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Diseases and Treatment with NOA: Mini Review of Trauma Coagulopathy

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ABSTRACT

Background: *A key element of a geriatric patient is the problem of frailty. We generally identify a frail subject through sarcopenia, that is, the progressive reduction and thinning of the muscle mass. The sarcopenic subject falls because he cannot stand on his legs, including a whole series of endocrine, glucidic and neurological dysregulations that should have an extremely significant probability of falling.*

Objective: *The purpose of this article is, starting from pharmacological aspects of noa, to evaluate how to deal with a traumatized patient in the treatment with noa.*

Methods: *Both personal knowledge of pharmacology and the use of both paper books and international website databases such as pubmed, scopus, google scholar, researchgate were used to develop the article, typing in keywords such as "trauma coagulopathy" or "elderly patient treatment with noa" associated with specific compound names.*

Conclusions: *In an elderly subject who reports a head injury, even a mild one, we may find a chronic subdural hematoma that is so easily achieved due to cerebral atrophy, the greater excursion of the brain into the skull that tears the subdural vessels. In addition, why frequently the elderly subject takes the antithrombotic drug: cardioaspirin, warfarin, but above all the new oral anticoagulants.*

Keywords

Trauma, Hypothermia, Acidosis, Moschcowitz Syndrome.

Introduction

Trauma-associated coagulopathy is part of the fatal triad process along with hypothermia and acidosis. The motive for the process would be the condition of systemic shock and hypoperfusion. Most of the acquired coagulopathies depend on a defect of hepatic synthesis, primary (severe liver disease, hepatic immaturity in the newborn) or secondary to vitamin deficiency. K. Acquired haemophilia is very rare, and is caused by the development of specific autoantibodies capable of inhibiting clotting factors, especially FVIII.

Disseminated Intravasal Coagulation (DIC)

It is an acute, subacute, or chronic thrombotic-hemorrhagic syndrome, in which there is excessive activation of blood clotting, which causes thrombus, excessive consumption of platelets, and clotting factors (consumption coagulopathy), favoring bleeding episodes [1]. It is generally caused by sepsis due to Gram-negative bacteria, obstetric problems: Abortion, Retention of the dead fetus, Embolism of the amniotic fluid, by neoplasms (generally acute promyelocytic leukemia) and by autoimmune processes that promote platelet aggregation, damage endothelial cells, induce the synthesis of tissue thromboplastin by the monocyte/macrophage system or from severe trauma or shock, through: Extensive endothelial damage (hypoperfusion, hypoxia, acidosis). The reduction of splanchnic circulation greatly reduces the hepatic clearance of activated factors and FDPs.

DIC leads to the consumption of platelets and clotting factors, and the severity of the final deficit of platelets and plasma factors depends not only on the rate at which they are consumed but also on the rate at which they are replaced [2]. In fact, consumption can be compensated or decompensated: in the latter case, thrombocytopenia and the deficit of plasma factors leads to hemorrhagic syndrome. The intravasal deposition of fibrin clots, together with the reduction of antithrombin and protein C, can lead to particularly frequent vascular occlusion in renal microcirculation [3]. Vascular occlusion is opposed by fibrinolysis, which, in DIC, is not a pathological phenomenon, but a physiological one. The D-dimers and FDPs that are formed in large quantities aggravate the hemorrhagic syndrome, interfering with platelet function, with the action of thrombin, and with the polymerization of fibrin [4]. Following the excessive consumption of platelets and coagulation factors, the opposite phenomenon occurs in the terminal phase of the disease, that is, generalized bleeding. Occasionally, thrombi may be found in large-caliber vessels. Acute DIC leads to death rapidly either from CNS haemorrhages or from rapid blood loss or necrosis of the parenchyma. As for the diagnosis, thrombocytopenia occurs, lengthening of the bleeding time, PT and PTT, decrease in fibrinogen and coagulation factors, decrease in antithrombin III (consumed in an attempt to curb excessive coagulation). The treatment, on the other hand, involves the administration of low molecular weight heparin to decrease blood clotting (only in chronic DIC, because in the acute form it would cause hemorrhage). Transfusions are also recommended when there is a marked reduction in the number of platelets [5].

