CASE REPORT

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Ischemia and perioperative infarction

Isquemia e infarto perioperatorio

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Keywords: Myocardial infarction, Ischemia, injury, Troponin (T/I), Anesthesia, Surgery

Palabras clave: Infarto de miocardio, Isquemia, Lesión, Troponina (I/T), Anestesia, Cirugía

Abstract

Introduction: Perioperative medicine has provided anesthetists with a proactive role in the prevention of perioperative complications, in particular cardiovascular events such as myocardial injury after non-cardiac surgery.

Objective: Using cardiovascular risk concepts, pre-operative assessment for non-cardiac surgery, optimization of the hemodynamic status, determination of differences between elective and urgent patients, monitoring, close follow-up after surgery, and measurements of ultrasensitive troponin in the first 48 hours postoperatively, anesthetists are now able to identify and address early clinical manifestations of perioperative ischemia and myocardial infarction (MI) in patients at risk.

Materials and methods: *Narrative review:* Queries in various databases on perioperative ischemia and non-fatal infarction in Pubmed, Science Direct, and Ovid.

Results: The analysis of cardiac troponin levels is of the utmost importance in the prognosis of perioperative MI. Diagnosis can be made earlier, and it has been shown that the majority of these perioperative events have their onset within the first 48 hours of the postoperative period, when the physiological stress is highest in patients taken to non-cardiac surgery.

Resumen

Introducción: La medicina perioperatoria ha permitido que el anestesiólogo asuma un rol proactivo en la prevención de las complicaciones perioperatorias, especialmente las cardiovasculares, entre ellas la lesión miocárdica que ocurre después de cirugía no cardiaca (MINS- Myocardial injury after noncardiac surgery).

Objetivo: A partir de conceptos de riesgo cardiovascular, evaluación preoperatoria para cirugía no cardiaca, optimización del estado hemodinámico, establecimiento de diferencias entre pacientes programados y urgentes, monitoria, vigilancia estrecha de la evolución y toma de niveles de troponina ultrasensible en las primeras 48 horas del posoperatorio, el anestesiólogo ha logrado identificar e intervenir de manera precoz los cuadros clínicos relacionados con isquemia e infarto de miocardio perioperatorio en los pacientes de riesgo.

Materiales y métodos: Revisión narrativa. Consulta de diferentes bases de datos sobre isquemia e infarto no fatal perioperatorio, en Pubmed, Science Direct y Ovid.

Resultados: El análisis de los niveles de troponina cardiaca tiene gran importancia en el pronóstico del infarto de miocardio perioperatorio. El diagnóstico se hace más temprano y se ha demostrado que la mayoría de estos eventos perioperatorios

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inician en las primeras 48 horas del postoperatorio, momento del mayor estrés fisiológico en el paciente de cirugía no cardiaca.

Introduction

At present, close to 234 million people undergo surgery in the world every year,[1] increasing the percentage of adverse events that may result in perioperative death (1 million patients per year).[2] More than 5% of patients over 45 years of age taken to non-cardiac surgery will have cardiac complications, non-fatal myocardial infarction (MI) being the most frequent. Mortality associated with perioperative MI ranges between 15% and 25%, and myocardial injury in non-cardiac surgery or myocardial injury after non-cardiac surgery (MINS), occurs in approximately 10 million patients.[3]

In practice, acute MI is diagnosed on the basis of clinical findings, electrocardiogram (EKG), cardiac troponin levels (cTn), invasive and non-invasive imaging, and pathology evaluation.[4,5]

Cardiac complications are the most relevant causes of perioperative morbidity and mortality and have a significant impact on length of stay and hospitalization costs.[6,7]

This narrative review started with the search for articles on the topics of ischemia, perioperative myocardial infarction, troponin, anesthesia, and non-cardiac surgery. Of a total of 205,000 articles retrieved, 141,000 were removed due to title and abstract duplication; of the 64,000 remaining articles, 24 were considered for analysis and complete review due to their relevance in terms of myocardial injury or type-2 infarction, differences with the etiology and pathogenesis of type-1 infarction, biomarkers, and international classification, in adult patients taken to non-cardiac surgery (Fig. 1).

This review includes a description of the importance of type-2 infarction and the purpose of including it in this article, the current MI classification, etiology, diagnosis, pre-operative assessment, benefit of using biomarkers such as ultrasensitive troponin, precautions and recommendations for management during the perioperative period and, finally, conclusions.

