



## To determine the frequency of intracerebral haemorrhage (ICH) in patients taking antiplatelet therapy.

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**Article received on:**

08/04/2020

**Accepted for publication:**

27/06/2020

**ABSTRACT... Objectives:** To determine the frequency of Intracerebral Haemorrhage (ICH) in patients taking antiplatelet therapy. **Study Design:** Cross-Sectional Study. **Setting:** Emergency Department at Ziauddin Hospital. **Period:** 2014-2016. **Material & Methods:** A total number of 75 patients with ICH, diagnosed by C.T Scan Brain Plain were included in this study. After the diagnosis of ICH on C.T scan Brain, patients were selected as with prior use of antiplatelets or secondary to other causes. Brief history was taken from the patients and attendants regarding the history of antiplatelets use. **Results:** The average ages of the patients were  $59.97 \pm 12.46$  years. There were 57.33% male and 42.67% female. Out of 75 ICH patients 44% (33/75) were taking antiplatelet therapy. Median duration of APT was 12[IQR=24] months. Out of these 33 patients 78.8% (26/33) were taking single APT and 21.2% (7/33) were taking dual APT. Mean age was significantly high in patients those who are on antiplatelet therapy as compare to those who was not on APT ( $p=0.033$ ). Gender and systematic finding of patients were not significant those who are not on APT and on APT. Comorbid like DM, HTN and IHD were significant high in patients on APT and in hospital mortality was also not significant in patients on APT and not on APT. **Conclusion:** In this study overall in hospital mortality was observed in 13.33%. These study suggests there is only modestly increased mortality in patients taking pre-ICH APT, and little or no increase in poor functional outcomes there are a substantial number of ICH patients taking pre-ICH APT who could be at risk. For the reduction in morbidity related to APT-ICH Prevention of risk factor like HTN is most antonyms strategy.

**Key words:** Antiplatelet Therapy, Basal Ganglia Bleed, Intracerebral Haemorrhage, SDH, SAH, Thalamic Bleed.

**Article Citation:** Shehbaz L, Nasir S, Khan AN. To determine the frequency of intracerebral haemorrhage (ICH) in patients taking antiplatelet therapy. Professional Med J 2020; 27(12):2601-2607. <https://doi.org/10.29309/TPMJ/2020.27.12.4704>

### INTRODUCTION

Intracerebral hemorrhage (ICH) is a neurological emergency contributing to 15- 20% of cases in U.S and is associated with worst prognosis accounting for 30 day mortality of 40%.<sup>1,2</sup> However there has been a decline since 1950s but still greater than 20,000 patients die annually in US.<sup>2</sup> Increasing incidence has been seen in Asians. Incidence of ICH not well studied in Pakistan but estimates of 20-36% has been found.<sup>3,4</sup> Different studies determining the effects of antithrombotic therapy on ICH has shown contradictory results. Patient's presenting to emergency departments is more frequently on antiplatelets than anticoagulants. However there is a 7-10 times increased risk of ICH in patients taking oral anticoagulants with an overall incidence of 2-9 per 100,000 every year. The mortality rate is much higher than

those patients not on anticoagulation i.e. 52 to 67%.<sup>5,6</sup> However the antiplatelet (mostly Aspirin) induced hemorrhage reported to be 31.3%.<sup>7</sup> The Rotterdam scan study found antiplatelets to be associated with micro bleeds, 23.1% vs. 5.9% taking anticoagulants.<sup>8</sup> The use of the antithrombotics also influences the extension of hematoma, clinical decline and dynamic reversal from coagulopathy. While the study by Campbell on ICH patients found difference in mortality among two antiplatelets i.e. Clopidogrel to have an inhospital mortality of 28.6% compared to patients taking Aspirin 14.3%.<sup>9</sup> The Medline and Embase database in their systematic review found increased mortality but not a worse outcome in patients taking prior antiplatelet therapy.<sup>10</sup> Naedich et al demonstrated that increased platelet inhibition has been associated

with increased ICH volume at 12 hours and poor outcome after 3 months of hemorrhage.<sup>11-13</sup> Our study aim to determine the incidence of ICH in patients presenting in emergency department with prior history of antiplatelets use. This will help us in determining the risk of bleed in patients on antiplatelet therapy.

To determine the frequency of Intracerebral Haemorrhage (ICH) in patients taking antiplatelet therapy

**MATERIAL & METHODS**

It is a cross-sectional Study conducted in Emergency Department at Ziauddin Hospital, Karachi from 2014-2016. Data was collected from patients having intracerebral hemorrhage (ICH) admitted through Emergency Department at Ziauddin Hospital (north campus) meeting inclusion criteria. Informed and written consent was taken from the patient or the patient's attendant, by researcher. After taking brief history and examination, patient's Computed Tomography (C.T) Scan Brain plain was done. After diagnosing the cases of ICH on C.T scan Brain, patients were selected with prior use of antiplatelets or secondary to other causes. Brief history was taken from the patients regarding history of antiplatelets use.

