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Review Article

Anesthetic Control in Patients With Hyperhomocysteinemia in Eye Surgery

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Abstract

Hyperhomocysteinemia is a metabolic situation in which the patient has plasma homocysteine levels higher than 12μmol/L. This fact is a risk to patient's health because it increases the pro-atherothrombotic and platelet aggregation mechanisms, being a problem for the patient in a basal situation and even more, when some surgical intervention must be performed. When undergoing a surgical process to a patient with a metabolic disease that presents hyperhomocysteinemia, a special surgical algorithm must be considered to minimize the risks of developing intraoperative or postoperative thromboembolism. Patients affected by homocystinuria have a very high risk of developing a certain blindness because of the disfunction of the lens. Due to that, this review develops how the anesthetic protocol must be done in this specific type of surgical process.

Introduction

Hyperhomocysteinemia is defined as the increase in plasma homocysteine concentration above 12μmol/L

(1). Its elevation can be caused due to disorders in the metabolism of cobalamin (vitamin B12), genetic alterations in enzymes such as cystione-β-synthase (CBS), methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MS), among others, or deficiency of vitamin B12 or B6 in the diet [1]. In hyperhomocistinemic patients this molecule is elevated in both blood and urine, which is why the determination of homocysteine by HPLC (High Performance Liquid Chromatography) is essential for the diagnosis of these metabolic alterations [2]. Homocysteine in blood undergoes autoxidation processes that raise oxygen free radicals (ROS) such as hydroxyl and superoxide anions [3]. Although the patient has an adequate lipid profile, LDL molecules that are present in the bloodstream can be oxidized and can be captured by the SR-A receptors of subendothelial macrophages [4], thus initiating an atherogenic process, which is further aggravated by the direct ability of homocysteine to induce hyperproliferation of vascular smooth muscle cells (CMLV) by increasing the biosynthesis of its DNA by 25% at moderate concentrations of homocysteine, due to an increase in Cyclin D1 gene expression [5,6].

In the same way that occurs in the atherogenic process of Type 2 Diabetes Mellitus (DMT2), there could be a migration of CMLVs along the subendothelial space until it is located below the endothelial cells, thus reinforcing the wall of the incipient atheroma plaque. In addition, hyperhomocistinemia favors atherogenesis by other mechanisms such as increased collagen production, abnormalities in the release of nitric oxide due to vascular damage, inhibition of endothelial growth or due to the increase in the expression and activity of proinflammatory factors [2]. Oxidative stress generates endothelial damage that exposes collagen fibers to the vessel light that cause platelet aggregation and subsequent activation of the coagulation cascade. There is also hyperactivation of coagulation factors V, X and XII, increased expression of tissue factors, inhibition of components of the thrombomodulin-C protein system [1,2] and decreased production of the S1 protein. Likewise, hypercalcemia developed in these patients further favors the prothrombotic environment. Several models have been proposed to explain the alteration in calcium metabolism; among them alterations in signaling pathways, inflammatory processes or mitochondrial oxidative stress and endoplasmic reticulum [7].

Homocysteine interferes with the stability of the connective tissue, so that they weaken. In this type of patients, most of the surgical interventions performed fall within the field of ophthalmology because they develop ectopia lentis. This dislocation of the lens is due to the accumulation of altered collagen in the suspensory ligament of the lens [8], causing bilateral inferonasal subluxation of the same characteristic of this pathology. Another theory that supports the crystalline suspensory ligament degeneration states that the zonular fibers that hold it are rich in cysteine and, due to the mutation in the CBS enzyme, the synthesis of this amino acid decreases so that the ligament weakens [9].

Due to the hemodynamic instability of this type of patients and the high probability of ophthalmic alterations that require surgery for resolution, an anesthetic protocol should be standardized that minimizes the risks of vascular complications during surgical interventions.

Materials and Methods/ Headings

A review of online databases was performed for well-designed trials which examined analgesia practices with a special emphasis on undertreatment of pain or oligoanalgesia in the acute setting. Papers were examined for methodological soundness before being included. Online searches were performed using the following

search keywords and terms: 'homocystinemia AND 'ectopia lentis AND 'surgery, AND 'anesthesia, AND 'clinical cases.

Discussions

Preoperative Process

Patients with hyperhomocistinemia are treated with cobalamin, pyridoxine, betaine and folates, but in none of the cases studied was this treatment withdrawn for surgical intervention, such cases being glaucoma interventions due to ectopia lentis [10], cataracts [11,12], vitrectomy with lensctomy [13-16] and phacoaspiration with iridectomy [17]. All interventions were performed on pediatric patients. The preoperative fasting period for liquids ranged between 2 and 3 hours since fasting between 4 and 6 hours, which is the usual protocol, can induce dehydration that increases preoperative morbidity and anesthetic risk [18]. It has been proven that the consumption of clear liquids such as water 2 hours before surgery does not affect the volume or gastric pH and does not increase the risk of Mendelson's Syndrome [14,15,18-21]. Hydration in this type of patients is essential since it must be higher than normal before, during and after surgery to reduce blood viscosity and reduce the risk of platelet aggregation [10].

