



HIPOVOLEMIC SHOCK SECONDARY TO USE OF ANTICOAGULANTS

ORIGINAL ARTICLE

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ABSTRACT

Hemorrhagic disorders can be related to physical elements such linings and blood vessels, or plasma elements, such as clotting factors. In this discussion we will address hemorrhagic disorders caused by drugs, with an emphasis on warfarin. Shock is defined as the failure of the circulatory system to supply oxygen to tissues to meet metabolic demands. There are 4 types of shock, divided according to the pathophysiological mechanisms that cause the disorder: hypovolemic, obstructive, cardiogenic, distributive. In this study, we will address more deeply the hypovolemic shock, as well as the management and indications of vasoactive drugs for this situation when necessary.

Keywords: Shock, hypovolemia, anticoagulation, bleeding, warfarin.

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INTRODUCTION

In the face of a patient with excessive and / or unexplained bleeding, the first step to be taken is to identify whether this bleeding is being caused by a systemic coagulopathy, or due to anatomical / mechanical disorders involving the blood vessels (SCHAFER, 2014). Hemorrhagic disorders can be considered primary when they are caused by factors related to blood vessels and platelets, while secondary disorders are related to plasma factors and the coagulation cascade (RIZZATTI e FRANCO, 2001).

AIM

Approach the bleeding disorders caused by drugs, with emphasis on anticoagulants, the type of medication used by the patient.

CLINICAL CASE

A 66-year-old male patient was admitted to the emergency department complaining of weakness, brought by the Mobile Emergency Service (MECS) due to hematemesis (vomiting with blood) and hematuria (urine with blood) from start to 3 days, associated with weakness and diffuse abdominal pain. Hypertensive, not undergoing treatment. Using Marevan (warfarin) due to stenting due to previous infarction. Companion reports that one week before the onset of symptoms, it was prescribed for the patient to start using Apixaban due to better ease. However, the patient did not understand that he needed to suspend warfarin to start Apixaban, and has been on dual anticoagulation therapy ever since. In addition to anticoagulants, he was using carvedilol, simvastatin and spironolactone.

Physical Examination: Vital Signs (Fr: 21. Fc 107. Sat 98. T ° 35.8°C. Pa 80/53) REG, pale +++ / 4+, dehydrated ++ / 4+, presence of bruises on limbs and chest. Weak and filiform pulses, cold extremities with TEC > 4s, absence of edema, free calves. Globose abdomen, distended, with the presence of multiple diffuse hematomas. Audible RHA,



painful on superficial / deep palpation, without CMV, signs of defense or peritoneal irritation.

Laboratory Tests: Blood count (Red blood cells 3.78 // Hemoglobin 12 // Hematocrit 37 // Leukocytes 12.360 without deviation // platelets 311.000), Lactate: 12.6, CKMB: 12, CPK: 176, PCR: 1.3, NA : 142, K: 8.4, KPTT: incoagulable, TAP: incoagulable

Conduct: Initially, vigorous hydration was performed with 3,000 ml of saline in 3 steps of 1,000 ml each. Even so, after this hydration, the patient remained with hypotension and signs of poor peripheral perfusion, requiring the initiation of Noradrenaline. The drug was initially started at 10 ml / h, receiving staggered increases up to 40 ml / h. In addition to this, conducts were performed to manage hyperkalaemia, with the administration of a polarizing solution and calcium gluconate.

ANTICOAGULANT THERAPY

Our patient was using anticoagulant therapy due to recent stent placement. The new guidelines of 2018, published by the international Delphi consensus, confirm that anticoagulation is more effective in reducing adverse events in the patient after stent placement, when compared to the treatment previously recommended, of double antiplatelet therapy (MILINIS *et al.*, 2018).

Warfarin is a vitamin K antagonist, which acts by inhibiting the production of vitamin K-dependent clotting factors (II, VII, IX, X) (WEITZ, 2017). Hemorrhage is the main complication of this drug, and it is more common in the first 3 months of use, and in patients over 65 years of age. (CASTRO *et al.*, 2014). In addition, the presence of comorbidities such as arterial hypertension, cancer, cerebral vascular disease, severe heart disease, kidney failure, alcoholism and liver disease are also risk factors for bleeding in patients using warfarin. (TERRA-FILHO e MENNA-BARRETO, 2010). Apixaban belongs to the class of new oral anticoagulants. This class acts by directly inhibiting the activated factor X from the coagulation cascade (LORGA FILHO *et al.*, 2013). They are better and more comfortable options than warfarin because they can



be administered in fixed doses, without the need for laboratory monitoring (WEITZ, 2017).

