The Clinical Profile of Patients with Intracerebral Hemorrhage After Receiving Acute Coronary Syndrome Regimen in a Tertiary Hospital: A Case Series

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ABSTRACT

Coronary heart disease, which includes acute coronary syndromes (ACS) is a major cause of death and morbidity. Treatment for this condition includes dual anti-platelet treatment combined with an anti-coagulant and an anti-dyslipidemic. Bleeding complications may occur and one fatal adverse event is intracerebral hemorrhage (ICH). ACS cases in a tertiary hospital for the years 2014-2018 showed that there were 7 patients who presented with symptomatic ICH after treatment administration that accounts for 0.01% of a total of 1,097 patients. These patients were over the age of 50, but with no sex predilection. Common comorbidities were hypertension and malignancy. All patients presented with acute onset neurologic deficits within 1-4 days after administration of ACS regimen, with ICH scores of 3-4 signifying a high mortality rate of 72-90%. 6 out 7 patients had significant volume of ICH with mass effects, and 1 with subarachnoid hemorrhage. This lead to poor outcome in all patients with 6 out of 7 mortalities and 1 left with substantial disability. It was found that given the total number of patients administered with the said treatment, there is a low incidence of ICH.

Keywords: *Bleeding complications of dual antiplatelet therapy; Intracerebral hemorrhage after Acute Coronary Syndrome; ICH and ACS; ICH and Myocardial Infarction; Neurologic complications after Dual Anti-platelet Therapy*

INTRODUCTION

Coronary heart disease, which includes acute coronary syndromes (ACS) is a major cause of death and morbidity[1] According to the latest WHO data published in 2017 Coronary Heart Disease Deaths in Philippines reached 122,950 or 19.86% of total deaths, indicating the level of disease burden in the country.[2] Management include dual antiplatelets, anticoagulant, and an anti-dyslipidemic. This includes aspirin (150-300mg loading dose) and a P2Y12 inhibitor such as ticagrelor (loading dose of 180mg) or clopidogrel (300mg loading dose) combined with an anti-coagulant (loading dose of 70-100U/kg of Unfractioned Heparin).[3] In a Meta Analysis done by Mahaffey in 2015, incidence, predictors, and outcomes of Inracerebral Hemorrhage (ICH) in 4 contemporary anti-thrombotic trials for ACS were determined and results showed that only 0.4% of the selected population developed ICH. Independent predictors of ICH were older age, prior stroke/transient ischemic attack, higher systolic blood pressure; HR per 10 mm Hg increase, larger number of antithrombotic agents, were fatal.[4]

This study aims to identify the clinical profile of patients with ICH after receiving ACS regimen. Its significance would be determining the possible risk factors that

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would cause an adverse outcome for a life-saving treatment regimen.

METHODOLOGY

Study Design

This is a retrospective case series done in a single private tertiary hospital.

Population and Sample

Chart review of patients who were admitted for ACS during the period of January 2014- December 2018 and developed ICH after being administered with ACS regimen. Patients excluded were those that had a Cerebrovascular Infarct initially and had hemorrhagic conversion post ACS regimen.

DISCUSSION

During the collection and review of cases, there were 1,097 cases of ACS either Non-ST Elevated Myocardial Infarction (NSTEMI) or ST-Elevated Myocardial Infarction (STEMI). Among those are 12 patients who developed ICH after receiving ACS regimen, however 5 cases were excluded due either presenting as an ischemic stroke with subsequent hemorrhagic conversion, or with an existing ischemic stroke prior to admission. The remaining 7cases were admitted due to symptoms related to ACS (i.e. shortness of breath, chest pain) and after receiving ACS regimen would then develop new onset neurologic deficits.

Case 1

Patient is a 62 year old male, hypertensive and with no vices, coming in due to chest pain. He had elevated cardiac enzymes, was diagnosed as ACS-NSTEMI and received ACS regimen (aspirin 80mg/tab x 4; ticagrelor 90mg/tab x 2, enoxaparin 0.6ml SC; atorvastatin 80mg/tab). On the second hospital day, the patient was referred due to unresponsiveness and was found to be Glasgow coma score (GCS) of 5 (E1V1M3), with elevated blood pressure (BP) of 200/100. Plain Cranial Computed Tomography Scan was done which showed ICH on the left cerebral hemisphere amounting to 121ml, with an ICH score of 3. Patient expired on the fourth hospital day due to brain herniation syndrome.