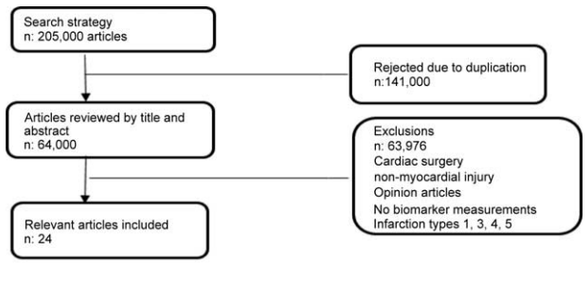

Figure 1. Data search strategy.

Figure 2. Types of acute MI according to the universal definition. MI = myocardial infarction. Taken and translated under license from Creative Commons (CC BY 4.0)[5]. AQ12

As the population ages, the odds for surgical interventions increase, and perioperative MI (PMI) is a growing outcome.[8,9] Thirty-day postoperative mortality following non-cardiac surgery is close to 1% in the United States, and approximately 2% in hospitalized patients (outpatients die less frequently). Almost half of all 30-day postoperative deaths are cardiovascular or related to cardiovascular events (myocardial ischemia being the most common).[10] PMI is associated with 11.6% in-hospital mortality, of which, 74% are deaths that occur within the first 48 hours, with the majority of patients (65%) not exhibiting clinical symptoms.[11]

Of inpatients over 45 years of age, 8% suffer a postoperative myocardial injury as defined by elevation of ultrasensitive troponin T, cTn, (≥0.03 μg/L) associated with ischemic etiology; only 42% of these events meet the diagnostic criteria of the universal definition of acute MI. Only 14% of patients who suffer a PMI have chest pain and 65% are clinically silent, meaning that the patients will be discharged without a diagnosis of PMI due to failure to perform routine measurements of cTn levels (Fig. 2).[10] AQ8

This article seeks to answer the following question: Can MINS be diagnosed pre-operatively using biomarkers in patients with cardiovascular risk?

Classification of acute MI

The classification proposed by the third universal definition of acute MI takes into consideration the presence of ST-segment elevation (STEMI) or no ST elevation (non-STEMI) in the EKG, and includes 6 types: AQ9

– Type 1: Ischemic MI due to a primary coronary event associated with plaque erosion, rupture, fissure, or dissection.
– Type 2: MI secondary to ischemia due to oxygen supply/demand imbalance.
– Type 3: Unexplained sudden cardiac death with suggestive symptoms of myocardial ischemia, without biomarker or EKG confirmation.
– Type 4:
o Type 4a: MI related to percutaneous coronary intervention (angioplasty).
o Type 4b: MI related to coronary stent thrombosis.
– Type 5: MI related to coronary arterial by-pass surgery.
– Myocardial injury: Multifactorial etiology; based on acute or chronic changes in cTn concentration with serial testing.[4,5]

This classification was based more on an expert consensus than on evidence from randomized clinical trials. Patients classified under type-2 acute MI are heterogenous and have myocardial ischemia secondary to a wide range of acute medical or surgical conditions, even in the absence of coronary artery disease. There are no current guidelines or consensus papers regarding optimal cardiac workup, or about management or treatment strategies for patients with acute type-2 MI.[5]

Etiology

Historically, two main mechanisms have been described to trigger this phenomenon in an equal proportion: rupture of a fragile unstable plaque and oxygen supply/demand imbalance. However, recent studies including postmortem data, pre-operative coronary angiography imaging, troponin surveillance, other non-invasive preoperative studies, and perioperative hemodynamic predictors of ischemia or MI have shown that the supply/demand imbalance mechanism is the one that predominates during the early postoperative period. Blood stagnation and thrombi formation are important disease pathways for the development of infarction and have been found to be related to perioperative tachycardia. In contrast, plaque rupture has shown to trigger only a small proportion of random perioperative events.[12–14]

Coronary heart disease can be divided into 4 groups according to the etiology[5]:

(1) Primary myocardial ischemia: atheroma plaque rupture, intraluminal thrombus, distal microembolization, coronary artery dissection.
(2) Oxygen supply/demand imbalance leading to ischemia: anemia, aortic dissection, aortic valve dissection, tachyarrhythmia or bradyarrhythmia, coronary embolism or vasculitis, coronary endothelial dysfunction, coronary vasospasm, arterial hypertension, left ventricular hypertrophy, hypertrophic cardiomyopathy, respiratory failure, shock (cardiogenic–hypovolemic–septic).
(3) Injury not related to myocardial ischemia: ablation, cardiac contusion, cardiac surgery, cardiotoxic drugs, cardioversion, cytokine-mediated injury, myocarditis, pacemaker, rhabdomyolysis.
(4) Multifactorial or indeterminate etiology: critical illness, infiltrative diseases (amyloidosis–sarcoidosis), pulmonary embolism, pulmonary hypertension, acute renal injury, chronic renal disease, extreme exercise, takotsubo cardiomyopathy, stroke, subarachnoid hemorrhage.

Surgical patients are exposed to potential sources of inflammation, hypercoagulabilty, anesthesia/surgery-induced stress, hypoxia.[15]

Initial assessment

It is difficult to recognize an adverse cardiovascular event during the perioperative phase; typical angina symptoms are usually masked by strong analgesics, whereas EKG changes are subtle or transient, and diagnosis is made on the basis of biomarkers like cTn.[16]

Coronary artery disease is a risk factor which varies depending on whether the patient has had a prior acute MI or not, or has symptoms of angina. Pandey et al showed that the incidence of PMI was higher among patients with pre-operative angina symptoms (8.5% vs. 5%, $P=0.035$), as was also the case with reintervention rates and prolonged hospital stay. Odds ratio for pre-operative angina as a predictor of PMI is 2.49 (95% confidence interval [CI]: 1.2; 5.81) and as a predictor of reintervention is 2.4 (95% CI: 1.44; 3.82).[17]

Initial risk assessment in patients with suspected acute coronary syndrome may be performed with the help of two models developed for that purpose: TIMI (thrombolysis in MI) and GRACE (Global Registry of Acute Coronary Events), which are available online and may be useful during initial patient care (Class IIa recommendation, level of evidence B, American College of Cardiology–American Heart Association [ACC–AHA]).[4]

Historically, clinical assessment has been based on various risk assessment tools, including the Goldman (1976), Detsky (1986), and Eagle (1989) indices, and, more recently the Revised Cardiac Risk Index, used by the American Heart Association and the American College of Cardiology as a basis for their consensus on pre-operative assessment for non-cardiac surgery in 2007.[18]

Pre-operative assessment is aimed at identifying patients with coronary heart disease, symptomatic or asymptomatic, determine tolerance to exercise, and the risk of the type of scheduled surgery, to determine the need for diagnostic testing. However, indications for coronary interventions are the same as for patients who need not be taken to surgery. Potential courses of action

depending on the pre-operative assessment include the following:

– Perform the surgery as scheduled
– Change the surgery to be performed
– Delay the surgery until unstable syndromes have been treated
– Modify perioperative medical therapy
– Modify postoperative care
– Schedule revascularization before non-cardiac surgery
– Change treatment and care site

Four active cardiac conditions are defined:

(1) Active coronary syndromes
(2) Decompensated cardiac failure
(3) Significant arrhythmias
(4) Significant valvular disease

Five risk factors are defined:

(1) Ischemic heart disease
(2) History of cardiac failure
(3) History of cerebrovascular events
(4) Diabetes mellitus
(5) Creatinine above 2.0 mg/dL

A simple algorithm that considers tolerance to exercise and the risk of the surgery is applied to make a decision that seeks to diminish the perioperative risk of a MI.[19]

Tests for confirming acute MI

A 12-lead EKG (Class I recommendation, level of evidence C, ACC–AHA), to obtain a diagnosis of STEMI, non-STEMI, or non-ischemic chest pain.[4]