Data was analyzed by statistical software package SPSS version 20.0. Statistical analysis was expressed as frequencies and percentages. Descriptive statistics including patient's age, gender and admission number was entered. Mean +/- SD was calculated for quantitative variables like age of patient while frequency of intracerebral hemorrhage (ICH), duration of antiplatelet therapy, hypertension, diabetes, ischemic heart disease, atrial fibrillation, Peripheral artery disease and prior ischemic stroke. P <0.05 was considered significant. Stratification was done with regards to age, gender, different antiplatelet and their duration.

**RESULTS**

A total numbers of 75 patients with ICH diagnosed by C.T Scan Brain Plain in Emergency Department were included in this study. Most of the patients

were above 50 years as referred in Figure-1.

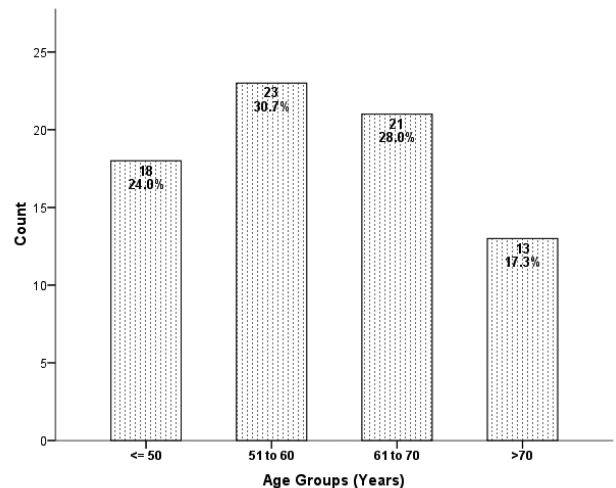


Figure-1. Distribution of age

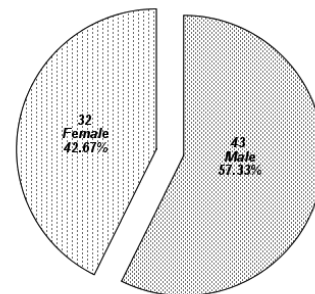


Figure-2. Gender distribution

This study showed the average age of the patients' 59.97±12.46 years, of which males were 57.33% and females were 42.67% shown in figure 2. Regarding comorbidity, the most common cause was hypertension which was observed in 82.7% cases, diabetes mellitus 29.3%, CVA 9.3% and other comorbid are also presented in the figure 3.

Similarly in systemic examination of patient's drowsy but arousable, right and left side upper and lower limbs, slurring of speech, unconscious were the commonest finding in ICH patients as shown in Table-I.

Basal Ganglia Bleed, thalamic bleed, SDH, SAH, SAH with SDH, partial bleed were observed in ICH patients. Overall in hospital mortality was observed in 13.33% (10/75) cases (Figure-4).

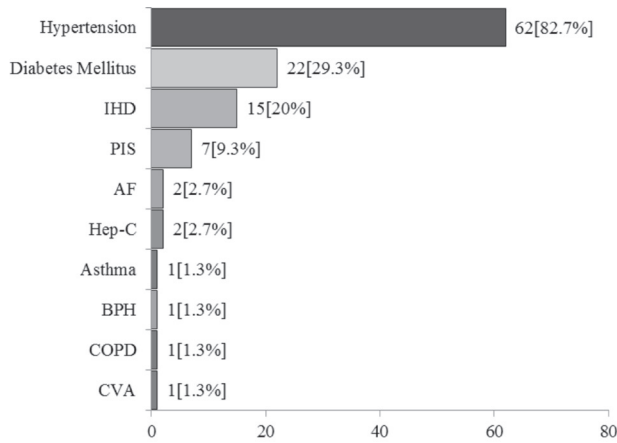


Figure-3. Comorbidity status of patients

Out of 75 ICH patients 44% (33/75) were taking antiplatelet therapy as shown in figure 5. Median duration of APT was 12[IQR=24] months. Out of these 33 patients 78.8% (26/33) were taking single APT in which 72.7% (24/33) were taking Aspirin , 6.1% (2/33) were taking Clopiogrel and 21.2% (7/33) patients were taking two antiplatelets, Aspirin with Clopiogrel as shown in Table-II.

Mean age was significantly high in patients those who are on antiplatelet therapy as compare to those who were not on APT (p=0.033) while other physiology status were not significant in patients on APT and not on APT. Mean GCS scores was not significant on APT and not on APT. Gender and systemic finding of patients were not significant not on APT, those on APT.