Purple Thrombotic Thrombocytopenic (PTT) or Moschcowitz Syndrome

Thrombotic thrombocytopenic purpura is a severe acute blood disease, characterized by the pathological formation of platelet aggregates (thrombus) which, by blocking the blood vessels, cause a dangerous decrease in the supply of oxygen to various organs (kidneys, liver, heart, brain, etc.) [6].

There are two forms

1) Acquired. Over 99% of cases
2) Hereditary (Upshaw-Shulman syndrome)

NOA

NAOs are drugs with a low therapeutic index that require the administration of constant daily doses and do not require periodic checks of anticoagulant activity, which is why they are preferred over other drugs [7]. They can be direct thrombin inhibitors (eg: dabigatran), or factor X inhibitors (eg: rivaroxaban). They have a rapid therapeutic action and disappearance of the effect (useful in case of overdose). PK and PD are very predictable. Furthermore, they have limited drug and oral interactions and fewer side effects, and ultimately low prices. In addition, the clinical effect is present for a few hours after taking and disappears on average in 24 hours about renal function, which, among other things, makes "bridging therapy" with heparin unsuitable in the case of surgical interventions [8]. About treatment with oral anticoagulants in non-valvular atrial fibrillation, all elderly patients indicate oral anticoagulant therapy, regardless of the bleeding risk [9]. New oral anticoagulants, even in elderly patients, should be preferred over warfarin. Dabigatran etc. as the elderly have a high prevalence of AF and a greater risk of thromboembolic and haemorrhagic complications [10].

The elderly are certainly the category most at risk because they undergo chronic treatment being subject to long-term therapies. After all, there are pharmacokinetic alterations in these and above all, they have multiple pathologies for which multiple therapies are necessary (the elderly have a risk of developing pathologies almost double iatrogenic compared to younger subjects, one in ten hospitalization in a geriatric ward is related to iatrogenic pathologies therefore due to this kind of drug interactions). In the case of elderly patients, it is necessary to adjust the dosage as the elimination half-life is 2-3 times longer than in adults. In the elderly, aminoglycosides should be avoided if possible [11].

APIXABAN

Indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as a previous stroke or transient ischemic attack It is also used in the treatment of venous thrombosis deep (Tvp) and pulmonary embolism (Ep) and in the prevention of relapses [12].

DABIGATRAN (Pradaxa)

It has a low bioavailability, so it has fewer indications than other classic noa. The fundamental renal excretion with this oral anticoagulant is today only indicated if creatinine clearance> 30 ml/min, unlike Warfarin. It has a low protein binding and its effect

lasts for 12-24h (versus 2-3 days of Warfarin): this is an advantage in the case of an overdose, but if the patient forgets to take it is not covered and is at risk increased in thrombosis. Pradaxa 150 mg and 110 mg for example are indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, arterial hypertension, age> 75 years, previous diabetes mellitus stroke, or TIA. The latter is also used for the primary prevention of thrombo-embolic episodes in adult patients undergoing elective total hip and knee replacement surgery.Its antidote is Idarucizumab (Ab monoclonal) [13,14].

EDOXABAN – (Lixiana, Daiichi Sankyo)

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, arterial hypertension, age 75 years or more, diabetes mellitus, previous stroke, or transient ischemic attack (TIA). It is used for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the prevention of recurrence of DVT and PE in adults [15].

