INTRODUCTION

Acute myocardial infarction is the most severe manifestation of coronary artery disease, which causes more than 2.4 million deaths in the USA, more than 4 million deaths in Europe and northern Asia, and more than a third of deaths in developed nations annually ***(Yeh et al., 2010 and Nichols et al., 2014).*** Primary PCI is the treatment of choice for acute coronary syndrome with STEMI ***(Saeed et al., 2012).***

CIN is an iatrogenic disease occurring after the intravascular injection of radiographic contrast media ***(Bartels et al., 1954).*** In 2004, CIN was indicated as the third leading cause of hospital-acquired acute renal failure (ARF) being responsible for 12% of all cases of ARF in hospital ***(Mussap & Merlini, 2014).*** In a cohort study, CIN incidence in STEMI patients undergoing primary PCI was 19.8% which was significantly higher than the known CIN incidence in patients undergoing elective PCI (1-3%) ***(Mehran & Nikolsky, 2006 and Koowattanatianchai et al., 2019).***

CIN is defined by renal function impairment after IV contrast as mirrored by an absolute increase by 0.5mg/dL (or greater) or relative increase by 25% (or greater) of baseline serum creatinine over 48 hours or, better, by a decrease in the estimated glomerular filtration rate (eGFR) to a value ≤ 60ml/min. eGFR is the creatinine clearance calculated using the modification of diet in renal disease (MDRD) formula ***(Levey et***

al., 1999) or the chronic kidney disease epidemiology collaboration (CKD-EPI) equation ***(Levey et al., 2009),*** or the very simple Cockcroft-Gault formula ***(Cockcroft & Gault, 1976).*** CIN occurs within 24-72 hours of administration of IV contrast ***(Andreucci et al., 2014-a).***

Oxidative stress, leading to increase in reactive oxygen species, with resultant inflammatory response, is known to play a role in pathogenesis of CIN ***(Heyman et al., 2010).***

Colchicine is an inexpensive, orally administered, potent anti-inflammatory medication that was initially extracted from the autumn crocus plant and has been used for centuries. Its mechanism of action is through the inhibition of tubulin polymerization and microtubule generation and, possibly, effects on cellular adhesion molecules, inflammatory chemokines, and the inflammasome ***(Perico et al., 1996; Ravelli et al., 2004 and Pope & Tschopp, 2007).*** This anti-inflammatory effect of colchicine has been recently shown to improve cardiovascular outcomes in patients with STEMI, at daily dose of 0.5mg ***(Tardif et al., 2019).***

Aim of the Work

The aim of this work is to study the efficacy of colchicine administration as a preventive tool for CIN in patients with STEMI undergoing primary PCI.

Chapter 1

MYOCARDIAL INFARCTION ST ELEVATION (STEMI)

Introduction

Myocardial infarction (MI) is a clinical entity involving myocardial ischemia that manifests with ECG changes and chest pain ***(Wilson, 1994).*** The current 2018 clinical definition of MI is based on the confirmation of the myocardial ischemic injury with abnormal cardiac biomarkers ***(Thygesen et al., 2018).*** An acute ST-elevation myocardial infarction (STEMI) entails a transmural myocardial ischemia that results in myocardial injury or necrosis ***(Alpert et al., 2000).***

Etiology

An ST-elevation myocardial infarction occurs from occlusion of one or more of the coronary arteries that supply the heart with blood. The cause of this abrupt disruption of blood flow is a result of an obstructing thrombus on top of plaque rupture, erosion, fissuring or dissection of coronary arteries. Dyslipidaemia, diabetes mellitus, hypertension, smoking and family history of coronary artery disease are the major risk factors for STEMI ***(Canto et al, 2011 and Hartikainen et al., 2020).***

Myocardial infarction can be classified according to **Mozaffarian et al. (2016)** from Type 1 to Type 5 MI based on the etiology and pathogenesis. Type 1 MI is due to acute coronary atherothrombotic myocardial injury with plaque rupture. Most patients with STEMI and many with non-ST-segment elevation MI (NSTEMI) belongs to this type. Type 2 MI, with demand-supply mismatch resulting in myocardial ischemia, is the most common encountered type. This mechanism can be due to presence of a fixed stable coronary obstruction, tachycardia, hypoxia or stress. However, the presence of fixed coronary obstruction is not necessary. Other possible mechanisms are coronary vasospasm, coronary embolus, and spontaneous coronary artery dissection (SCAD). Sudden cardiac death patients who succumb before any troponin elevation represent Type 3 MI. Types 4 and 5 MIs are related to coronary revascularization procedures like Percutaneous Coronary Intervention (PCI) or Coronary artery Bypass Grating (CABG) ***(Mozaffarian et al., 2016).***

Epidemiology

In the United States, the estimated annual incidence of MI is 550,000 new and 200,000 recurrent patients. In 2013, a fatal MI was diagnosed in 116,793 persons in the United States with 57% occurring in men and 43% in women. The average age of incidence of a first MI is 65.1 years for men and 72 years for women. The ST-elevation myocardial infarction represents 38% of acute coronary syndrome ***(Kolodgie et al., 2001).***