High-sensitivity cardiac troponin T and I testing (cTnI y cTnT) (Class I recommendation, level of evidence A [ACC–AHA]). Routine monitoring of cardiac biomarkers has become necessary to identify patients at risk of early postoperative cardiovascular events.[20] Serial measurements are useful for observing cTn elevation or fall patterns, at least a value above the 99th percentile of the normal upper reference limit, cTnI (sensitivity 77% and specificity 93%) and cTnT (sensitivity 80% and specificity 90%).[18] High-sensitivity cTn testing has a lower clinical specificity for acute MI due to causes like myocarditis and other heart lesions; cardiac, renal, and respiratory failure; thrombosis or intracranial bleeding; septic shock and chronic structural heart disease. The size of cTn elevation in acute coronary syndrome correlates with the short-term mortality risk.[4,15] Some patients may have low detectable levels of cTn outside the setting of acute coronary syndrome. Causes of cTn elevations suggestive of stress or cardiac injury but not associated with coronary atherosclerosis include sepsis, pulmonary embolism, renal failure, brain thrombosis, perimyocarditis, endocarditis, takotsubo cardiomyopathy, radiofrequency ablation, cardiac contusion, extreme exercise, and sympathomimetics.[10,21] Retrospective studies show that high pre-operative cTnI levels have been associated with high postoperative mortality, and waiting time before surgery appears to reduce the risk in patients with mildly elevated pre-operative cTn.[21] High postoperative concentrations of cTn have shown to be a strong predictor of 30-day morbidity and mortality in patients taken to non-cardiac surgery.[21] There has been no research into the effect of the time interval between peak cTnI levels and surgery, and prospective studies are required to determine whether delaying surgery in patients with high cTn levels improves postoperative outcomes.[21]

Importance of troponin as a marker of myocardial injury

Troponin analysis appears to be appropriate for inpatients over 45 years of age, and it should be included in the first 3 postoperative days, while patients are in the hospital. Follow-up after that time may not be necessary because 75% of PMIs occur within the first 48 hours after surgery, or because close to 80% of 30-day mortality occurs during initial hospital stay.[10]

CPK-MB measurements or myoglobin levels are not recommended (Class III recommendation, level of evidence A [ACC–AHA]).[4]

Initial symptoms are non-specific given that the patient is still under the effect of anesthetics and analgesics, including opioids and multimodal analgesia. Consequently, they do not report chest pain, although they may exhibit dyspnea, hypoxia, hypotension, or tachycardia.[21] Therefore, PMI is usually recognized 3 to 5 days into the postoperative period, leading to a high mortality rate ranging between 30% and 70%.[16]

Recommendations for the management of patients with potential ACS

(1) Perform triage for acute coronary syndrome (STEMI, non-STEMI, probable unstable angina, or non-ischemic disorder) on the basis of history, clinical findings, EKG parameters, and nTc levels.[4,22]
(2) Assess the risk of cardiovascular death or recurrent ischemia (high, intermediate, or low risk) based on the clinical characteristics, EKG findings, and nTc levels. The use of TIMI or GRACE is recommended.
(3) Provide general initial care: rest, aspirin, nitroglycerine, and a statin; consider oxygen (when oxygen saturation is <90%, or in respiratory distress), the use of a beta-blocker (should be avoided in patients with risk factors for cardiogenic shock), or morphine.
(4) Select an initial strategy, either invasive or non-invasive; the choice of early invasive management is based on risk assessment and patient preferences.
(5) Select a second anti-platelet agent to add to aspirin (P2Y inhibitor$_{12}$ or glycoprotein IIb/IIIa inhibitor) according to the risk of thrombosis, timing of the

invasive strategy, probability of requiring surgical revascularization, and risk of bleeding.
(6) Select an anti-coagulant (unfractionated heparin, low-molecular-weight heparin, or bivalirudin) in accordance with the initial management strategy (invasive or non-invasive) and the risk of bleeding.

Patients with acute coronary syndrome without STEMI must be managed early on with a pharmacological approach in accordance with the etiologic target[4]:

(1) Myocardial oxygen supply–demand imbalance:
(a) O_2: Only if O_2 saturation <90% (Class I recommendation).
(b) Analgesics: Intravenous morphine (1–5 mg, can be repeated every 5–30 minutes) may be a reasonable option for persistent ischemic pain (Class IIb recommendation).
(c) Nitrates: Sublingual nitroglycerine (0.3–0.4 mg, may be repeated twice at 5-minute intervals) for ischemic pain and intravenous nitroglycerine for persistent ischemia, heart failure, or hypertension (Class I recommendation).
(d) Beta-blockers: An oral beta-blocker may be initiated in the first 24 hours in the absence of heart failure, low output state, risk of shock, or any other contraindication (Class I recommendation).
(e) Calcium channel blockers: These agents may be used for persistent ischemia when the beta-blocker has failed, is contraindicated or has side effects (Class I recommendation). Calcium channel blockers are contraindicated in left ventricular dysfunction, risk of cardiogenic shock, a PR interval >0.24 seconds, and second and third degree A-V block in a patient with no cardiac marker.
(2) Coronary thrombus:
(a) Anti-platelet therapy: Oral aspirin (initial dose 162–325 mg; followed by 81–325 mg/day indefinitely) plus one $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) (Class I recommendation).
(b) Anti-coagulant therapy: Use the intravenous route in all cases in accordance with the treatment strategy (Class I recommendation).
(3) Unstable atheroma plaque or disease progression:
(a) Statins: Start or continue high-intensity oral statins (atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily from the start) for cholesterol management (Class I recommendation).
(b) Angiotensin-converting enzyme inhibitors: May be initiated in all patients with a left ventricular ejection fraction <0.4 and in patients with hypertension, diabetes mellitus, or stable chronic renal disease (Class I recommendation).

