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REVIEW ARTICLE

Neurogenic Shock in ICU

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ABSTRACT

Neurogenic shock is a state characterized by hypotension, bradycardia, and dysautonomia. It is an important condition associated with lesions in various regions along the neuraxis. The most common cause is acute spinal cord injury (SCI). Because the typical autonomic reflexes may be either abolished or dysregulated, appropriate treatment requires an understanding of the neuroanatomic substrate for the change. The time frame for manifestation of neurogenic shock is variable and can quickly progress to cause secondary injury or death, so appropriate monitoring requires a high level of suspicion and diligence. Many pharmacological interventions are tried but their efficacy is still questionable and need more prospective studies to accurately assess their real value. The best timing for neurosurgical intervention is also debatable. The initial management in the emergency room is fundamental for improved outcome with respect to neuroplasticity and neuronal rehabilitation.

Keywords: *dysautonomia, neurogenic shock, spinal cord injury.*

INTRODUCTION

Traumatic injuries of the neuraxis constitute one of the major causes of morbidity and mortality observed in the emergency room of trauma reference centers. The annual incidence varies between 15 and 52 cases per million people in the world. About 80% of the patients are young men between 15 and 35 years of age, with only 5% being children. The traumatic lesion can cause spinal cord shock, present frequently in lesions above T6, with neurogenic shock due to loss of sympathetic autonomic control. Classically, neurogenic shock has a triad of: hypotension, bradycardia, and autonomic dysreflexia.[1,2]

Shock is the clinical expression of vascular inability to adapt to the demand for tissue oxygen. It is a frequent and serious condition that endangers the integrity of the vital organs, with a high mortality rate if not radically reversed. Neurogenic shock is a distributive shock attributed to disruption of autonomic pathways within the spinal cord. Systolic blood pressure (SBP) of less than 90 mm Hg and/or mean arterial pressure (MAP) of less than 65 mm Hg are considered as hypotension and shock is a state of organ hyoperfusion with resultant cellular dysfunction. Other clinical signs include the presence of cold and clammy or even hot and dry skin, reduced urine output representing renal hypoperfusion; and altered mental status, with confusion, drowsiness, dizziness, numbness, and coma. Laboratory abnormalities that are significant for diagnosis and prognosis include hyperlactatemia (indicative of tissue anaerobiosis), increase in C-reactive protein and pro-calcitonin. Markers of organs dysfunctions are considered: creatinine, urea, bilirubin and clotting times.[3–5] Shock pathophysiology includes a variety of mechanisms: hypovolemia (loss of blood, diarrhea, vomiting, fever); cardiogenic factors (arrhythmias, myocardial ischemia, ventricular dilatation, valvulopathies); obstructive factors (cardiac tamponade, pericardial effusion, pulmonary thromboembolism, pneumothorax) or distributive factors (inability to adequately control vascular tone for tissue metabolic demand, examples being anaphylaxis, sepsis and neurological lesions that compromise response of the autonomic sympathetic nervous system). Neurogenic shock is a type of distributive shock and is usually associated with the neuraxial trauma.

PATHOPHYSIOLOGY

Several supratentorial regions, such as the insula cortex, medial prefrontal cortex, hypothalamus, and brainstem nuclei, are responsible for autonomic functions. The concept of a two-stage injury was described around 1900 by Allen.[6]

A first lesion occurs immediately after the trauma, followed by secondary lesions, triggered by the primary mechanical injury, resulting in microvascular damage, edema, demyelination, ischemia, excitotoxicity, electrolyte changes, free radical production, inflammation, and late apoptosis. Kaptanoglu et al observed that melatonin, propofol, erythropoietin and thiopental may prevent lipid peroxidation soon after the injury in experimental models. Opioids are potentially lethal to injured cells, causing blockage of the microcirculation and impairing functional restoration by acting as neurotransmitters at kappa receptors. In several models, including phase I studies in humans, the use of naloxone (opioid antagonist) improves medullary functional recovery.[7–9]

Following the spinal cord trauma, in addition to the sensory and motor deficits observed, dysautonomia is typical of neurogenic shock. During neurogenic shock, there is a predominance of the parasympathetic system over the sympathetic one, which can lead the patient to death.[10]

Hypotension as well as orthostatic hypotension improves over a few days or weeks, due to compensatory mechanisms that include: skeletal muscle activity, spasticity, increased muscle tone, resurgence of medullary sympathetic reflexes, and readaptation of the renin-angiotensin-aldosterone system.[1]

MEDULLARY SHOCK VERSUS NEUROGENIC SHOCK

During the acute phase following spinal cord trauma, massive sympathetic stimulation, mediated by α-adrenergic receptors, occurs due to the release of noradrenaline and adrenaline from the medullary layer of the adrenal gland as well as due to the disconnection of sympathetic supraspinal neurons. After 3-4 minutes, the parasympathetic nervous system predominates, with cutaneous vasodilatation, venodilatation, reduced venous return, systemic arterial hypotension, brady-arrhythmias with atrioventricular nodal blockade due to loss of sympathetic tone and absence of inotropic stimulus.

Neurogenic shock, therefore, is caused by disconnection between sympathetic supraspinal centers and their target organs. The term medullary shock refers to the transient event that follows the trauma, with suspension of the medullary reflexes below the lesion level. Spinal cord shock is characterized by sensory deficiency, flaccid paralysis, absence of spinal reflexes, and changes in thermoregulation below the level of the lesion. If the spinal cord injury is topographically elevated (cervical and/or thoracic), it may present with respiratory involvement, tetraplegia, anesthesia and neurogenic shock with associated ipsilateral Horner syndrome. In the lower thoracic lesions, there will usually be no respiratory compromise and/or neurogenic shock. Medullary shock may last for days or weeks, with an average of 4 to 12 weeks for resolution.