According to the latest WHO data published in 2018 Coronary Heart Disease Deaths in Egypt reached 163,171 or 29.38% of total deaths ***(WHO, 2018).***

Pathophysiology

For an acute thrombotic coronary event to cause ST-segment elevation on a surface ECG, there should be a complete and persistent occlusion of blood flow. Sudden onset plaque rupture can occur on top of Coronary atherosclerosis in the presence of high-risk thin cap fibroatheroma (TCFA) ***(Scharf, 2018).*** This results in changes in vascular endothelium resulting in cascade of platelet stimulation including adhesion, activation and aggregation resulting in thrombus formation ***(Reimer and Jennings, 1979).***

In animal models, coronary artery occlusion shows a "wave-front" of myocardial injury spreading from the sub-endocardial myocardium to the sub-epicardial myocardium. This results in a transmural infarction that appears as an ST elevation on surface ECG. Sudden onset acute ischemia results in severe microvascular dysfunction. Myocardial damage occurs as soon as the blood flow is interrupted which makes timely management essential ***(Amsterdam et al., 2014).***

History-Taking and Physical Examination

Prior to performing an ECG and collecting troponins the initial history and physical examination provide the only clues

that lead to a diagnosis of myocardial infarction. Information should be collected about the characteristics of the pain and associated symptoms, risk factors or history of cardiovascular disease, and recent drug therapy ***(Torpy et al., 2009).*** Age, gender, family history of premature coronary artery disease, tobacco use, dyslipidaemia, diabetes mellitus, hypertension, abdominal obesity, sedentary lifestyle, a diet low in fruits and vegetables, psychosocial stressors are risk factors for an ST-elevation myocardial infarction ***(McCord et al., 2008).*** Cocaine use can cause an ST-elevation myocardial infarction regardless of risk factors ***(Akbar et al., 2020).*** History of congenital abnormalities as anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) syndrome may be suggestive of the cause ***(Peña et al., 2009 and Thygesen et al., 2012).***

Evaluation

Evaluation of patients with acute chest pain should begin with an electrocardiogram (ECG) and troponin level. The American College of Cardiology, American Heart Association, European Society of Cardiology, and the World Heart Federation committee established the ECG criteria for ST-elevation myocardial infarction (STEMI) (Table 1) ***(Thygesen et al., 2018)***.

Table 1: ECG criteria for ST-elevation myocardial infarction ***(Thygesen et al., 2018):***

▪ New ST-segment elevation at the J point in 2 contiguous leads with the cut-off point as greater than 0.1 mV in all leads other than V2 or V3
▪ In leads V2-V3 the cut-off point is greater than 0.2 mV in men older than 40 years old and greater than 0.25 in men younger than 40 years old, or greater than 0.15 mV in women
▪ Patients with a pre-existing left bundle branch block can be further evaluated using Sugarbush's criteria ***(Smith et al., 2012 and Stub et al., 2015)***: ✓ ST-segment elevation of 1 mm or more that is concordant with (in the same direction as) the QRS complex ✓ ST-segment depression of 1 mm or more in lead V1, V2, or V3 ✓ ST-segment elevation of 5 mm or more that is discordant with (in the opposite direction) the QRS complex

Treatment / Management

After making the diagnosis of acute ST-elevation myocardial infarction, intravenous access should be obtained, and cardiac monitoring started immediately. In presence of hypoxemia (Sao2 < 90% or Pao2 < 60 mm Hg) or at risk for hypoxemia oxygen therapy can help; however, recent studies show possible bad omen effects in normoxic patients ***(O'Gara et al., 2013 and Hofmann et al., 2017)***. Patients should undergo percutaneous coronary intervention (PCI) within 60 minutes of presentation at a PCI capable hospital or within 120 minutes if transfer to a PCI capable hospital is required ***(Ibanez***

et al., 2018). Fibrinolytic therapy should be initiated within 10 minutes of arrival at the hospital if PCI is not possible within the first 120 minutes of first medical contact ***(Ibanez et al., 2018).***

Patients with an acute myocardial infarction should be started on a beta blocker, aspirin, high intensity statin, and a P2Y12 inhibitor as soon as possible, with some exceptions. Nitroglycerine administration reduces anginal pain but it should be avoided in patients kept on phosphodiesterase inhibiting medication within the last 24 hours and those with right ventricular infarction. Further pain relief with morphine can be given cautiously for patients that continue report discomfort after nitroglycerine administration ***(Wiviott et al., 2007).***

Antiplatelet medication (P2Y12 inhibitor) choice depends on whether the patient underwent PCI or fibrinolytic therapy. Several trials showed superiority of Ticagrelor and prasugrel over clopidogrel in patients who undergo PCI ***(Sabatine et al., 2005 and Wallentin et al., 2009).*** Patients undergoing fibrinolytic therapy should be given clopidogrel. It is important to be careful about relative contraindications of P2Y12 inhibitors. Prasugrel is contraindicated in patients with history of transient ischemic attack and stroke ***(Braun and Kassop, 2020).***

Anticoagulation is used parallel to previous protocol with unfractionated heparin, low-molecular-weight heparin, bivalirudin, or fondaparinux ***(McManus et al., 2011).***