The therapeutic target during anticoagulation is to keep the INR between 2 and 3 (TERRA-FILHO e MENNA-BARRETO, 2010). However, the anticoagulant effects of warfarin therapy alone are delayed (WEITZ, 2017). When we want to reach the anticoagulant potential quickly, as in patients at high risk for thrombotic events, it is common to associate another parenteral anticoagulant drug until the desired INR is achieved (LORGA FILHO *et al.*, 2013). It is indicated to associate drugs such as common heparin, low molecular weight heparin or fondaparinux for at least 5 days when starting warfarin therapy (WEITZ, 2017).

The principles of treatment in patients with bleeding using anticoagulants are: suspend the causative drug, support measures (hydration, transfusion, vasoactive drug), consider an antidote or stop bleeding measures (aminocaproic acid, tranexamic acid and prothrombinic complex) (CASTRO *et al.*, 2014). The warfarin antidote is vitamin K, while new oral anticoagulants do not have specific antidotes (MARTINS, 2017; WEITZ, 2017).

WHAT IS SHOCK?

Our main syndromic diagnosis in this case was shock, caused by a probable blood dyscrasia secondary to the erroneous use of anticoagulants. But what would be a shock? Shock is defined as the failure of the circulatory system to supply oxygen to tissues to meet metabolic demands (SIQUEIRA e SCHMIDT, 2003). There are 4 types of shock, divided according to the pathophysiological mechanisms that cause the disorder: hypovolemic, obstructive, cardiogenic, distributive (MARTINS, 2017a). Hypovolemic shock is caused by a reduction in blood volume (hypovolemia), being the most common type of shock (MOURAO-JUNIOR e SOUZA, 2014).



PATHOPHYSIOLOGY

Regardless of the etiology of shock, they all share in common the reduction of capillary filling, with consequent less oxygen supply to the tissues (MOURAO-JUNIOR e SOUZA, 2014). As a consequence of hypoxia, with less oxygen supply to cells, mitochondrial activity decreases, depleting ATP reserves in the organelle (MAIER, 2017). In order to maintain the production of ATP, the body goes into anaerobic metabolism, with an increase in intracellular lactate, and a decrease in PH (MARTINS, 2017). The accumulation of these metabolites of anaerobic metabolism triggers the release of inflammatory mediators and systemic inflammatory activation (MAIER, 2017). This inflammation causes damage to the vascular endothelium, worsening hypoperfusion (MARTINS, 2017a). All of these substances are cytotoxic, and induce cellular damage (mainly mitochondrial damage). This further reduces the production of ATP, perpetuating the cycle (MAIER, 2017).

Acidification of the intracellular environment, and mitochondrial damage, are accompanied by endothelial injury, which stimulates platelet aggregation and activation of coagulation (MARTINS, 2017a). Due to this, disseminated intravascular coagulation can occur, with thrombotic phenomena, associated with hemorrhagic phenomena secondary to the consumption of components of the hemostatic system. (SCHAFER, 2014).

In order to prevent hypoxia, and to restore circulation, the body triggers numerous compensation mechanisms (MARTINS, 2017a). Initially, the sympathetic nervous system releases norepinephrine and other mediators (such as vasopressin, endothelin, thromboxane and others) that will cause vasoconstriction in order to improve perfusion (MAIER, 2017). After that, the cardiac function is directly stimulated by these same mediators, in order to increase the heart rate (chronotropism) and the contraction force (inotropism) (BIAGGIONI e ROBERTSON, 2014). Then, activation of the renin-angiotensin-aldosterone system begins at the renal level, which will increase the reabsorption of sodium and water in order to increase blood pressure, to optimize tissue perfusion. (MARTINS, 2017a).



CLINICAL MANIFESTATIONS

Each part of this complex mechanism explains the appearance of the main signs / symptoms related to shock. The reduction in tissue perfusion is expressed by hypotension and inadequate peripheral perfusion (SIQUEIRA e SCHMIDT, 2003). Poor peripheral perfusion is evidenced by findings of cold, sticky skin with slow capillary filling (> 3 seconds) (MARTINS, 2017). The release of neurotransmitters to increase cardiac function is responsible for tachycardia and tachypnea (MOURAO-JUNIOR e SOUZA, 2014).

