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A STUDY ON EVALUATION OF THE ROLE OF PRE-EXISTING ANTIPLATELET THERAPY IN INTRACRANIAL HEMORRHAGE BY USING STANDARDIZED SCORES: PILOT STUDY

Dr. Malini Gopinath*[1], Krishnaja R.J.[2], Lekshmi Johnson Maithyli[2], Babitha M.[3]

[1]Senior Consultant (MD), Neurology (DM), Department of neurology, Cosmopolitan hospital, TVM, Thiruvananthapuram, Kerala.
[2]Doctor of Pharmacy Students, Sreekrishna College of Pharmacy and Research Centre , Thiruvananthapuram, Kerala.
[3]Assistant professor, Sreekrishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala.

*Corresponding Author: Dr. Malini Gopinath

Senior Consultant (MD), Neurology (DM), Department of neurology, Cosmopolitan hospital, TVM, Thiruvananthapuram, Kerala.

ABSTRACT

Background: Intra-cerebral haemorrhage (ICH) is defined as bleeding into the parenchyma of the brain. **Aim & Objective:** The purpose of the study was to evaluate the role of pre-existing anti-platelet therapy in causing and worsening of intracranial haemorrhage. **Materials and Methods:** Consecutive thirty patients of either sex more than 18 years of age with intracranial haemorrhage were taken and divided equally on the basis of their pre-existing anti-platelet therapy. In order to analyse the relationship between pre-existing anti-platelet use and occurrence as well as worsening of intracranial haemorrhage, a number of parameters including history of anti-platelet use*, GCS*, MRS*, ICH risk score*, S2TOP BLEED SCORE*, GOS*, etc., were collected and analysed properly. All statistical analysis was performed with SPSS and Minitab software. Result: The observed difference in risk of major bleeding defined by S2TOP BLEED score was 33.3% higher (95% confidence interval -1.6090 to 59.2923) in patients on pre-existing anti-platelet therapy. By statistical comparison of proportions, after analysing the severity at the admission time, ICH risk score, unfavourable functional outcome and mortality rate were found to be higher in patients on pre-treatment with anti-platelets. Conclusions: Based on the study, pre-treatment with anti-platelet agents is found to play a role in worsening or unfavourable outcome in patients with Intra-cranial haemorrhage.

KEYWORDS: Intracranial haemorrhage, GCS, mRS, S2TOP BLEED score, GOS, antiplatelets.

INTRODUCTION

Intra-cerebral hemorrhage (ICH) is defined as bleeding into the parenchyma of the brain which may further extend into ventricles. Intra-cerebral haemorrhage (ICH) is the most devastating and least treatable form of stroke causing severe disability among survivors. ICH is primarily intra-cerebral and less frequently subdural and subarachnoid and is associated as a lethal complication of anti-thrombotic therapy. Among the antithrombotic therapeutic regimens, anti-platelet therapy either single or dual anti-platelet agents may influence the risk of ICH. ICH occurs in 15 to 20% of all strokes. Compared to ischemic stroke, it more often results in death and increased disability.

Spontaneous non-traumatic intra-cerebral haemorrhage (ICH) is the second most prevalent subtype of stroke and is associated with high mortality and morbidity. Various clinical trials related to the medical and surgical manage-ment of ICH have been conducted to overcome its devastating clinical course. ICH can be localized in the different parts of the brain and large hematoma is accompanied with spreading of blood into ventricles. While traumatic ICH is by far the most common type of ICH, implying bleeding that occurs due to a known bleeding causes such as an arterio-venous malformation, cerebral aneurysm or tumor.

The most important risk factor is hypertension, which increases the risk of ICH by approximately four times. Improved hypertension control, reduces the incidence of intra-cerebral haemorrhage.

Many patients with Intracranial haemorrhage may either suffer from history of ischemic events or ischemic pathologies which frequently requires antithrombotic therapy. This is not surprising as intracranial haemorrhage (ICH), ischemic stroke and myocardial infarction (MI) have some shared risk factors, particularly increasing age and hypertension. Antithrombotic therapy is a cornerstone in secondary

stroke prevention or in patients with a cardioembolic stroke, cardiovascular disorders etc.

