more than 37% of cases. This was significantly higher in comparison to absence of APs, single or double APs use for less than two years duration. This was also consistent with the results of the study done by **Yamashiro and colleagues(8).**However, our findings are in contrast to those of the Rotterdam Scan Study**(20)**.This may be explained by the difference in study population. The Rotterdam Scan Study was a population-

based study, whereas our study was a hospital-based study in which patients with ischemic cerebrovascular disease were examined. This difference in study design may account for the difference in the prevalence of vascular risk factors and in the severity of cerebrovascular disease, which may affect the prevalence and location of microbleeds.

Conclusion:

CMBs are significantly associated with long term use of antiplatelets, so careful clinical and radiological follow up of ischemic stroke patients with CMBs using antiplatelets for risk of future intracranial hemorrhage. Patients on dual antiplatelets for more than two years presenting with recent ischemic stroke should be assessed thoroughly before thromblysis due to the high susceptibility of hemorrhagic transformation because of their higher prevalence of CMBs.

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خطر النزف الدماغي الدقيق في مرضى السكتة الدماغية الاقفارية الذين يستخدمون الأدوية المضادة للصفائح الدموية

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خلفية البحث:بدأت فى منتصف تسعينات القرن الماضى تظهر تقاريرعن آفات نزفية صغيرة فى دراسات الرنين المغناطيسي على المخ. وقد وصفها سكارف وآخرون انها نقاط سوداء من فقدان الإشارة فى الرنين المغناطيسى T2 للمرضى بالنزيف الدماغي التلقائي و سميت بالفجوات النزفية.ويعكس النزف الدماغي الدقيق مناطق صغيرة من النزيف و هى اكثر شيوعا فى كلا من السكتات الدماغية الاقفارية والنزيف الدماغى.

الهدف من البحث: تقييم مدى انتشار النزيف الدقيق والمخاطر المحتملة بين مرضى السكتة الدماغية باستخدام مضادات الصفيحات.

المرضي وطرق البحث:أجريت هذه الدراسة على ١٥٠ مريضاً مصرياً تم تشخيصهم بالسكتة الدماغية الاقفارية.هولاء المرضى تم تقسيمهم الى ثلاثة مجموعات:المجموعه الأولى من المرضى الذين لا يستخدموا أياً من مضادات الصفائح الدموية . المجموعة الثانية من المرضى الذين يستخدمون الاسبرين فقط.المجموعة الثالثة من المرضى الذين يستخدمون عقارين مضادين للصفائح الدموية (اسبرين-كلوبيدوجريل أو اسبرين- سيلوستازول). و قد تلقى جميع المرضى العلاج اللازم لهم وفقا لحالتهم الإكلينيكية.

نتائج البحث:تمثل المجموعة الأولى المرضى الذين لا يستخدمون أياً من مضادات الصفائح الدموية وعددهم ٥٠ مريض وقد وجد بها معدل النزف الدماغى الدقيق بنسبة ٢٦%ووجد فى المجموعة الثانية بنسبة ٣٢% وفى المجموعة لثالثة بنسبة ٣٦% ولم تظهر الدراسة أى اختلافات احصائية بين الثلاث مجموعات.وعند تقسيم المرضى إلى مجموعتين من حيث مدة استخدام الأدوية المضادة للصفائح الدموية إلى أقل من عامين وأكثر من عامين أوضحت الدراسة وجود اختلاف احصائى حيث كان معدل حدوث النزف الدماغى الدقيق أعلى فى المجموعة التي استخدمت مضادات الصفائح الدموية لأكثر من عامين.

الاستنتاج:خلصت الدراسة إلى وجود علاقة وثيقة بين مدة استخدام الأدوية المضادة للصفائح الدموية ومعدل حدوث النزف الدماغى الدقيق مما يثير الاهتمام لعمل دراسات طويلة المدى على مجموعات أكبر من المرضى لدراسة تأثيرها على المآل الوظيفي والمعرفي.