Activation of the renin-angiotensin-aldosterone system increases the reabsorption of water and sodium from the urine, causing the oliguria or even anuria seen in shock (MAIER, 2017). Oliguria / anuria can also be explained by renal hypoperfusion, which causes a decrease in the glomerular filtration rate (MARTINS, 2017a). Decreased body perfusion in the nervous system manifests itself with changes in mental status, ranging from agitation, delirium or mental confusion, to fogging or coma (SIQUEIRA e SCHMIDT, 2003). It is worth mentioning that each shock etiology will present different manifestations, which can contribute to the diagnosis (MARTINS, 2017a).

HYPOVOLEMIC SHOCK

After this general approach, we will focus on our patient's specific type of shock. As we discussed above, hypovolemic shock is one that occurs due to blood loss, with reduced blood volume (hypovolemia)(MOURAO-JUNIOR e SOUZA, 2014). Blood loss can be hemorrhagic or non-hemorrhagic. Hemorrhagic is related to blood loss, which may be related to trauma, or non-traumatic (digestive hemorrhage, spontaneous bleeding, ruptured aneurysm, vascular lesions, among others)(MARTINS, 2017a). Non-hemorrhagic loss, on the other hand, involves loss of fluid in a way that does not involve bleeding, such as fluid loss through the gastrointestinal tract (diarrhea, vomiting) or urinary tract, loss to the third space, insensible losses, among others (MAIER, 2017).



TREATMENT

The pillars of treatment are: restoring systemic perfusion and correcting hypoxia, and identifying the underlying cause for specific treatment. To restore the perfusion, we started an aggressive volume replacement (20 ml / kg). Volume response should be monitored by decreasing tachycardia, improving urine output and neurological status (MARTINS, 2017a). The type of solution used will depend on the degree of shock. Crystalloid is generally used, with blood and blood products restricted to losses greater than 30% of the total volume (SIQUEIRA e SCHMIDT, 2003). In patients suffering from heavy bleeding, compound therapy, performed with the transfusion of fresh frozen plasma and platelets, as well as the use of specific coagulation factors and vitamin K increases survival in these patients. (MAIER, 2017; MARTINS, 2017a). In an emergency, only vitamin K alone cannot control bleeding, requiring the use of fresh frozen plasma, which contains the clotting factors already synthesized (BIAGGIONI e ROBERTSON, 2014; MARTINS, 2017a).

The goals for volume replacement are to reach the following parameters: TEC <3s, urine output > 0.5 ml / kg / h and MAP > 65. If there is no response to volume replacement, vasoactive drugs should be associated (MAIER, 2017). The main vasoactive drugs we have today are: Noradrenaline, Epinephrine, Dopamine, Dobutamine, Phosphodiesterase 3 inhibitors, levosimendan and methylene blue (MARTINS, 2017a). According to the pharmacological mechanism, each drug can act by stimulating chronotropism, inotropism, or by vasopressor action (BIAGGIONI e ROBERTSON, 2014).

NORADRENALINE

It is an endogenous catecholamine, which interacts with alpha and beta adrenergic receptors. Alpha 1 receptors, when activated, have a vasoconstrictor effect, causing an increase in blood pressure. While alpha 2 receptors have local vasoconstrictor effects, however their sympatholytic effect on the central nervous system predominates, becoming a hypotensive (BIAGGIONI e ROBERTSON, 2014). Beta receptors have the effect of increasing cardiac output and stimulating heart contractility



(MARTINS, 2017a). It is worth mentioning that beta 1 receptors have an effect only on the heart, whereas beta 2 receptors have effects on the heart and bronchial muscles, causing bronchodilation when stimulated. (BIAGGIONI e ROBERTSON, 2014).

Noradrenaline has a predominant stimulating effect on alpha 1 and beta 1 receptors, having no effect on alpha 2 and beta 2 receptors (MARTINS, 2017a). Its pharmacological properties make it a potent chronotropic, inotropic agent with vasopressor properties (BIAGGIONI e ROBERTSON, 2014). Therefore, this is the drug of choice in hypovolemic shock. (MARTINS, 2017a). The usual dose is 0.03 to 2 µg / Kg / min (SIQUEIRA e SCHMIDT, 2003).