Patients who experience an intra-cerebral hemorrhage (ICH) while taking oral anticoagulants or anti-platelets tend to have larger hematomas and a worse prognosis compared with patients who are not on antithrombotic therapy. Recent investigations suggests that pretreatment with anti-platelet agents could also be associated with hematoma expansion, an increased mortality rate, and a poor functional outcome. However, those studies were hampered by relatively small numbers of patients, making it difficult to control for the effects of potential confounders. For instance, patients taking anti-platelet drugs were shown to be significantly older and to have a worse pre-hospital status than those without such medication. Antiplatelet therapy successfully reduces the number of serious vascular events. Despite its proven benefit, antiplatelet therapy may increases the risk of bleeding. More potent treatment strategies such as dual antiplatelet therapy increase this risk even further.

Therefore the use of antiplatelet medications following intracerebral haemorrhage (ICH) is usually perceived as being contraindicated because of the possibility of increased risk of further bleeding. Clinicians therefore are presented with a therapeutic dilemma whereby treating infers an increased risk of recurrent intracerebral haemorrhage, whereas not treating infers an increase of thrombotic complications. Despite the importance of this dilemma, there is very little guidance for prescribers as there is a lack of randomized and observational data addressing this issue. Prediction of bleeding risk based on patient characteristics may help physicians to balance benefits and risks of antiplatelet therapy for individual patients. Also, risk stratification may guide treatment decisions for other preventive strategies. Here we present data showing the apparent effects of antiplatelet pretreatment on mortality and unfavorable functional outcome in patients on Intra-cranial hemorrhage.

METHODS

This study was conducted to investigate the effect of preexisting antiplatelet therapy on severity, bleeding risk, ICH risk and functional outcome in patients with intracerebral hemorrhage (ICH). The study was conducted in Neurology Department of Cosmopolitan Hospital, Pattom, TVM, Kerala. The study was conducted for 2 months i.e. February 2018 to April 2018. A written informed consent will be taken from the parents or caregiver of patients with ICH satisfying the inclusion and exclusion criteria.

Inclusion Criteria
- ICH Patients of either sex more than 18 years of age.
- ICH patients with a measurable focal deficit.
- Patients on ICH with prior antiplatelet therapy (both single and dual APT).

- Patients on ICH but without prior antiplatelet therapy.
- All the patients were ambulatory and functionally independent before stroke.

Exclusion Criteria
- Patients with coma.
- Patients with severe co-existing terminal systemic illness.
- Radiological evidence of brain tumour.
- Patients who require surgery within 24 hours.
- Patients who had drug addiction related disorder.

A pilot study was conducted in a small population of 30 patients. A written informed consent was taken from patients or caregivers of ICH cases satisfying the inclusion and exclusion criteria. All parameters relevant to this analysis including age, International Classification of Diseases–based diagnosis, pretreatment with antiplatelet agents, severity at the time of admission(according to the Glasgow coma scale GCS, MRS), bleeding risk associated with antiplatelets (according to S2TOP BLEED), ICH risk score assessment and main outcome measures were mortality rate, functional status after discharge (GOS) were determined from case records and direct interview with the patients or caregivers. Data was collected by using a specially designed proforma and was analysed.

Analysis is done by comparing the scores of patients with and without pre-existing antiplatelets to establish the role of antiplatelet use and occurrence of ICH through a standardised risk scoring method. The data thus gathered was statistically analyzed by using SPSS (Statistical Package for Social Sciences). The study employed chi square test, correlations. P values indicate probability value.

RESULTS

Between February 2018 and April 2018, 30 patients with a final diagnosis of ICH were documented as 46.6%female and 53.4% male and the severity status according to the Glasgow coma scale was 73.3% in patients with prior antiplatelets which shows severe disability while only 33.3% of patients without prior antiplatelets shows severe disability at the time of admission. Another scale for assessing the severity index used here was modified rankin scale which shows 80% severe disability in patients with prior antiplatelets and only 26.6% severity shown by patients without prior antiplatelets. After comparing the ICH risk score, about 46.6% patients with prior antiplatelets shows high risk and only 27% of patients without prior antiplatelets showed high risk for ICH. The bleeding risk associated with antiplatelets defined by S2TOP BLEED score in patients with prior antiplatelets was found to be 67% and without prior antiplatelets was 33.3%.

The unfavorable functional outcome with prior antiplatelets defined by mortality was 20% in patients with prior antiplatelets and 6.6% in patients without prior antiplatelets and the recovery rate defined by GOS after hospital discharge was 53.3% in patients without prior antiplatelets and only 33.3% in patients with prior antiplatelets indicating higher recovery rate in patients who are not on anti-platelet therapy.