Case 2

Patient is a 66 year old female, hypertensive and with hypothyroidism, came in for chest heaviness. Workup done showed elevated cardiac enzymes and was treated as a case of ACS-NSTEMI (aspirin 80mg/tab x 4; ticagrelor 90mg/tab x 2, enoxaparin 0.6ml SC; atorvastatin 80mg/tab). No neurologic deficits then until the first hospital day where she was found to have decreased sensorium and left sided weakness. Plain Cranial CT Scan was done showed ICH on the right cerebral hemisphere amounting to 84ml. Patient expired on the third hospital day due to brain herniation syndrome.

Case 3

Patient is a 67 year old male, known hypertensive and with Melanoma, came in due to chest pain. ECG done at the ER showed left anterior fascicular block. He was treated as a case of ACS-NSTEMI and given ACS regimen (aspirin 80mg/tab x 4; clopidogrel 75mg/tab x 4; fondaparinux 2.5ml SC; atorvastatin 80mg/tab). On the same day, patient suffered a fall due to sudden onset one sided weakness. Plain Cranial CT Scan showed ICH on the right frontal area amounting to 91ml associated with mass effects. Patient then underwent evacuation of hematoma, with no improvement of neurologic status He expired on the fourth hospital day.

Case 4

Patient is a 64 year old female with no known comorbidities came in due to epigastric pain. Workup was done and revealed elevated cardiac enzymes, hence was treated as ACS-NSTEMI and given ACS regimen (aspirin 80mg/tab x 4; clopidogrel

75mg/tab x 4; enoxaparin 0.6ml SC; atorvastatin 80mg/tab). She then developed bifrontal headaches and progressed to decreased sensorium. Plain Cranial CT Scan showed ICH amounting to 54ml with an ICH score of 3. After which, she was referred to neurosurgery service and underwent evacuation of hematoma. She had residuals of left sided weakness up until her discharge.

Case 5

Patient is a 57 year old male, known to have Chronic Myelogenous Leukemia, came in due to chest pain. ECG showed sinus tachycardia but with elevated cardiac enzymes. He was then treated as ACS-NSTEMI and given ACS regimen (Aspirin 80mg/tab x 4; Clopidogrel 75mg/tab x 4; Enoxaparin 0.6ml SC; Atorvastatin 80mg/tab). Patient then had new onset focal weakness and decrease in sensorium. Plain Cranial CT Scan done showed ICH amounting to 177ml. No surgical interventions were done and patient worsened to GCS 3. He then expired on the third hospital day due to brain herniation syndrome.

Case 6

Patient is an 83 year old female, hypertensive and without vices. She was brought to the hospital due to dizziness, but her workup showed elevated cardiac enzymes, hence she was given ACS regimen (aspirin 80mg/tab x 4; clopidogrel 75mg/tab x 4; enoxaparin 0.6ml SC; atorvastatin 80mg/tab). Patient developed subarachnoid hemorrhage as seen in a Cranial CT Scan a day after being loaded with ACS regimen causing decreased sensorium and prolonged intubation. Case was furthermore complicated by the presence of pneumonia. Palliative measures were done, however, patient expired after 30 hospital days.

Case 7

Patient is an 86 year old male, known with hypertension, chronic kidney disease, hypothyroidism was brought in due to difficulty of breathing. He was admitted and managed as a case of Pneumonia with Pleural Effusion and Chronic Kidney Disease leading to the initiation of hemodialysis and prolonged confinement. During his 38th hospital day, the patient had recurrence of dyspnea and workup showed elevated cardiac enzymes, hence treated as ACS-NSTEMI and given ACS regimen (Aspirin 80mg/tab x 4; Clopidogrel 75mg/tab x 4; Enoxaparin 0.6ml SC; Atorvastatin 80mg/tab). In 4 days, the patient then was unresponsive and with elevated BP of 180/100, and a Cranial CT Scan done showed ICH on the right thalamus amounting to 24ml but with intraventricular extension and severe hydrocephalus. Patient expired the day after due to brain herniation syndrome.