ADRENALINE

Like norepinephrine, it is also an endogenous catecholamine (MAIER, 2017). The difference between them is that in addition to the stimulating effect of alpha 1 and beta 1 receptors, this drug also has an effect on beta 2 receptors (BIAGGIONI e ROBERTSON, 2014). Due to its stimulating effects of beta 2 with bronchodilation induction, it is the first drug indicated in anaphylactic shock (MARTINS, 2017). It also has inotropic, chronotropic and vasopressor action (BIAGGIONI e ROBERTSON, 2014).

DOPAMINE

It is a natural precursor of catecholamines (BIAGGIONI e ROBERTSON, 2014). The standard dose is 2 to 20 mcg / kg / min. In doses of 5 to 10 mcg / kg / min it has beta-adrenergic action, with increased frequency and inotropism. Dose greater than 10 mcg / kg / min alpha adrenergic action predominates, with increased peripheral vascular resistance and blood pressure (MARTINS, 2017a).

DOBUTAMINE

It is a synthetic catecholamine, with selective beta 1 action that has predominantly inotropic action (BIAGGIONI e ROBERTSON, 2014). Used at a dose of 2.5 to 20 mcg



/ kg / min, it is indicated in cases of heart failure and cardiogenic shock (MARTINS, 2017a).

PHOSPHODIESTERASE 3 (MILRINONE) INHIBITORS

It has a positive inotropic action, as it increases the force of cardiac contraction, and induces pulmonary vasodilation, being very useful for situations of right ventricular dysfunction. (MARTINS, 2017a).

LEVOSIMENDAN

It is a drug that acts by increasing the sensitivity of cardiac fibers to calcium ions, stimulating the contraction of these (BIAGGIONI e ROBERTSON, 2014). Increases cardiac contractility without increasing O₂ consumption, however its vasodilating effect contraindicates it in a situation with low blood pressure (MARTINS, 2017a).

METHYLENE BLUE

Nitric oxide is an important endogenous vasodilator (MAIER, 2017). It works by stimulating an enzyme called guanylyl cyclase, which will decrease the amount of intracellular calcium in smooth muscles. This action prevents the contraction of the smooth muscle of the endothelium, and favors vasodilation (STOCHE *et al.*, 2004). Methylene blue is a competitive antagonist of this enzyme, which, by inhibiting it, causes vasoconstriction (GARCIA e OLIVEIRA, 2013). It is indicated in catecholamine-refractory shock (STOCHE *et al.*, 2004).

DISCUSSÃO

Our patient is an elderly man, who had just undergone a catheterization with stent placement, and was using anticoagulant. As we saw earlier, anticoagulation is more effective in reducing adverse events in the patient after stent placement, when compared to the treatment previously recommended, with double antiplatelet therapy (MILINIS *et al.*, 2018). However, when talking to the companion, he reports that the patient was using two simultaneous anticoagulants. We also saw earlier that it is



indicated to associate drugs such as common heparin, low molecular weight heparin or fondaparinux for at least 5 days when starting warfarin therapy, until the anticoagulant potential is reached (WEITZ, 2017). As far as we can understand, the patient should have stopped one of the anticoagulant medications after a certain period. However, the patient did not suspend one of the medications, and remained using the combination of anticoagulants indefinitely, causing the INR to leave the therapeutic range, increasing to an incalculable value.

What led him to seek help was a complaint of severe weakness, after 3 days with hematemesis and hematuria. On physical examination, we see clear signs suggestive of shock: hypotension, decreased capillary filling time, weak, filiform pulses with cold extremities, and dehydration. Spontaneous abdominal pain and during the examination leads us to believe that there is intra-abdominal bleeding. This suspicion becomes even stronger in view of the presentations of hematemesis and hematochezia that the patient continually presented during hospitalization. Another important sign is the multiple hematomas observed in the chest, abdomen and limbs. These represent hemorrhages in the skin, caused by the leakage of blood cells to the dermis and subcutaneous tissue (RIZZATTI e FRANCO, 2001). These signs found in the physical examination, if added to the complaint of spontaneous bleeding and weakness, allow us to confirm the syndromic diagnosis of poor perfusion or shock. Now we have to think, what is causing this shock? We can hypothesize innumerable causes, such as dengue or other hemorrhagic diseases, hemophilia or other diseases of hemostasis. However, the fact of being a patient using oral anticoagulant, with spontaneous bleeding, strongly points to a probable blood dyscrasia caused by inappropriate use of the anticoagulant.