In three cases [10,13,16] drugs of the benzodiazepine family were used, in particular 0.25mg/kg of alprazolam or 0.25mg/kg of midazolam, the latter being the most appropriate for pediatric surgeries [21,22]. The use of this type of benzodiazepine increases gastric emptying. However, the administration of morphine (7.5-15mgIM) with atropine (0.4-0.6mgIM) or morphine (0.15mg/kg) with promethazine (0.5mg /kg) has no such effect [18]. The purpose of the administration of these drugs is the treatment of preoperative anxiety and they must fulfill a series of requirements: they must induce sleep between 6 and 8 hours before the operation; they should not produce drowsiness the next morning; they should not accumulate in the body in such a way that they interfere with anesthetic drugs; its pharmacokinetics should not be modified due to moderate renal or hepatic impairment; they should not have serious side effects [23]. There are two cases in which promethazine is administered preoperatively [11] or intraoperatively [17] to control nausea and vomiting in the postoperative period associated with certain types of anesthesia and to induce a preoperative and intraoperative sedation, although it can also be used as an adjunct to general anesthesia [24]. The use of promethazine and benzodiazepines is not indicated in children under 3 months due to deficiency of the detoxifying enzyme and decreased renal function. In addition, a paradoxical reaction characterized by hyperexcitability and nightmares can be induced in children receiving doses between 75 and 125mg [24]. In this type of patients, it is recommended to incorporate an anticonvulsant prophylaxis as described in 2 cases [11,12] with phenytoin infusion at 2mg/kg/h associated with dextrose to prevent hypoglycemia [11] or 100 mg intravenous [12]. Children who are premedicated with anticonvulsants with pentobarbital (2.2mg/kg), glycopyrrolate (7.5-10μg/kg) or morphine (0.18mg/kg) do not show changes in gastric volume nor do they significantly alter pH [19]. The use of glycopyrrolate in two cases of those studied [11,13] is indicated by its potent antisialogue effect (twice as long as atropine and lasts 3 times longer) since it helps intubation, does not generate effects on the central nervous system (CNS) , induces lower tachycardia, as does atropine, and protects against the bradycardiating effects of neostigmine and pyridostigmine [25].

It is very important to start an anticoagulant prophylaxis with acetylsalicylic acid (ASA), which is widely accepted, since it was performed in all the cases studied [10-15,17]. The ASA is a COX inhibitor and of the synthesis of TXA2 in the platelet, preventing the formation of the primary hemostatic plug and its effect lasts for approximately 7 days, since it generates an irreversible inhibition and only disappears once new platelets have been generated [26]. Dipyridamole, meanwhile, is an inhibitor of phosphodiesterase and adenosine deaminase, which generates an increase in cAMP levels [26]. Its anticoagulant effect is not very potent, but in combination with ASA it enhances its effect [26] as was done in a case of those studied [15] due to its vasodilator properties, in addition to the incorporation in the latter of a type of heparin. The suspension of aspirin with dipyridamole is not necessary during superficial surgeries (such as dermatological ones), of small territories (such as inguinal hernia) or of poorly vascularized areas (such as cataracts or lectomy) [26]. Only the treatment with these drugs should be suspended in those interventions that condition its success, such as those that present significant hemorrhagic risk or in which hemostasis is difficult [26]. The French Society of Anesthesia and Resuscitation (SFAR) states that there is no laboratory hemostasis test that has a predictive value of hemorrhagic risk and that when the use of this type of antiaggregant cannot be suspended, they are replaced by short-lived NSAIDs like flurbiprofen [26].

Intraoperative Process

Once the patient is transferred to the surgical area, proper monitoring of vital signs must be performed. Emphasis should be placed both on respiratory parameters, in order to control apneic or desaturation episodes that warn of possible pulmonary thromboembolism, such as cardiac parameters, by means of a continuous ECG reading that can reveal any sign of the oculocardiac reflex, OCR (bradyarrhythmias, blockages or even cardiac arrest) [19]. This reflex is caused by applying pressure on the eyeball, which activates afferent fibers through the ophthalmic branch of the trigeminal nerve to the Gasser ganglion, which acts by stimulating parasympathetic tone, reflecting this in cardiac activity [27]. In most of the cases studied [10,11,13,14,17] endotracheal intubation (ETI) was used as a measure of airway management, using endotracheal tubes for which the caliber was adapted to the patient's age, oscillating between 4 to 8mm. At present, the use of the laryngeal mask, as has been seen in one of the cases16, is gaining interest, as a substitute for ETI due to the advantages it presents against it, since it does not produce changes in intraocular pressure (IOP) or in hemodynamic stability [21,28]. However, the practice of ETI is not eclipsed, as there are studies that demonstrate that this technique, in combination with the immediately preoperative administration of corticosteroids such as dexamethasone, reduces the risk and complications of extubation in pediatric patients [29]. However, in the retrospective study conducted by Romero *et al*. at the Hospital of San José (Bogotá), it was concluded that, despite being a common technique, a method should be established that matches the necessary measures for its correct performance, considering the dose and duration of this corticosteroid [25].

