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Research Article

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Cardioprotection with Nitroglycerin in Cardiovascular Anesthesia

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Abstract

Introduction: *For the anesthesiologist, it is very important to consider cardiovascular protection at the time of each procedure. Especially if the patient represents a high risk for presenting coronary or vascular involvement, although the surgical approach is not more complex, since the fact of using anesthesia in a patient already leads to being under perioperative risks to which they must be subjected. Nitroglycerin is a widely used vasodilator in patients with coronary disease. However, the study of its concomitant use in anesthetized patients who will undergo surgery is not very clear.*

Materials and methods: *A narrative review was carried out, in which different databases were used such as Scielo, PubMed, ScienceDirect, academic google, among others. The selection of articles was made through indexed journals in English and Spanish languages from 2010 to 2021.*

Results: *Myocardial ischemia is one of the most frequent causes of perioperative morbidity and mortality. Nitroglycerin is a vasoactive agent that has been used in patients under anesthesia with highly variable results. However, it has had a beneficial effect in patients with significant hemodynamic or cardiovascular compromise. Conclusion: The use of nitroglycerin in the patient under anesthesia could have a cardioprotective effect if it is used safely, and not prolonged. In addition, the adverse effects that this can generate in the patient must be considered and each case should be evaluated individually, interposing the benefit, but not as a routine use, especially in patients with great hemodynamic compromise.*

Keywords: CardioProtection, Anesthesia, Nitroglycerin, Myocardial Ischemia, Cardiovascular.

Introduction

According to the WHO, cardiovascular diseases are the main cause of death in the world, presenting 17.9 million deaths each year. These diseases are a group of disorders of the heart and blood vessels that include coronary heart disease, cerebrovascular disease, and rheumatic heart disease. Today, around 234 million surgical procedures are performed each year in the world, with a high percentage of adverse events, which can lead to perioperative death in approximately 1 million patients per year. More than 5% of patients older than 45 years suffer cardiac complications in non-cardiac surgery. The most common is non-fatal myocardial infarction. Perioperative myocardial infarction has a mortality that ranges between 15%-25% and "myocardial injury in non-cardiac surgery" occurs in about 10 million patients [1].

For the anesthesiologist, the study of perioperative medicine has allowed him to participate in the prevention of complications that occur during the surgical act, such as cardiovascular or myocardial injury. Regarding cardiovascular anesthesia, it has contributed to the development of cardiovascular surgery, helping to improve patient safety during surgery. On the other hand, patients with heart disease are susceptible to hemodynamic changes and depend on compensatory cardiovascular mechanisms. Therefore, anesthesiologists who face this type of patient every day must be prepared by knowing the additional risks, particularities of the pathology itself, and individual characteristics of each patient in order to reduce perioperative complications [2].

Materials and Methods

A narrative review was carried out, in which different databases were used, such as Scielo, PubMed, Sciencedirect, academic Google. A search for articles was carried out in indexed journals in English and Spanish languages from 2010 to 2021. The keywords used were according to the DeCs and MeSH terms. They were used: Cardioprotection, anesthesia, nitroglycerin, myocardial ischemia, cardiovascular. In this review, 20 original and review publications related to the subject under study were identified, of which 14 met the inclusion criteria used. Within the inclusion criteria are: that they were full text articles, that at the time of the search they allowed the reading of the abstract, that they were related to the subject studied and that they were within the established years. As exclusion criteria: That they had a publication date of less than 2010 and that they did not allow the reading of the full text.