Risks and Benefits of NAO

Noa are much more manageable than other anticoagulants, they do not need dosage, the dose is given about weight, and the kidney conditions are evaluated and that's it. Yes, but with bleeding risk, a risk of bleeding that is almost double that of warfarin and cumadin, if the range of INR is between 1 and 3 [16]. When a patient is given, for example, fibrillating, a very frequent condition, cumadin is by force because the fibrillating patient must do prophylaxis for the thromboembolic risk, otherwise, the patient gets a stroke, and then this administration is done perhaps because we want to do more than a rate control because amiodarone is also among other things a little bradycarding, but if you want to prevent ventricular events because the patient also has the heart already put under stress and therefore has many arrhythmic events, before starting to put a device, a defibrillator, amiodarone is administered [17]. And it happens that amiodarone raises the INR too much, then amiodarone is burdened with a whole series of side effects, and everyone thinks of the thyroid, it can give both hypothyroidism and hyperthyroidism, but it can give a whole other series of side effects such as pulmonary fibrosis, in fact, is feared by pulmonologists [18].

Why Is The Risk So Big With Amiodarone?

Because amiodarone is a classic drug that is given to the patient on discharge from the PS or the hospital. The patient is put on therapy with this drug to send it to the washout, to suspend it or modify it in the short term and do so for life. In addition, 75% of patients who take amiodarone have one or more complications of amiodarone, some patients already after two or three months have a thyroid problem for example [19].

When an elderly patient comes to the emergency room, the first thing you do is remove all the drugs, not because the therapy is wrong but simply because the elderly are suffering from chronic treatment and because the problem is not giving the drugs but is give them together; it is used especially in real life, when the patient is an advanced liver disease, when he is nephropathy who has a low GFR in which certain drugs either do not give them precisely because they are contraindicated or you have to reduce the dosage for the toxic effect. Among other things, amiodarone also has a cardioprotective action. Today this condition has been a bit scotomized but amiodarone has been used extensively over the years as a drug also for the ischemic patient; it was known to be an antiarrhythmic from the beginning, but it is used a lot as a coronary protector in the ischemic patient, in fact, it is not by chance that it is associated with nitro derivatives [20].

STROKE

The risk of stroke is calculated based on the CHA2DS2VASc score, which assigns a numerical value to the risk factors taken into consideration. This score turned out to be better than the previous one (CHADS2) in identifying low-risk patients who probably do not indicate anticoagulant treatment. The risk of stroke decreases by about 60% with anticoagulants; it decreases by about 20% with antiplatelet agents [21]. The risk of subdural hematoma also increases with minor trauma if the patient takes anticoagulants; this effect worsens if anticoagulants are associated with antiplatelet agents.

With these new oral anticoagulants, there are lower risks for intracranial hemorrhage but quite similar to the old anticoagulants for gastric bleeding [22]. Therefore, the old anticoagulants have intracranial hemorrhage as a problem, which of course, is frightening, since it is a serious event. This, in the literature, is reported for patients who respond well, in 1 patient out of 100. If we do the risk-benefit ratio, this, will be favorable because we have 13 "saved", with complications prevented, against 1 who may have bleeding. Moreover, when you know what the complications may be, the important thing is to implement procedures to reduce their occurrence. There may be what we now call "risk management" and we try to avoid certain "dangerous" situations [23]. Then you can decide if the patient is suitable for treatment with anticoagulant; many situations that can make the decision lean towards the opposite way; all this must be evaluated very seriously and critically by the doctor, and then proposed to the patient.

In the case of a geriatric patient with trauma, we go by steps, that is:

- Any bleeding is checked
- It treats the hemorrhagic shock
- Coagulopathy is prevented

Nothing should slow down the treatment or lengthen the surgical time.

For years it has been adopted as a necessity to reach a pressure target, with an uncontrolled filling of lactated ringer and physiological solution, creating an iatrogenic coagulation problem. The iatrogenic problem of coagulation is also linked to the inability to realize that the patient's body temperature is essential for coagulation [24].

First of all, compressible foci of bleeding must be checked using a Tourniquet (recommended by the European guidelines on the management of trauma bleeding) in complex trauma with crush or the case of massive bone or soft tissue injuries.