By descriptive statistical analysis of comparison of proportion of two sample of ICH patients (with and without prior antiplatelet therapy), pretreatment with antiplatelet agents was found to be significantly affecting the severity index, bleeding risk as well as unfavourable functional outcome and mortality rate.

Baseline Characteristics of 30 Patients With ICH

	Without prior antiplatelets	With prior antiplatelets
Age,		
>75	40%	66.66%
<75	60%	33.33%
sex, n (%)		
Male	33.33%	73.3%
Female	66.66%	26.6%
Heavy alcohol use, n (%)	26.6%	53.33%
Current smoker, n (%)	20%	40%
Trauma (n%)	60%	33.3%
Obesity (n%)	33.3%	33.3%
Seizure	20%	26.6%
Hypertension, n (%)	80%	100%
Hypercholesterolemia, n (%)	13.3%	73.3%
Diabetes, n (%)	33.3%	53.3%
Prior stroke, n (%)	0%	60%
History of cardiovascular disease, n (%)	0%	73.3%
Antiplatelet regimen, n (%)		
Aspirin		26.6%
Clopidogrel	Nil	20%
Aspirin + dipyridamole		0%
Aspirin +clopidogrel		53.3%
Severity index		
mRS at admission	26.6%(severity)	80%(severity)
GCS	33.3%(severity)	73.3%(severity)
ICH risk score		
ICH	27%(high risk)	46.6%(high risk)
Bleeding risk assessment		
S2TOP BLEED	33.3%(high)	67%(high risk)
Functional outcome status		
GOS	53.3%(recovery)	33.3%(recovery)
Unfavorable outcome		
Death	6.6%	20%

DISCUSSION

Many patients with Intracranial hemorrhage may either suffer from history of ischemic events or ischemic pathologies which frequently requires antiplatelet therapy. Long term use of such blood thinners may increase the bleeding risk and in some cases this will results in producing intracranial haemorrhage (ICH). In this study we mainly aims to identify the role of pre-treatment with antiplatelets in disease prognosis, severity index and unfavourable outcome / mortality in ICH patients. For that purpose we compared the two group of ICH patients dividing equally with those on pretreatment with antiplatelets and another sample without pretreatment with antiplatelets.

A. Comparison Of Severity Index
For comparing the severity index of two sample of ICH patients we used modified rankin scale (MRS) and glasgow coma scale (GCS) at the time of admission.

1) Modified Rankin Scale (mRS)
The modified Rankin Scale (mRS) is a clinician-reported measure of global disability that has been widely applied for evaluating severity as well as recovery associated with brain damage. The scale consists of well-defined and easily understood grades that describe the range of global disability.[1] When properly administered, the mRS exhibits a strong relationship with clinical measurements of disease severity in addition to other disability and outcome end points. As intra-cerebral

hemorrhage is a type of hemorrhagic stroke, we used this scale here to assess the severity of two samples of intra cerebral hemorrhagic patients with and without pretreatments with anti-platelets inorder to find out the sample showing high severity index.

2) Glasgow Coma Scale
The Glasgow Coma Scale (GCS) was devised to assess injury severity after severe brain damage. Assessment is mainly done by allotting numbers to each responses and overall score allows to assess the overall severity of brain injury. Outcome correlates well with the early GCS both in head injuries and other intensive care patients. When early sedation and ventilation after head injury, makes GCS assessment difficult, the motor score is often available and is a useful index of injury severity. The GCS also facilitates monitoring in the early stages after injury, allowing rapid detection of complications. Even among mild injuries (GCS 13 ± 15) the scale can discriminate between those more or less likely to have detectable brain damage and to be at risk of complications.

Analysis and Interpretation of Data for Severity Index

➢ **mRS At Admission**
After analysing the statistical data of comparative proportions, the modified rankin scale (MRS) shows 80% severe disability in patients with prior anti-platelets and only 26.6% shows severe disability in patients without prior anti-platelets. This data is suggestive of an increased severity index in intra-cranial hemorrhagic patients who are on pre-existing anti-platelet therapy. The result is significant at p value <0.05.