Results

Myocardial ischemia

The factors that determine the specific clinical presentation of myocardial ischemia are:
-The degree of coronary occlusion
-The volume of the affected ischemic myocardium
-The extension of collateral circulation
-The pre-existing myocardial metabolic rate
-Genetic factors and intrinsic survival capabilities of myocytes

The atherosclerotic endothelium is dysfunctional, normal is the expression of nitric oxide synthase, therefore, when this does not occur, a prothrombotic and vasoconstriction state is generated, which increases the probability of developing the formation of occlusive thrombi during rupture of the atherosclerotic endothelium. the plate. Atherosclerosis is a chronic disease that can be morphologically present in coronary arteries as eccentric or concentric lesions. This can result in myocardial ischemia or infarction through different pathophysiological mechanisms. Compensatory outward enlargement of atherosclerotic arteries helps prevent stenosis of the lumen, a common finding associated with coronary plaque growth. Therefore, there may be extensive plaques on the walls of the affected arteries without causing symptoms or being detected, so luminal stenosis will occur only when plaque growth exceeds the compensatory expansion capacity of the artery (Figure 1). The heart is an aerobic organ, dependent on coronary perfusion and consequently on oxygen. Therefore, the ability to supply to meet increased demand is highly dependent on the ability of the coronary circulation to dilate and increase flow as needed [3].

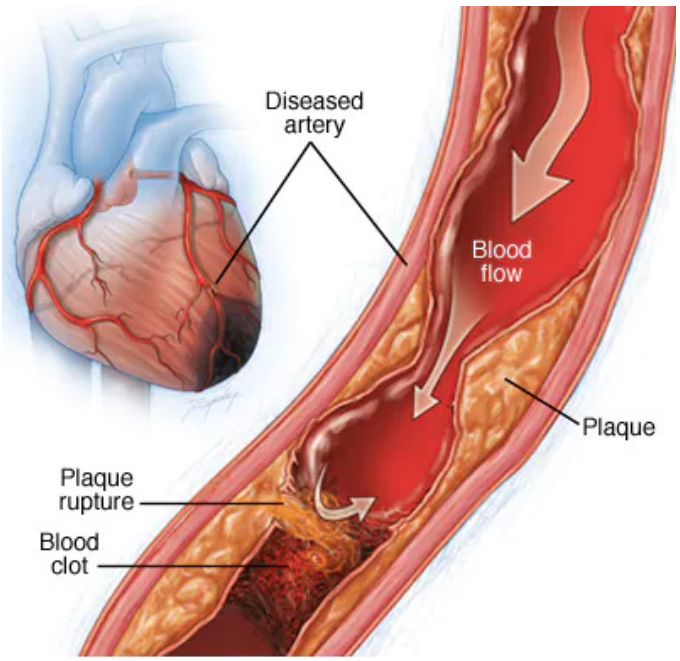

Figure 1: Myocardial ischemia secondary to atheromatous plaque ruptura

Ischemia occurs when the oxygen demand of the heart muscle exceeds its supply, there is a decrease in the elimination of

anaerobic metabolism products, which generates alterations in the electrical and mechanical functions of the heart. Ischemic heart disease is based on this, which is defined as a decrease in coronary blood flow that is insufficient to meet the metabolic demands of the myocardium. When the arteries are clogged and there is an increased demand for oxygen, an imbalance between oxygen supply and demand can occur. The conditions that can condition a person to suffer from myocardial ischemia are: coronary artery disease, left ventricular hypertrophy, severe aortic valve stenosis and systemic arterial hypertension. However, it is coronary blood flow, coronary perfusion pressure, oxygen saturation, and hemoglobin content that determine supply itself [4].

Nitroglycerine

Myocardial ischemia is one of the most frequent causes of perioperative morbidity and mortality. Postoperatively, 2% of these patients experience major cardiac complications and 8% develop signs of substantial myocardial injury. Therefore, it is of great importance to prevent perioperative myocardial infarction. Nitroglycerin reverses myocardial ischemia intraoperatively by improving coronary arterial blood flow. However, its intraoperative prophylactic use in high-risk patients may have insignificant benefits or may even be harmful, since it can lead to cardiovascular decompensation that compromises preload, reducing it and aggravating the patient's situation. In a study by Hiroshi Hoshijima et. which consisted of a systematic review and meta-analysis, where the efficacy of intravenous nitroglycerin in the prevention of intraoperative myocardial ischemia under general anesthesia was evaluated, it did not show, as a prophylactic, a reduction in the incidence of intraoperative myocardial infarction. Furthermore, they significantly reduced mean arterial pressure both before and after induction of anaesthesia [5].