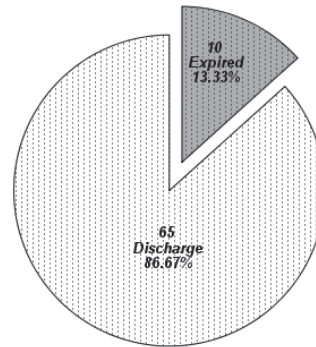


Figure-4. In hospital mortality

Variables	Antiplatelet Therapy (APT)		P-Value
	APT(+) (n=33)	APT(-) (n=42)	
<b>Gender</b>			
Male	19(57.6%)	24(57.1%)	0.97
Female	14(42.4%)	18(42.9%)	
<b>Systematic Examination</b>			
Facial Deficit	2(6.1%)	1(2.4%)	0.42
Drowsy but Arousable	7(21.2%)	12(28.6%)	0.46
Disoriented	5(15.2%)	5(11.9%)	0.68
Chest Aspiration	1(3%)	3(7.1%)	0.43
Unconscious	8(24.2%)	4(9.4%)	0.08
Right side UL and LL	8(24.2%)	9(21.4%)	0.77
Left side UL and LL	9(27.3%)	8(19%)	0.39
Difficult/ Unable to Speak	3(9.1%)	4(9.5%)	0.94
Slurring of Speech	6(18.2%)	7(16.7%)	0.86
<b>Comorbidity</b>			
Diabetes mellitus	14(42.4%)	8(19%)	0.027
Hypertension	32(97%)	30(71.4%)	0.004
IHD	14(42.4%)	1(2.4%)	0.0005
CVA	5(15.2%)	2(4.8%)	0.125
AF	2(6.1%)	0(0%)	0.106
Others	7(21.1%)	4(9.5%)	0.156
In hospital mortality	5(15.2%)	5(11.9%)	0.68

Table-I. Comparison of variables of ICH.

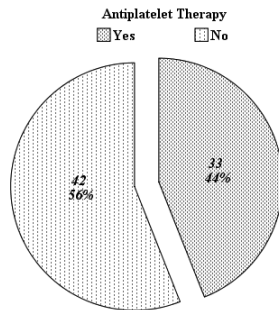


Figure-5 Frequency of ich in patients taking APT

Comorbid like DM, HTN and IHD were significant high in patients on APT and in hospital mortality was also not significant in patients on APT and not on APT In comparison of single and dual APT, significant difference were not observed in median age and other physiologic parameters. Similarly gender difference and mortality were not significant in patients with single and dual APT while Multiple APT was taking those cases who IHD and CVA comorbid as shown in Table-III.

Variables	Antiplatelet Therapy (APT)		P-Value
	Single APT (n=26)	Two APT (n=7)	
<b>Gender</b>			
Male	16(61.5%)	3(42.9%)	0.375
Female	10(38.5%)	4(57.1%)	
<b>Comorbidity</b>			
Diabetes mellitus	11(42.3%)	3(42.9%)	0.97
Hypertension	25(96.2%)	7(100%)	0.59
IHD	8(30.8%)	6(85.7%)	0.009*
CVA	2(7.2%)	3(42.9%)	0.021*
AF	1(3.8%)	1(3.8%)	0.30
Others	6(23.1%)	1(14.3%)	0.61
In hospital mortality	3(11.5%)	2(28.6%)	0.28

Table-III. Comparison of ICH patients based on APT therapies

	Median [IQR]	Min-Max
<b>Duration of Treatment (Months)</b>	12[24]	1-180
<b>Number of Antiplatelet Use</b>	<b>N</b>	<b>%</b>
1	26	78.8%
2	7	21.2%
<b>Drug</b>		
Asprin	24	72.7%
Asprin+Clopiogrel	7	21.2%
Clopiogrel	2	6.1%

Table-II. ICH patients taking APT

**DISCUSSION**

An annual incidence of stroke (common medical emergency) is between 180 and 300 per 100,000, and the leading cause of disability. It is the second common cause of mortality worldwide.<sup>14</sup> Three million deaths (and rising) in developing countries are due to stroke<sup>15</sup> and in Asians one of the major cause of mortality and morbidity.