The time must be greater than 2 hours to avoid ischemia or nerve vascular lesions and the pressure of 250 mmHg NEVER more than an hour and a half [25]. Then we have the T-POD, a lifesaver in all respects (its positioning is a priority maneuver concerning the execution of radiographic examinations to identify the fracture) because girding a broken pelvis, especially the Santori plexus which absolutely does not go to be treated surgically, and rarely from an endovascular point of view, it allows us not to lose a lot of blood, it means not to transfuse a lot, and to avoid a series of pathologies on a respiratory basis and the basis of the transudation of the interstitium. Finally, we have the nasopharynx tamponade with Foley catheter. 1 or 2 large-caliber bladder catheters in the choanas inflated with air or water and pulled outwards to avoid bleeding of the facial mass.

The evaluation of the circulation is linked to a late marker of shock, because in some way there is a passage between the various spaces of the interstitial blood circulation and vice versa which allows in some way, if the bleeding is slow, a compensation of the volume.

Hypotension is only a late marker of shock. In fact, there is activation of physiological mechanisms of compensation: increase in HR and SV, vasoconstriction [26]. Normal blood pressure is restored but tissue perfusions may already be compromised.

If no energy arrives, the cell can die, at the mitochondrial level, the pump stops working and the potassium goes out and the sodium goes in. Some antifungals work just like that, by creating pores inside the membranes of the fungi that let electrolytes enter. In the shock, the cell of that tissue that constitutes that organ dies and thus we arrive at the MOF. When we talk about shock, we are not just talking about low blood pressure but we are talking about the delivery of O2 to the tissues (availability). So this oxygen is used for metabolism, from which CO2 waste products are formed. Actually exhaling I eliminate CO2 and H2O therefore CHO. Carbon and hydrogen derive from food (Carbohydrates, lipids, proteins) [27]. We must bring back to the metabolism everything that happens in shock, which can be defined as a reduced or inadequate supply of oxygen to the tissues, essential for keeping the cells and its functions alive, especially the Na / K ATPase. Shock is often linked to low blood pressure (hemodynamic problem) but fundamentally it is an oxygen problem, also associated with hemodynamics, since if there is no blood, there is not even oxygen, but not only, in fact in intoxication from CO the blood arrives but the patient dies, so it is not just a hemodynamic problem. At first it has the possibility of reversibility (it is time to intervene), then later it becomes irreversible and even with a therapeutic maneuver we will not have any results [28].

We can have various types of shock due to or due to a cardiogenic cause, which is due to the heart; it is perhaps the most important cause. Just think of Acute Coronary Syndrome, acute left ventricular failure, that is, the ischemic heart does not pump so the pressure is lowered and if the pressure is lowered, oxygen does not go to the tissues, etc [29].

Another cause is the hypovolemic one; for example from haemorrhage following orthopedic surgery, to a lower limb then great blood loss and therefore damage to the heart, lung, kidney. Healthy brain because the damage was to the lower limb. When the patient passes from 14 Hb before surgery to 6, we put the whole system to the test and can go into shock. Therefore, the guidelines say to administer the blood immediately if we know its group, otherwise zero negatives if we do not know. Then other causes are vomiting, diarrhea, dehydration that contribute to hypoperfusion. Here we have, in addition to oxygen-related problems, also hydro electrolytic problems [30]. The most serious hydro electrolytic problem is the loss of K, given by vomiting, which is more serious than oxygen. In addition, as a physiological aspect, it recalls the Na / K pump. If a person has gastroenteritis and diarrhea, he is in acidosis. Hyperkalaemia in acidosis is not dangerous. The dangerous one will be only in the insufficiency of the kidneys [31]. If there is no kidney failure, it is not dangerous. On the other hand, acidosis hyperkalemia is due to redistribution, that is, if there is acidosis, the H + increases, these H + go into the cell and K comes out because the cell is rich in K (150). So the K rises from 4 to 6.5.