One of the complications with the greatest impact on morbidity and mortality in this setting is acute perioperative myocardial infarction; this shows the importance of early recognition and adequate prophylaxis of acute myocardial ischemia. A single-blind, randomized, controlled, therapeutic clinical trial was conducted to evaluate the cardioprotective effect against acute myocardial ischemia of diltiazem and nitroglycerin, by Julián D Guzmán Bonilla et. 175 patients were studied, being 90 those of nitroglycerin and 85 those of diltiazem. Acute myocardial ischemia was defined as significant alteration of the ST segment, when it shifts >0.2 mv, in 2 contiguous leads, in either direction. The anesthetic protocol was similar in both groups; It was concluded that the perioperative intravenous infusion of nitroglycerin provides a better cardioprotective effect than diltiazem, this is evidenced in the prevention of sustained myocardial ischemia, associated with a lower release of troponin T in coronary revascularized patients. Nitroglycerin showed better hemodynamic stability and tolerance in these patients. In addition, the mean intraoperative blood pressure value was 80 mm/Hg vs. the group exposed to diltiazem, which was 61.4 mm/Hg. The mean heart rate in group N=63 bpm vs. group D=50 bpm. The most frequent arrhythmia was atrial fibrillation [6].

One of the most important complications of nitroglycerin infusion during surgery is methemoglobinemia. Nitroglycerin, a drug with a lowering effect on blood pressure, is also known as one of the most effective agents for causing methemoglobinemia. Although there are few studies on the effect of nitroglycerin in inducing this state, there are studies that have shown that the high rate of nitroglycerin infusion can lead to the incidence of methemoglobinemia with symptoms such as cyanosis, lethargy and hypoxemia. Methemoglobinemia is a blood disorder caused by the oxidation of iron in hemoglobin from the Fe 2+ state to Fe 3+. This condition leads to the inability of hemoglobin to transport oxygen and causes coma leading ultimately to the death of the patient when the methemoglobin level exceeds 60%. Farsad Imani et. investigated the prevalence of methemoglobinemia and its association with nitroglycerin to control blood pressure during anesthesia. We found that more than half of the patients undergoing surgery had a methemoglobin level greater than 2% after nitroglycerin infusion, and the only predictor of abnormal methemoglobin was the total dose of nitroglycerin. Consequently, for each unit increase in the total dose prescribed to a patient, the probability of abnormal methemoglobin increased by 5% [7].

Nitroglycerin remains a first-line treatment for angina pectoris and acute myocardial infarction. In addition, it achieves its benefit by giving rise to nitric oxide, which causes vasodilation and increases blood flow to the myocardium. However, continuous administration results in tolerance, which limits the use of this drug. Tolerance to nitroglycerin is the result of inactivation of aldehyde dehydrogenase 2 (ALDH2), an enzyme essential for cardioprotection in animals subjected to myocardial infarction. The effects are also vasodilation of systemic veins which reduces cardiac preload and further decreases myocardial wall stress. This drug is effective in restoring the balance of oxygen and nutrient supply; that is, it increases the demand on the ischemic heart. However, sustained administration not only causes tolerance but is associated with prooxidant effects, endothelial dysfunction, and increased sensitivity to vasoconstrictors. The effects of nitroglycerin on the vasculature have been extensively investigated, but little is known about the effect on cardiac cells. Recently, sustained treatment with this drug has been found to result in increased infarct size and cardiac dysfunction, the tolerance-mediated deleterious effects on the heart being associated with inactivation of ALDH2 [8, 9, 11].