The functional impairments causes of, with 20% of survivors requiring institutional care after three months and permanently disabled were 15%-30%.<sup>16</sup> In industrialized country, about 85-90% of strokes are secondary to cerebral infarction and ICH is 10-15%. But in Asian hemorrhagic stroke constitutes a high proportion. The incidence of hemorrhagic stroke in different Asian countries are: 33% in Malaysia, 26% in Indonesia and Singapore, 28% Taiwan, Thailand, Hong Kong, Philippines and Korea 30 % and India, ranges 35-40 %.<sup>17</sup> Pakistan has similar outcomes.<sup>18</sup> The portion of ischemic stroke diverse 55% to 70.1% in the regional studies and 60% to 84% in western. Most of the regional, South Asian and the eastern studies have 21% to 45% ICH while west is 10% to 20%.<sup>19,20</sup> In Pakistan studies revealed 31-40% cases of stroke is due to ICH and ischemic stroke are 60-69%.<sup>21,22</sup>

This study showed the average age of the patients'

59.97 ± 12.46 years, of which males were 57.33% and females were 42.67%. Regarding comorbidity, the most common cause was hypertension which was observed in 82.7% cases followed by diabetes mellitus 29.3%, CVA 9.3%. In Aziz MS<sup>3</sup> male to female ratio is 1.9:1, male 53(66.2%) and female 27 (33.8%) The age fluctuates between 50 to 80 years, and mean age of 63.75 years. From total 80 patients, 42 (52.5%) had ischemic stroke, hemorrhagic stroke 35 (43.75%) and 3 (3.75%) had subarachnoid hemorrhage.

The mortality rate is much higher than those patients not on anticoagulation i.e. 52 to 67%.<sup>5,6</sup> In this study overall in hospital mortality was observed in 13.33% (10/75) cases. While the study by Campbell on ICH patients found difference in mortality among two antiplatelets i.e. Clopidogrel to have an in hospital mortality of 28.6% compared to patients taking Aspirin 14.3%.<sup>9</sup> The Medline and Embase database in their systematic review found increased mortality but not a worse outcome in patients taking prior antiplatelet therapy.<sup>10</sup> Naedich et al demonstrated that increased platelet inhibition has been associated with increased ICH volume at 12 hours and poor outcome after 3 months of hemorrhage.<sup>11-13</sup>

In this study out of 75 ICH patients 44% (33/75) were taking antiplatelet therapy. Out of these 33 patients 78.8% (26/33) were taking single APT in which 72.7% (24/33) were taking Aspirin, 6.1% (2/33) were taking Clopiogrel and 21.2% (7/33) patients were taking more than two antiplatelets. In Creutzfeldt et al study<sup>7</sup> ICH patients of whom 121 (31.3%) were on APT. All but three, who were taking clopidogrel alone, were on aspirin (118/121), either alone (105/121) or in combination with clopidogrel (11/121) or extended release dipyridamole (2/121). Of the 121 patients on APT, 53 received PIT.

Patients on APT are elderly and with comorbidities conditions than those not on APT, identification of and adjustment for possible confounders was only done in a few.<sup>23,24</sup> Loss of association between APT and its outcome is adjustment for age and premorbid conditions<sup>23</sup>, in other study,

mortality was still increased in the patients taking after adjusting for age, hypertension and alcohol use.<sup>24</sup> In the other earlier studies,<sup>25-27</sup> it is possible that adjustment for other confounders In this study mean age was significantly high in patients those on antiplatelet therapy as compare to those who was not on APT (p=0.033).

While gender and systemic finding of patients were not significant on APT, those on APT. Comorbid like DM, HTN and IHD were significant high in patients on APT and in hospital mortality was also not significant in patients on APT. For stroke patients current treatments are relatively ineffective and are the real hope of reducing stroke morbidity and mortality in populations are risk factor interventions.<sup>28</sup> Stroke may be attributable to 50% of elevated blood pressure and the important modifiable risk factor is hypertension. The risk of stroke has been directly proportional to systolic and diastolic blood pressure elevation in men and women of all ages the strongest association being with systolic blood pressure. With each 10 mm of Hg rise in systolic blood pressure the risk of stroke is increased by 25% and diastolic blood pressure of more than 110 mm of Hg risk is 15 times more than of individual with less than 80 mm of Hg.<sup>29</sup> Stroke is about 3 or 4 times common in hypertensive patients and with the control of hypertension the risk reduced by 38%.<sup>30</sup>

## CONCLUSION

In this study overall in hospital mortality was observed in 13.33%. These study suggests there is only modestly increased mortality in patients taking pre-ICH APT, and little or no increase in poor functional outcomes there are a substantial number of ICH patients taking pre-ICH APT who could be at risk. The pre-ICH APT mortality is correlated, which can be improved by therapies to restore normal platelet function which is uncertain and to demonstrate needs comparatively large trials, given the modest increase in risk. For the reduction in morbidity related to APT-ICH Prevention of risk factor like HTN is most antonyms strategy.



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### AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Lal Shehbaz	Conceived, Concept design and definition of intellectual content, literature search, data acquisition.	
2	Shua Nasir	Did literature search and manuscript preparation did final layout and data entry.	
3	Abdul Naveed Khan	Did write up, manuscript preparation, final layout.	