Severity Index Statistics

| Difference	53.4%
95% CI	17.7119 to 73.7867
Chi-squared	8.306
DF	1
Significance level	P= 0.0040
Z value	2.65207
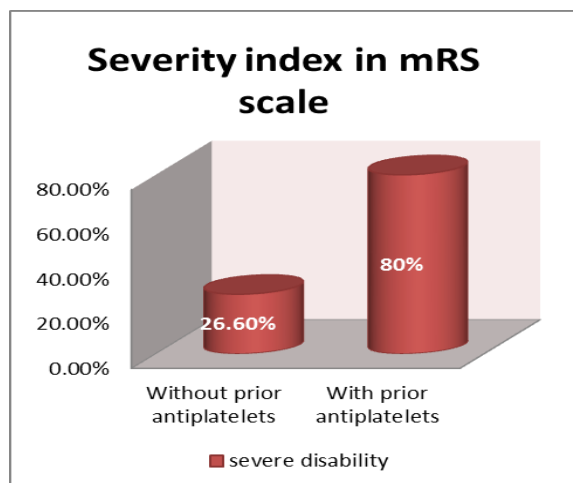
MRS Scale
GCS at Admission
After analysing the statistical data of comparative proportions, the glasgow coma scale (GCS) shows 73.3% severe disability in patients with prior anti-platelets and only 33.3% shows severe disability in patients without prior anti-platelets. This data is also suggesting of an increased severity index in intra-cranial hemorrhagic patients who are on pre-existing anti-platelet therapy. The result is significant at p value <0.05.

Severity Index Statistics

Difference	40%
95% CI	4.4750 to 64.0490
Chi-squared	4.660
DF	1
Significance level	P= 0.0309
Z value	1.86773

GCS Scale
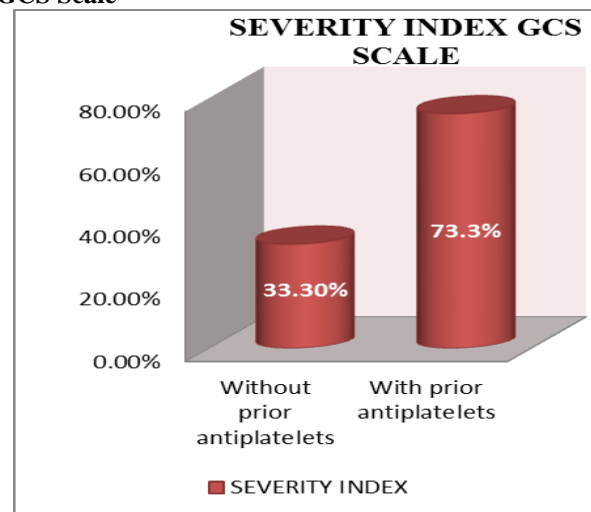
B) Comparison of ICH Risk and Bleeding Risk
For comparing the risk of ICH as well as the bleeding risk of two samples of ICH patients we used ICH risk score and S2TOP BLEED score at the time of admission.

1) ICH risk score
The ICH Score is a risk stratification scale was developed with weighting of independent predictors based on strength of association. Factors independently associated with 30-day mortality were Glasgow Coma Scale score (P<0.001), age $>/=80$ years (P=0.001), infratentorial origin of ICH (P=0.03), ICH volume (P=0.047), and presence of intraventricular hemorrhage (P=0.052). The ICH Score was the sum of individual points assigned as follows: GCS score 3 to 4 (=2 points), 5 to 12 (=1), 13 to 15 (=0); age $>/=80$ years yes (=1), no (=0); infratentorial origin yes (=1), no (=0); ICH volume $>/=30$ cm(3) (=1), <30 cm(3) (=0); and intraventricular hemorrhage yes (=1), no (=0). The ICH Score is a simple clinical grading scale that allows risk stratification on presentation with ICH. The use of a scale such as the

ICH Score could improve standardization of clinical treatment protocols and clinical research studies in ICH.[5] In our study, we compared two samples of ICH patients for identify the group with high risk for ICH. The result is significant at p value <0.05.

2) S2TOP BLEED Score

Recently, the S2TOP-BLEED score was developed to predict risk of major bleeding in patients with a TIA or ischemic stroke on antiplatelet agents. Calibration over time was assessed across risk groups that were predefined as low risk (0– 10 points on the S2TOP-BLEED score), medium risk (11–15 points), and high risk (>15 points). 6 Model performance was also assessed separately by severity of bleeding (non major, and life-threatening, or fatal) and by site of bleeding (intracranial, upper GI, lower GI, epistaxis, genitourinary, or other).[6] We performed a sensitivity analysis aiming to investigate whether there is a chance for bleeding risk in the intra-cranial hemorrhagic patients who are on pre-treatment with anti-platelets by comparing with intracranial hemorrhagic patients who are not on antiplatelet therapy by allotting proper scores in S2TOP-BLEED scale.