Another cause is distributive including anaphylaxis and sepsis. The permeability of the endothelium can be altered in anaphylaxis due to the influence of cytokines given by the degranulation of the mast cells with the release of a large amount of histamine which increases permeability and a transudate is formed which goes towards the third space. At this point, the patient cannot be intubated because a tube does not pass and therefore the only solution is the tracheostomy (these are poorly supplied areas and there is no risk of injuring the thyroid because it is higher). In sepsis, there is no longer the regulation of the capillary circulation so there is a great

redistribution of the circulation towards the periphery, the opening of the shunts, an increase in permeability, a reduced venous return (the so-called preload) and the heart is not well filled, therefore not it gives pressure and if it does not give pressure it cannot even redistribute oxygen to the tissues and the tissues go into anoxia and it is not good for their cellular metabolism [32].

Another cause is cytopathic, rarer (reduced mitochondrial energy activity): CO poisoning cyanide poisoning. The vital function of ATP production cannot be completed because the respiratory chain is blocked and one dies of shock even though the pressure may be normal, but this irreversible bond is formed. CO is tasteless and odorless. One of the first symptoms of this poisoning is a very severe headache. Consequently, if this subject, near combustion, has a headache, it must be removed immediately because it may be the beginning of an intoxication [33].

Is Acidosis Hyperkalemia Less Dangerous Than Others?

Dangerous hyperkalemia is renal hyperkalemia, due to organ failure because it cannot be displaced; in acidosis, it is enough to breathe a little more quickly, there is no more hyperkalemia or you need to administer a little bicarbonate. The kidney works, therefore, potassium does not exceed 6.5 and if it does not exceed 6.5 it is not life-threatening hyperkalaemia; it can trigger an arrhythmia but cardiac arrest with ventricular fibrillation occurs with a minimum of 8.5. There is a big difference between 6.5 and 8.5 [34].