Prognosis

Mortality rates at 30 days for patients presenting with ST-elevation myocardial infarction are between 2.5% to 10%. The most commonly used scoring system for 30-day mortality is the TIMI risk score as shown in (Table 2) ***(Morrow et al., 2000; Jernberg et al., 2011 and Rosamond et al., 2012).***

Table 2: TIMI risk score ***(Batts et al., 1990).***

▪ Age older than 75 years (3 points); Age 64 to 74 (2 points)
▪ Diabetes, hypertension, or history of angina (1 point)
▪ Systolic blood pressure less than 100 mm Hg (3 points)
▪ Heart rate greater than 100 beats per minute (2 points)
▪ Killip class II to IV (2 points)
▪ Body weight less than 150 lbs (1 point)

Patients were categorised as low risk if their TIMI score was 0–4 and as high risk if their TIMI score was ≥ 5 ***(González-Pacheco et al., 2012).***

Chapter 2

CONTRAST INDUCED NEPHROPATHY (CIN)

Contrast induced nephropathy (CIN), also called contrast-induced acute kidney injury (CI-AKI), occurs after the intravascular injection of iodinated radiographic contrast media. It was first described in a patient with multiple myeloma receiving intravenous pyelography **(Bartels et al., 1954)**. CIN is the third leading cause of hospital-acquired acute renal failure (ARF) after surgery and hypotension. It is responsible for 12% of all cases of ARF in hospital ***(Gleeson and Bulugahapitiya, 2004).***

Contrast induced nephropathy may be defined as an ARF that occurs within 24–72 hrs of exposure to intravenous or intra-arterial iodinated contrast media and is not evidently attributed to other causes. In most cases it is a non-oliguric ARF with an asymptomatic transient decline in renal function. It may go undetected by clinicians if they do not check the renal function in the days following the contrast administration. The renal function impairment is defined by an absolute increase by 0.5 mg/dL (or greater) or relative increase by 25% (or greater) of serum creatinine from baseline. It may be better defined by a decrease to 30–60 mL/min (renal insufficiency) or less in the estimated glomerular filtration rate (eGFR), that is, the creatinine clearance calculated using the MDRD (modification of diet in

renal disease) formula ***(Levey et al., 1999)*** or the CKD-EPI (chronic kidney disease epidemiology collaboration) equation ***(Levey et al., 2009),*** or the very simple Cockcroft-Gault formula ***(Cockcroft and Gault, 1976).*** The rise in serum creatinine usually peaks on the third to fifth day, returning to baseline within 10–14 days ***(Andreucci et al., 2014-a).***

In some cases, CIN can cause a more severe impairment of kidney function with oliguria (<400 mL/24 hrs), requiring dialysis. In these cases, the mortality rate is high. The clinical features and the treatment of CIN are similar to ARF due to other factors ***(Andreucci et al., 1998-a; Andreucci et al., 1998-b and Briguori et al., 2004).***

Incidence of CIN

Earlier literature had greatly overestimated the incidence of CIN ***(Andreucci, 2014-b).*** CIN occurs in up to 5% of hospitalized patients with normal renal function before the contrast medium injection ***(Curtis & Agarwal, 2007)*** and in about 2% ***(Solomon, 2008)*** or even 1% of outpatients with eGFR > 45 mL/min per 1.73 m^2 ***(Weisbord & Palevsky, 2008).***

Therefore, CIN is rare in patients with normal pre-existing renal function. In fact, it is more common in patients with kidney failure, especially when associated with diabetic nephropathy ***(Katzberg & Newhouse, 2010).*** Of all procedures in which contrast medium are used for diagnostic or therapeutic

purposes, coronary angiography and percutaneous coronary interventions are associated with the highest rates of CIN ***(Mehran & Nikolsky, 2006).*** This is mainly related to (a) the intra-arterial injection, (b) the high dose of the contrast used, and (c) the type of patient who is usually elderly and has one or more comorbid conditions, such as advanced vascular disease, severe long-term hypertension, diabetes, and some kidney dysfunction ***(Solomon, 2008).***

In a previous research studying patients undergoing CT either without contrast or with the low-osmolar contrast medium iohexol or the isoosmolar contrast medium iodixanol. ***Bruce et al. (2009)*** found that the CIN incidence in the low-osmolar contrast medium group was similar to that of the control group up to a serum creatinine level of 1.8 mg/dL; but serum creatinine above 1.8 mg/dL was accompanying with a higher CIN incidence in the low-osmolar contrast medium group; there was no significant difference in the CIN incidence between the isoosmolar contrast medium and the control groups for all baseline serum creatinine values ***(Bruce et al., 2009).***

Davenport and his colleagues observed that I.V. low-osmolality iodinated contrast media (LOCM) is a nephrotoxic risk factor in patients who has stable eGFR < 30 mL/min/1.73 m2, with a tendency toward significance at 30–44 mL/min/1.73 m2. IV LOCM does not appear to be a nephrotoxic risk factor in patients with a pre-CT eGFR of 45 mL/min/1.73 m2 or more ***(Davenport et al., 2013).***