In this case series, all patients were found to be above the age of 50 years old, but without any sex predilection. Out of the 7 cases, 4 were hypertensive and 2 of them had known malignancies in remission. All 7 of them were cases of NSTEMI and loaded with 4 tablets of Aspirin 80mg, 1 tablet of Atorvastatin 80mg, but differed in the choice of the second anti-thrombotic and anti-coagulant. Only 1 case underwent percutaneous coronary angiogram. Coagulation studies done on all these patients did not exhibit any signs for bleeding tendencies. All cases presented with acute onset neurologic deficits associated with elevated BP in about 1-4 days after being given the ACS regimen, and almost all had significant bleed with ICH scores 3 and above which already signifies high mortality rates of 72-90% and were poor candidates for neurosurgical intervention. Only 1 patient had an evacuation of hematoma done but still left with substantial disability upon discharge.

A common factor among all cases were the indication of poor prognosis once the adverse outcome has occurred. 6 out of 7 cases expired due to direct effects of ICH. Also, the onset of ICH after the time of treatment were noted to be within 1-4 days, and progression of neurologic deficits were observed to be rapid. Incidentally, during the review of possible

cases for this paper, those excluded were patients with ischemic strokes and developing hemorrhagic conversion days after being given ACS regimen.

Accounting all the included cases over the total number of patients treated with ACS regimen in the years 2014-2018 and admitted in the Acute Stroke Unit or Intensive Care Unit due to Symptomatic ICH (7/1097 = 0.01%) seems insignificant to question the safety of the treatment. Giving dual antiplatelets combined with an anticoagulant still remains safe as the standard of treatment for ACS. But for those that do develop the adverse outcome, it can be expected that it renders a poor outcome for the patient.

SUMMARY

It was found that given the total number of patients administered ACS regimen, there is a low incidence of ICH. However, it has shown to be a poor prognostic sign owing to the high level of mortality among those who developed this adverse event.

LIMITATIONS AND RECOMMENDATIONS

Excluded cases such as those with ischemic infarct at onset with hemorrhagic conversion after ACS regimen can also be included in the study as another variable in risk assessment.

CONFLICTS OF INTEREST

There were no conflicts of interest in the making of this study

SOURCES OF FUNDING

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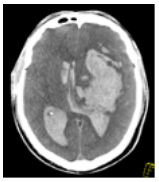
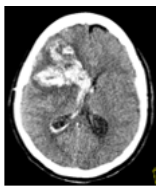
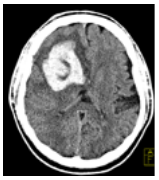
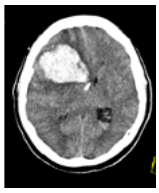
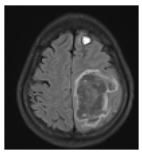
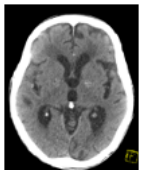
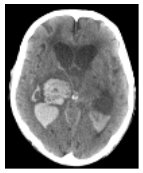
Table 1. Clinical Profile, ACS classification, and Treatment Regimen of Cases 1-6