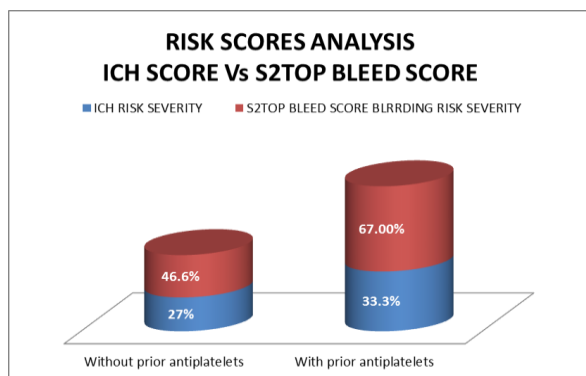### Analysis and interpretation of data- risk assessment Ich risk score interpretation

After analysing the statistical data of comparative proportions, the ICH risk score shows 46.6% severe disability in patients with prior anti-platelets and only 27% shows severe disability in patients without prior anti-platelets. This data is indicative of an increased mortality risk in intra-cranial hemorrhagic patients who are on pre-existing anti-platelet therapy.

S2top Bleed Score Interpretation

After analysing the statistical data of comparative proportions, the STOP BLEED risk score for assessing bleeding risk shows 67% severe disability in patients with prior anti-platelets and only 33.3% shows severe disability in patients without prior anti-platelets.This data is suggestive of an increased bleeding risk in intra-cranial hemorrhagic patients who are on pre-existing anti-platelet therapy.

Risk Score Statistics Ich Score S2top Bleed Score

Difference	19.6%	Difference	33.3%
95% CI	-13.8064 to 47.7479	95% CI	-1.6090 to 59.2923
Chi-squared	1.198	Chi-squared	3.294
DF	1	DF	1
Significance level	P= 0.2738	Significance level	P= 0.0696
Z value	0.60136	Z value	1.4787

RISK SCORES ANALYSIS
ICH SCORE Vs S2TOP BLEED SCORE

as a tool for assessing the nature of outcome showed by two sample population including the patients with and without prior anti-platelet therapy and thereby investigating the role of anti-platelet therapy in worsening of functional outcome in intra-cranial hemorrhagic patients.

C) Comparison of Outcome in Two Samples
1) Glasgow Outcome Scale

The GLASGOW OUTCOME SCALE (GOS) was devised to provide an overview of outcome and mainly to focus on social recovery. The GOS developed by several national bodies as the outcome measure for major trauma and for head injury. The enduring appeal of the GOS is linked to its simplicity, short administration time, reliability and validity, stability, flexibility of administration. These benefits apply to other derivatives of the scale, including the Glasgow Outcome at Discharge Scale (GODS). Since the initial development of the GOS, there has been an increasing focus on the multidimensional nature of outcome after head injury and functional outcome. We here used GOS

Analysis and Interpretation of Data- Recovery Rate Glasgow Outcome Scale Interpretation

After analysing the statistical data of comparative proportions, the GOS for assessing recovery rate shows 53.3% recovery rate in patients without prior anti-platelets and only 33.3% recovery is shown by patients with prior anti-platelets. This data is indicative of an increased recovery rate in sample population without prior anti-platelets when compared to intra-cranial hemorrhagic patients who are on pre-existing anti-platelet therapy.

FULL RECOVERY RATE ACCORDING TO GOS
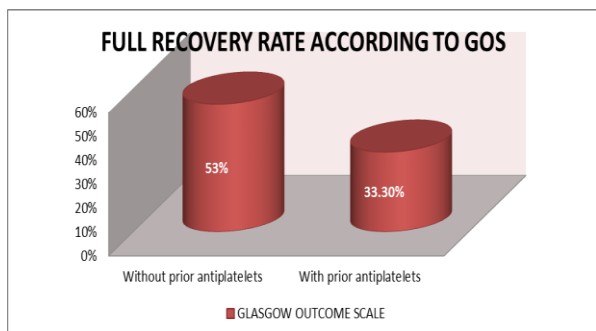
| Difference	20%
95% CI	-14.0809 to 48.4138
Chi-squared	1.181
DF	1
Significance level	P= 0.2771
Z value	0.59148