In a case report by Zheng Feng Gu et. of a 27-year-old pregnant woman with congenital heart disease and severe pulmonary arterial hypertension and hypoxemia, with arterial blood gas analysis showing oxygen saturation of 67.8% and a partial pressure of oxygen of 40.0 mmHg, which was performed surgical abortion under total intravenous anesthesia with nitroglycerin inhalation, being under invasive blood pressure monitoring, responding satisfactorily despite being a rare and complex case, nitroglycerin had an immediate beneficial effect on oxygen saturation, which remained above 90% during the procedure. This finding is relevant, as nitroglycerin inhalation can provide pulmonary artery dilation, reduction in pulmonary artery pressure, and improved oxygenation without an impact on systolic pressure [10].

The development of tolerance to nitroglycerin is defined as "the loss of hemodynamic and antianginal effects during sustained therapy." This is generated after chronic exposure and long-term treatment. Although the cause is not yet clarified, there are several hypotheses. One of which is based on chronic treatment, which triggers hypersensitivity to vasoconstrictors, which de-

creases the vasodilator effects of nitrates. This action is mediated by increased autocrine levels of endothelin within the vasculature, with subsequent activation of phospholipase C and protein kinase C. These pathways lead to increased actomyosin activity and myocyte contractility. Another hypothesis is that chronic organic nitrate therapy desensitizes S-nitrosylation of sGC is a means by which the "memory" of NO exposure is retained in smooth muscle cells, resulting in reduced responsiveness. to NO, and could be a mechanism of tolerance to NO. Nitroglycerin metabolism also promotes the production of reactive oxygen species. Oxidation of thiol groups in the active site of ALDH-2 by these reactive derivatives has been observed during chronic treatment with nitroglycerin. This post-translational modification may cause inhibition of ALDH-2 enzyme activity, which may lead to reduced biotransformation and efficacy of nitroglycerin [12].

In a coronary occlusion, the lack of oxygen affects ventricular function. As this occurs, sarcomeric calcium metabolism is altered, changing myocardial stiffness. Ischemia, if not corrected, will generate a persistent alteration in sarcomeric calcium metabolism leading to systolic dysfunction and subsequent hemodynamic instability. Myocardial metabolism changes from aerobic or mitochondrial to anaerobic glycolysis; This change occurs when the underperfused tissue consumes the oxygen reserves stored as oxyhemoglobin and oxymyoglobin, activating anaerobic glycolysis, providing 80% of new high-energy phosphates in the ischemic zone. However, anaerobic glycolysis becomes insufficient to meet myocyte demands, resulting in decreased ATP and accumulation of ADP. Subsequently, phosphocreatine, which is the largest energy reserve, also decreases by 90% and finally the body enters a state of tissue acidosis which, if not restored, will cause ATP levels to fall, initiating an irreversible cascade of myocyte death [13].

The vasoactive substances that are produced by the endothelium are: nitric oxide, prostacyclin, endothelin, among others. But the most potent vasodilator is nitric oxide, which is produced as a gas by the cholinergic cascade and diffuses to adjacent smooth muscle cells. Influencing the resistance of the coronary vessels by maintaining myocardial perfusion. Nitric oxide-dependent vasodilation is hindered in patients with endothelial dysfunction, when there is a persistent state where severe vascular injury occurs. Cell death of cardiomyocytes becomes irreversible, being mediated by 3 different cytological processes called: necrosis, apoptosis and autophagy. Hibernating myocardium is defined as a viable myocardial region, without contractility. This is due to a severe reduction in myocardial blood flow but insufficient to generate cell death, and when the irreversible state occurs, there is loss of myofilaments and sarcomeres inside the cell, the empty space is occupied by glycogen particles, the mitochondria they increase in number, but their size decreases, and the sarcoplasmic reticulum and T-tubules are absent. Already at this point cell death is inevitable [14].

Conclusion

Nitroglycerin is a vasodilator that can exert an effect both at the arterial and venous levels. It can be used keeping in mind the possible reduction in preload and cardiac output, which can lead to iatrogenic hypotension in volume-depleted patients. Its prolonged use is associated with methemoglobinemia and can generate tolerance, reducing its effect or aggravating the cardiovascular status of patients. It is recommended in patients with coronary syndromes or acute pulmonary edema.

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