Analyzing the laboratory exams, we have several indications that confirm the hypothesis of hemorrhagic disorder. In the blood count, the low red blood cells are compatible with the blood loss that the patient has been presenting. Hemoglobin and hematocrit are still normal. The KPTT and TAP tests are tests that assess blood clotting (WEITZ, 2017). These methods of coagulation assessment aim to determine the time of fibrin clot formation (BIAGGIONI e ROBERTSON, 2014). The fact that they are



incoagulable, confirms our hypothesis of anticoagulant misuse, causing blood dyscrasia.

Another important finding is lactate, which is increased. This metabolite is a marker of anaerobic metabolism, and when increased it represents the shift towards anaerobic metabolism, in response to tissue hypoxia (CICARELLI *et al.*, 2007). The CPK enzyme means creatine kinase, and it is an enzyme that is located inside the skeletal and smooth muscles. Its elevation represents that there was muscle injury (either smooth or skeletal) that caused its elevation. CK-MB represents the myocardial fraction of CPK, and rises when we have damage to the heart muscle (WILLIAMSON e SNYDER, 2016). In our patient, the increased CPK represents muscle damage, but does not specify which.

Another interesting aspect in this case is the hyperkalaemia presented by the patient. Depletion of intravascular volume reduces renal perfusion. As a result, the glomerular filtration rate is reduced, sodium is not reabsorbed, and potassium is not excreted. So our patient's potassium was high (MAIER, 2017). The treatment options for hyperkalaemia are: Furosemide, sorghum resin, inhalation with beta-agonists, polarizing solution (glucose + insulin), sodium bicarbonate, dialysis (MARTINS, 2017a). Furosemide is a loop diuretic that acts by inhibiting the reabsorption of sodium and water in the henle loop (BIAGGIONI e ROBERTSON, 2014). The loss of sodium and water stimulates the activation of the renin-angiotensin-aldosterone system that seeks to increase sodium reabsorption, with consequent potassium excretion (MAIER, 2017). Sorbal resin aims to reduce intestinal potassium absorption, and act as an ion exchanger, assisting in the excretion of potassium (MARTINS, 2017a). Beta agonists have the effect of stimulating cellular potassium transporters, and inducing their entry into the intracellular medium, decreasing the serum concentration (DUTRA *et al.*, 2012). Insulin has an important effect in stimulating the entry of potassium into the intracellular medium, decreasing the serum concentration of potassium (PONTES-NETO *et al.*, 2009). However, if only insulin were used, there would be a risk of causing hypoglycemia. Therefore, insulin is administered along with glucose 50%, to prevent this adverse effect, thus forming the polarizing solution. (MARTINS, 2017a).



Bicarbonato induces the exchange of potassium by H⁺ by the cell (potassium enters, H⁺ exits). Finally, calcium gluconate is a myocardial stabilizer. It will not act in reducing potassium, but it will antagonize its effects on nerve fibers (PONTES-NETO *et al.*, 2009). High potassium inactivates fast sodium channels, blocking the conduction of the myocardial action potential. Thus, the administration of calcium gluconate acts by normalizing the difference between the resting potentials and the activation threshold, restoring the excitability of the membrane (OLIVEIRA *et al.*, 2014). It is indicated whenever there is an electrocardiographic change associated with hyperkalemia (MARTINS, 2017a).

In view of this quick review, we have some options available for treating hyperkalemia. However, one of the listed options, furosemide, in this case is not indicated, because as it is a diuretic, it will deplete the patient's intravascular volume, and in this patient, with hypovolemic shock, the intravascular volume is already reduced, so furosemide will make this situation worse.

CONCLUSION

In view of this case, we were able to establish an etiological reasoning for the vast majority of the manifestations presented by this patient. The misuse of the anticoagulant triggered the hemorrhagic diathesis that led the patient to have multiple foci of bleeding, evolving to hypovolemic shock. It is noted here the importance of adequate patient guidance about treatment, in order to clarify any doubts that the patient may have, in order to avoid iatrogenies. The actions taken were all aimed at restoring the patient's perfusion and circulating volume, in addition to other measures to support complications (such as treating hyperkalemia resulting from renal hypoperfusion). Despite vigorous hydration, the use of norepinephrine cannot be avoided, and even with the use of the specific antidote for the anticoagulant in question (vitamin K), it was not possible to reestablish the normality of coagulation tests during the hospitalization period in the emergency room.



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