Mortality Rate According To GOS Interpretation
After analysing the statistical data of comparative proportions, the GOS for assessing mortality rate shows 20% mortality is shown in patients with prior anti-platelets and only 6.6% mortality is shown by patients without prior anti-platelets. This data is illustrates an increased mortality risk in intra-cranial hemorrhagic patients who are on pre-existing anti-platelet therapy.

mortality rate according to GOS
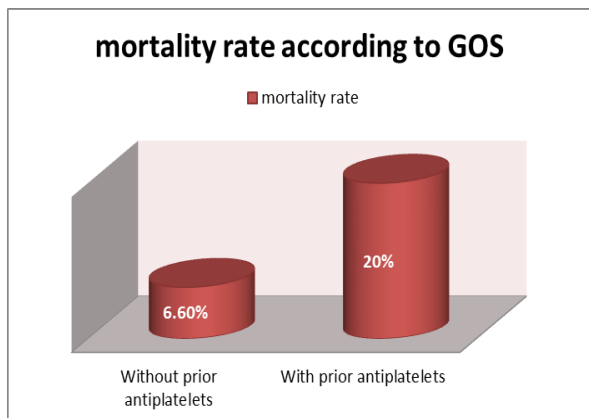
Comparison of Case Progression from the Day of Admission to Discharge – An Overview
We compared two samples of intra-cranial hemorrhagic patients with and without prior anti-platelet therapy by analysing their severity index, intra-cranial hemorrhagic risk, bleeding risk along with the nature of functional outcome shown by them. We simply illustrate below the nature of the disease progression shown by both samples from the time of admission till discharge. We comprehensively concludes the result obtained from various scores for assessing the severity, risk as well as functional outcome to identify whether there is role for pre-existing anti-platetelet therapy in producing intra-cranial hemorrhage or in the worsening of functional outcome and the mortality risk.

CASE PROGRESSION- AN OVERVIEW
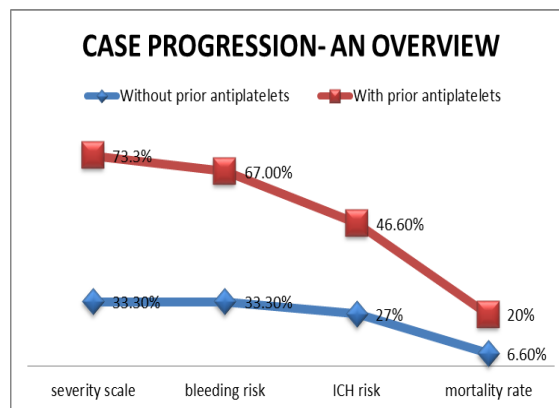
CONCLUSION
For the comparative analysis to investigate the risk of pre-existing anti-platelet therapy in two sample population (with and without pre-treatment with antiplatelets) of intra-cranial hemorrhagic patients, we utilised standard scores including Modified rankin scales (mRS), Glasgow coma scale(GCS), ICH risk score, S2TOP BLEED score and Glasgow Outcome Scale (GOS). Inorder to identify the above stated risk, we used these scores as tools and assessed the severity at the time of admission (mRS, GCS), the risk (ICH risk score), the bleeding risk due to antiplatelets (S2TOP BLEED score), unfavourable functional outcome and mortality (GOS) in two samples of intra-cranial hemorrhagic patients. After the analysis we identified an increased bleeding risk along with worsening and producing unfavourable outcome in the group who are on pre-existing anti-platelet therapy. And thus we conclude that there is a role for pre-existing antiplatelet therapy in worsening and producing unfavourable outcome after intra-cranial hemorrhage.

However some studies take the view that there is no increased risk with antiplatelet medicines following intracerebral haemorrhage .Which means the area is full of uncertainties, and owing to lack of clear evidence, it remains not possible to manage the dilemmas with full confidence This issue still demands answer to the questions of clinical importance like 1) should antiplatelets be continued following ICH? 2) timing of starting antiplatelet following ICH 3)which antiplatelet offers low risk for hemorrhagic recurrence and what dose? etc.. In our study we identified an increased risk in worsening of intra cranial haemorrhage which may be associated with pre-existing anti-platelet therapy. The continuation of antiplatelet therapy following intracranial haemorrhage for treatment of their ischemic pathologies, more randomised control trials and clinical studies are required for guiding the prescribers regarding the safe and effective use of anti-thrombotic regimen to make an authenticated advise to patients.

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CONFLICT OF INTEREST

None.

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