Precautions

Aspirin is associated with a mild increase in perioperative; its use and non-discontinuation have shown to reduce perioperative events in myocardial revascularization surgery, but not so in non-cardiac surgery.[23] Discontinuation is recommended only in patients that will be taken to interventions of the brain, spinal canal intervention, posterior chamber of the eye, or prostate surgery.

The following are the recommendations in patients with dual anti-platelet therapy (ASA + Clopidogrel):

– Patients with bare metal stents must be given dual therapy and continue it for at least 4 weeks; after that time, the incidence of perioperative infarction is similar as in the rest of the patients.
– In patients with covered stents, mortality is the same after 1 year of dual anti-platelet therapy. Consequently, if the patient needs surgery, clopidogrel must be discontinued and restarted in the immediate postoperative period. Bridging therapies with anti-thrombin, anti-coagulants, or glycoprotein IIb/IIIa-type drugs have not shown effectiveness.

Adequate pharmacological intervention is based on the continuation of the medication with cardiovascular effect and addition of statins as inflammation modulators during the perioperative period.

Myocardial revascularization: This intervention before surgery has been shown to result in a significant reduction of the incidence of ischemia and perioperative infarction.

In terms of scientific evidence, the authors propose the following steps:

Step 1: Have a high suspicion of perioperative ischemia or infarction if the patient has risk factors or if cardiac symptoms, hemodynamic instability, tachycardia, or lung congestion are present.

Step 2: Paraclinical tests, 12-lead EKG, blood gases (treat hypoxia, hypercapnia, acid–base abnormalities), whole blood count (treat anemia, Hb < 10 g%), measure ultrasensitive troponin levels.

Step 3: Evidence of ischemia on the 12-lead EKG:

- Depressed ST-segment (non-STEMI)
  In patients with tachycardia and normal blood pressure or hypertension, the treatment focuses on heart rate, blood pressure, and pain control; if the patient has tachycardia associated with hypotension, the causes must be identified promptly and hypotension needs to be addressed (hypovolemia, vasodilation, heart failure). Invasive hemodynamic assessment or echocardiography must be performed, controlling heart rate with cardioversion and using medications judiciously.
- STEMI requires urgent consult with interventional cardiology, measurement of ultrasensitive troponin levels, and urgent coronary angiography and reperfusion.

Conclusion

Given the high mortality rate in patients who suffer PMI, efforts must focus on the pathophysiological and clinical considerations to guide treatment options, and on early

patient identification using enzymatic markers such as ultrasensitive troponin. In this way, patients may benefit from the different invasive and non-invasive options.

Making a distinction between type-1 and type-2 MI is the basis for effective treatment.

Type-2 MI is secondary to ischemia due to oxygen supply/demand imbalance.

It is difficult to recognize an adverse cardiovascular event during the perioperative phase, and late diagnosis is a lost opportunity to initiate early treatment.

Only type-1 MI has been shown to benefit from aggressive anti-coagulation, platelet inhibition, and early coronary revascularization. Rapidly addressing the secondary condition is of benefit in type-2 MI (volume replenishment in case of hypotension or blood transfusion in case of anemia).[24]

Use of the 12-lead EKG has a Class I recommendation, level of evidence C.

Biochemical testing of cTnI or cTnT has a Class I recommendation, level of evidence A.

It is advisable to weigh carefully the risks and benefits of routine measurement of cTn in patients with risk factors (including age over 45) and the type of non-cardiac surgery.

Perioperative MI and myocardial injury are more frequent than previously thought and are associated with high postoperative mortality.

Controlled clinical trials are yet to be conducted that can help provide better recommendations regarding perioperative MI.

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Conflict of interest

The authors declare having no conflict of interest.

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