Likewise, the application of prophylaxis against deep vein thrombosis (DVT) is considered of vital importance due to the high risk that these patients present to suffer thromboembolic events. This prophylaxis can be achieved by: repeated lower limb massage every 5-10 minutes, leg elevation or pneumatic compression every 15 minutes, as has been observed in some of the cases seen [11,14,16].

When inducing and maintaining anesthesia, the risks and side effects of each of the drugs used in surgery must be considered. It has been proven that halothane has a greater bradycardiating and pro-arrhythmogenic effect than other halogenated anesthetics such as desflurane or sevoflurane, the latter being the one with more vagolytic activity, giving a lower incidence of OCR [21]. Similarly, rocuronium, a non-depolarizing amino-steroidal neuromuscular blocker, generates a decrease in the frequency of occurrence of OCR compared to other drugs such as vecuronium. The same applies to atropine, which has been proven that, if administered before eye surgery, it is capable, not only of reducing the risk of OCR, but also of generating a cardioprotective effect [27]. It has been shown that in anesthetic induction, the most commonly used general anesthetic in studies, propofol [12,15], can increase the incidence of OCR. However, an alternative to the use of propofol is thiopental, a barbiturate that was used in two of the cases studied [11,17] in combination with atropine.

A point to consider in the surgical interventions of patients with hyperhomocysteinemia is to induce and maintain anesthesia using nitrous oxide, a chemical compound capable of acting as an inhibitor of the enzyme methionine synthase because of its ability to inactivate vitamin B12, cofactor of said enzyme. In this way, there is a blockage of the homocysteine remethylation pathway, causing its accumulation in the blood and may aggravate the patient's long-term disease course [30]. Therefore, in most of the cases studied, it is recommended not to use it [10,12-14, 16,17], although in two of the studies it was used in an unjustified way [11,15].

Intravenous administration of dextran is indicated for the prevention of pulmonary thromboembolism and deep vein thrombosis due to its anticoagulant capacity, as seen in two of the cases studied [11,15], in which one was administered intraoperatively and continued until complete the 250 mL infusion [11], and in another it was used specifically in the postoperative period at a lower dose [15].

For the reversal of anesthesia, neostigmine was used in five of the cases [11-15], two of which was in combination with glycopyrrolate [11,13], which was done to avoid a cholinergic syndrome [31]. The average duration of the interventions studied [12-15] oscillates around two hours and they develop without incident.

Postoperative Process

One of the main postoperative complications in eye surgery, in addition to pain, are postoperative nausea and vomiting (PONV) [21], so one of the ideal objectives would be to minimize these risks and ensure a favorable evolution for the patient. Intraoperative intravenous lidocaine that was administered to one of the patients was performed as a prevention of pain generated during extubation [14]. Likewise, it has been proven that intravenous infusion of this local anesthetic improves the management of postoperative pain [32].

Other pharmacological measures of pediatric postoperative analgesia are the use of tramadol [11], paracetamol or diclofenac, which has shown, not only to alleviate pain, but to relieve PONV. The incidence of PONV can be reduced by: the use of dexamethasone [33,34], propofol [35], intraoperative oxygen therapy [35], hydration with colloids [35] or with intra and postoperative opioids [35]. In the same way that some drugs and measures act positively to relieve symptoms, there are others that have no effect on the appearance of NVPO, such as rocuronium [21], and others that worsen their situation, such as nitrous oxide [35], inhaled anesthetics [35], etomidate [35] or ketamine [35-37].

Conclusions

With the review of a series of clinical cases and studies, the need arises to establish an anesthetic strategy that encompasses a series of pre, intra and postoperative objectives in order to reduce the risks to which a patient with these characteristics is subjected in a surgical process.

Preoperative Objectives

o Hyperhydration.

o Vitamin pharmacological therapy.

o Anticoagulant prophylaxis.

o Anticonvulsant prophylaxis if there is a history of seizures.

o Avoid episodes of hypoglycemia by administering dextrose.

Intraoperative Objectives

o Patient monitoring: ventilatory and cardiac parameters.

o Fluid therapy with crystalliods.

o Prophylaxis of deep venous thrombosis.

o Anticoagulant prophylaxis.

o Minimize the likelihood of causing ocular-cardiac reflex.

o Avoid the use of nitrous oxide as an anesthetic.

o Oxygen therapy.

o Maintenance of anticonvulsant prophylaxis.

Postoperative Objetctives

o Ensure analgesia.

o Decrease the PONV.

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Conflicts of Interests

The article is free from any such conflicts between authors or with others in any aspect.

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