References

1. Clara L. Rodríguez-Bernal, Isabel Hurtado, Aníbal García-Sempere, et al. Oral Anticoagulants Initiation in Patients with Atrial Fibrillation: Real-World Data from a Population-Based Cohort. Front Pharmacol. 2017; 8: 63.
2. Damien Lanéelle, Charles Le Brun, Chadi Mauger, et al. Patient Characteristics and Preferences Regarding Anticoagulant Treatment in Venous Thromboembolic Disease. Front Cardiovasc Med. 2021; 8: 675969.
3. Annamaria Mascolo, Rosanna Ruggiero, Maurizio Sessa, et al. Preventable Cases of Oral Anticoagulant-Induced Bleeding Data from the Spontaneous Reporting System. Front Pharmacol. 2019; 10: 425.
4. Thorsten Haas and Melissa M. CUSHING - Hemostatic Balance in Severe Trauma
5. Kirsten Balvers, Mathijs R. Wirtz, Susan van Dieren, et al. Risk factors for trauma-induced coagulopathy- and transfusion associated multiple organ failure in severely injured trauma patients. Front Med Lausanne. 2015; 2: 24.
6. Maxim Grymonprez, Stephane Steurbaut, Tine L. De Backer, et al. Effectiveness and Safety of Oral Anticoagulants in Older Patients with Atrial Fibrillation A Systematic Review and Meta-Analysis. Front Pharmacol. 2020; 11: 583311.
7. Stein P, Kaserer A, Sprengel K, et al. Change of transfusion and treatment paradigm in major trauma patients. Anaesthesia. 2017; 72: 1317-1326.
8. Brett Mador, Bartolomeu Nascimento, Simon Hollands, et al. Blood transfusion and coagulopathy in geriatric trauma patients. Scandinavian Journal of Trauma. 2017; 33.
9. I nuovi anticoagulanti orali nel paziente anziano – giornale di gerontologia
10. Petros S. Trauma-Induced Coagulopathy. Hamostaseologie. 2019; 39: 20-27.
11. Kornblith LZ, Moore HB, Cohen MJ. Trauma-induced coagulopathy: The past, present, and future. J Thromb Haemost. 2019; 17: 852-862.
12. Duque P, Calvo A, Lockie C, et al. Pathophysiology of Trauma-Induced Coagulopathy. Transfus Med Rev. 2021; 35: 80-86.
13. Kobayashi LM, Brito A, Barmparas G, et al. Laboratory measures of coagulation among trauma patients on NOAs: results of the AAST-MIT. Trauma Surg Acute Care Open. 2018; 15: e000231.
14. Kaczynski J, Wilczynska M, Fligelstone L, et al. The pathophysiology, diagnosis and treatment of the acute coagulopathy of trauma and shock: a literature review. Eur J Trauma Emerg Surg. 2015; 41: 259-272.
15. Gratz J, Oberladstätter D, Schöchl H. Trauma-Induced Coagulopathy and Massive Bleeding: Current Hemostatic Concepts and Treatment Strategies. Hamostaseologie. 2021; 41: 307-315.
16. Gonzalez E, Moore EE, Moore HB. Management of Trauma-Induced Coagulopathy with Thrombelastography. Crit Care Clin. 2017; 33: 119-134.
17. Cohen MJ, Christie SA. Coagulopathy of Trauma. Crit Care Clin. 2017; 33: 101-118.
18. Lucisano AC, Leeper CM, Gaines BA. Trauma-Induced Coagulopathy in Children. Semin Thromb Hemost. 2020; 46: 147-154.
19. Kleinveld DJB, Hamada SR, Sandroni C. Trauma-induced coagulopathy. Intensive Care Med. 2022; 48: 1642-1645.
20. Godier A, Susen S. Trauma-induced coagulopathy. Ann Fr Anesth Reanim. 2013; 32: 527-530.
21. van Veelen MJ, Brodmann Maeder M. Hypothermia in Trauma. Int J Environ Res Public Health. 2021; 18: 8719.
22. DeBot M, Sauaia A, Schaid T, et al. Trauma-induced hypocalcemia. Transfusion. 2022; 62S280.
23. Brohi K. Trauma induced coagulopathy. J R Army Med Corps. 2009; 155: 320-322.
24. Peralta R, Thani HA, Rizoli S. Coagulopathy in the surgical patient trauma-induced and drug-induced coagulopathies. Curr Opin Crit Care. 2019; 25: 668-674.
25. Ramanathan K, Fan BE. Coagulopathy related to trauma: Is it time for a goal-directed approach. Ann Acad Med Singap. 2022; 51: 5-7.
26. Noel P, Cashen S, Patel B. Trauma-induced coagulopathy: from biology to therapy. Semin Hematol. 2013; 50: 259-269.
27. Savioli G, Ceresa IF, Macedonio S, et al. Trauma Coagulopathy and Its Outcomes. Medicina Kaunas. 2020; 56: 205.

28. Maegele M, Schöchl H, Cohen MJ. An update on the coagulopathy of trauma. Shock. 2014; 41: 21-25.
29. Hanke AA, Rahe-Meyer N. Traumainduzierte Koagulopathie Trauma-induced coagulopathy. Unfallchirurg. 2014; 117: 95-98.
30. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma. 2008; 65: 748-754.
31. Davenport RA, Brohi K. Coagulopathy in trauma patients: importance of thrombocyte function. Curr Opin Anaesthesiol. 2009; 22: 261-266.
32. Curry N, Stanworth S, Hopewell S, et al. Trauma-induced coagulopathy a review of the systematic reviews is there sufficient evidence to guide clinical transfusion practice Transfus Med Rev. 2011; 25: 217-231.
33. John AE, White NJ. Platelets and Fibrinogen Emerging Complexity in Trauma-Induced Coagulopathy. Semin Thromb Hemost. 2020; 46: 125-133.