Case	Age	Sex	Comorbidities	ACS[a] Class	ECG[b]	Loading ACS Regimen	Total Anti-Thrombotics/ Coagulants Received*	Labs	s/p PCI[c]
1	62	M	Hypertension	NSTE MI[d]	Sinus bradycardia; Non-specific T wave changes	Aspirin 80mg/tab x 4; Ticagrelor 90mg/ tab x 2, Enoxaparin 0.6ml SC; Atorvastatin 80mg/ tab	Aspirin 80mg/tab x 5 Ticagrelor 90mg/tab x 4 Enoxaparin 0.6cc	CBG[e]: 109 Trop I: 66.1 CK-MB[f]: 14 PT[g]: 14.1 PTT[h]: 39.0	No
2	66	F	Hypertension Hypothyroidism	NSTE MI	Sinus bradycardia	Aspirin 80mg/tab x 4; Ticagrelor 90mg/ tab x 2, Enoxaparin 0.6ml SC; Atorvastatin 80mg/ tab	Aspirin 80mg/tab x 8 Ticagrelor 90mg/tab x 6 Enoxaparin 0.6cc x 8	CBG: 139 Trop I: 39 CK-MB: 56 PT: 13.7 PTT: 30.1 CT[i]: 8 mins Fibrinogen: 417	No
3	67	M	Hypertension, Melanoma	NSTE MI	Sinus bradycardia; Left anterior fascicular block; ST and T wave abnormalities	Aspirin 80mg/tab x 4; Clopidogrel 75mg/tab x 4; Fondaparinux 2.5ml SC; Atorvastatin 80mg/tab	Aspirin 80mg/tab x 7 Clopidogrel 75mg/ tab x 7 Fondaparinux 2.5cc x 2 Enoxaparin 0.8cc	CBG: 122 Trop I: 10.1 CK-MB: 21 PT: 13.3 PTT: 28.8	No
4	64	F	None	NSTE MI	Sinus rhythm with premature atrial contractions	Aspirin 80mg/tab x 4; Clopidogrel 75mg/tab x 4; Enoxaparin 0.6ml SC; Atorvastatin 80mg/tab	Aspirin 80mg/tab x 5 Clopidogrel 75mg/ tab x5 Enoxaparin 0.6cc x 2	CBG: 100 Trop I: 114 CK-MB: 18 PT: 13.1 PTT: 25.5	Yes
5	57	M	Chronic Myelogenous Leukemia s/p Stem Cell Therapy	NSTE MI	Atrial fibrillation in rapid ventricular response; ST depression	Aspirin 80mg/tab x 4; Clopidogrel 75mg/tab x 4; Enoxaparin 0.6ml SC; Atorvastatin 80mg/tab	Aspirin 80mg/tab x 5 Clopidogrel 75mg/ tab x5 Enoxaparin 0.6cc x 2	CBG: 101 Trop I: 205 PT: 18 PTT: 36.6	No
6	83	F	None	NSTE MI	ST wave depression	Aspirin 80mg/tab x 4; Clopidogrel 75mg/tab x 4; Enoxaparin 0.6ml SC; Atorvastatin 80mg/tab	Aspirin 80mg/tab x 5 Clopidogrel 75mg/ tab x5 Enoxaparin 0.6cc x 2	CBG: 133 Trop I: 127 CK-MB: 238 PT: 13.3	No
7	86	M	Hypertension Chronic Kidney Disease Coronary Artery Disease Hypothyroidism	NSTE MI	Sinus rhythm with non-specific T wave changes	Aspirin 80mg/tab x 4; Clopidogrel 75mg/tab x 4; Enoxaparin 0.2ml SC; Atorvastatin 80mg/tab	Aspirin 80mg/tab x 8 Clopidogrel 75mg/ tab x8 Enoxaparin 0.2cc x 8	Crea: 3.31 PT: 13.1 CK-MB: 42 Trop I: 205	No

**Total of anti-thrombotics/anti-coagulants received prior to onset of symptomatic ICH*
a – Acute Coronary Syndrome; b – Electrocardiogram; c – Percutaneous Coronary Intervention; d – Non-ST Elevated Myocardial Infarction; e – Capillary Blood Glucose; f – Creatine Kinase –MB; g – Prothrombin Time; h – Partial Thromboplastin Time

Table 2. Clinical Course of Cases 1-6

Case	Ictus of ICH[a*]	BP[b]	ICH Volume/Location	CT Scan	ICH Score	Neurosurgical Intervention	Outcome
1	Day 1	200/100	121ml Left cerebral hemisphere; midline shift of 1.5cm		3	No	Mortality
2	Day 4	150/80	84ml Right frontal lobe; midline shift of 0.7cm		4	No	Mortality
3	Day 3	180/80	91ml Right frontotemporal area		3	Yes	Mortality
4	Day 1	210/70	53ml Right cerebral hemisphere; midline shift of 1.2cm		3	Yes	MRS[c]4
5	Day 1	140/90	177ml Right cerebral hemisphere		4	No	Mortality
6	Day 1	211/100	Subarachnoid hemorrhage		N/A	No	Mortality
7	Day 4	180/80	24ml Right thalamus with intraventricular extension and severe hydrocephalus		4	No	Mortality

a – Intracerebral hemorrhage after receiving treatment; b – Blood pressure; c – Modified Rankin Score*