CLINICAL PRESENTATION

Lesions involving only the first three cervical segments require immediate ventilatory support for loss of the excitatory supraspinal drive, disrupting the function of the motor neu-

rons of the phrenic nerve. In the lesions below C3, the patients present with symptoms of autonomic nervous system impairment, including the possibility of cardio respiratory arrest a few minutes after the injury.

Cardiac Arrhythmias

Cardiovascular changes in neurogenic shock represent 40% of the causes of death of these patients in the acute phase (with their peak incidence up to day 4 days post-trauma), being represented by atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, cardiac insufficiency, ventricular tachycardia, cardiomyopathy, brady-arrhythmias, atrioventricular block and Takotsubo cardiomyopathy.[11] Sinus bradycardia is the most commonly observed arrhythmia after neurogenic shock and may occur within the first 2 to 3 weeks after neurological injury.

Respiratory System

Injuries to the rib cage are responsible for the reduction of thoracic expandability. However, as in neurogenic shock there is sympathetic deafferentation, any stimulus to the airways, such as aspiration (vagal stimulation), causes marked bradycardia, which can lead to cardiorespiratory arrest. When airway manipulation is required, the use of anticholinergics is recommended to reduce the risk of hemodynamic instability.[12-15] Any injury to the brain or spinal cord can lead to pulmonary edema, with a higher mortality rate. Increased intracranial pressure (ICP) is thought to cause parenchymal compression and ischemia, resulting in the release of catecholamines: the genesis of brain-induced pulmonary dysfunction, perpetuating an endothelial lesion that would result in increased capillary permeability. Venular adrenergic hyperresponsiveness also correlates with the genesis of neurogenic pulmonary edema, because it has α and β-adrenergic receptors.[12,13]

MANAGEMENT

Early hemodynamic support is the therapeutic goal to avoid lesions of vital organs. The Advanced Trauma Life Support (ATLS) guidelines advocate the guarantee of a safe airway with previous stabilization of the cervical spine, thus maintaining the cervical collar throughout the evaluation and management.[16,17] Classification of hypovolemic/hemorrhagic shock, as advocated by the ATLS, should be observed with caution in the presence of neurogenic shock. Mutschler et al. propose an alternative classification for these cases, considering the base excess (BE) values for indications of blood products in polytraumatized patients with associated severe brain and/or medullary lesions.[18,19]

The administration of oxygen should be initiated immediately in patients in shock, so that there is adequate supply to the tissues as well as the microcirculation, also preventing pulmonary hypertension. The persistence of hypoxemia, dyspnea, lowering of consciousness level, ventilatory accessory muscle fatigue, acidosis and persistent cyanosis are indicative of orotracheal intubation with mechanical ventilation (MV). However, orotracheal intubation with laryngoscopy and tracheal stimulation induces bradycardia due to vago-vagal reflexes, and may lead to cardiorespiratory arrest, especially in hypoxemic patients.

The use of sedatives and hypnotics should be done in the smallest dose possible, reducing this frequently observed hypotensive effect. The use of succinylcholine during orotracheal intubation should be avoided in patients with neurogenic shock as this may lead to cardiorespiratory arrest and hyperkalemia due to hypersensitivity of the membranes of muscle cells. The use of opioids in the first 7 days after trauma is known to impair motor medullary rehabilitation and lead to the formation of hypersensitive fibers responsible for neuropathic pain.[20]

Resuscitation to restabilize the microcirculation perfusion is the initial goal in the treatment of shock. The mnemonic VIP alludes to the initial concerns about the patient in shock: V (Ventilatory support), I (Infusion - resuscitation with fluids) and P (Pump - administration of vasoactive drugs).

Infusion of fluids should take into account the type of fluid to be administered (crystalloids are the first options), indication, availability and the rate of infusion (should not exceed 300 to 500 mL over a period of 20 to 30 minutes). The goal of volume replacement is to target SBP of 120 mm Hg or higher, urinary output greater than 0.5 mL/kg/hr, central venous pressure (CVP) between 8 and 12 mm Hg and venous oxygen saturation (superior vena cava) of 70%. The concept of permissive hypotension cannot be considered in the presence of neurological injury. Volume caution should be taken as there is risk of concomitant pulmonary oedema.

In patients with neurogenic shock who remain hypotensive and bradycardic, administration of atropine in continuous infusion should be considered in combination with catecholamines. Adrenergic agonists are the first choice of vasoactive drugs in shock, since their high potency and rapid onset with short half-life facilitate their adjustment. Noradrenaline is the vasopressor of choice, possessing predominantly α- adrenergic properties (vasoconstriction and increased peripheral vascular resistance) associated with modest β-adrenergic activation, aiding in cardiac function. In the hyperkinetic forms of neurogenic shock, patients develop vasopressin deficiency and, at relatively low doses, they have an excellent response to blood pressure control.

Low-dose dopamine (5 to 10 mcg/kg/min) is a predominantly β-adrenergic agonist, but at high doses (> 10 mcg/kg/

min) it is α-adrenergic. However, the α-adrenergic effect of dopamine is poor compared with noradrenaline. The doses formerly described as nephroprotective are no longer used, no further doses of dopamine of less than 5mcg/kg/min are used for this purpose. Its interference in the hypothalamic-hypophyseal axis, with prolactin increase and immunosuppressive effect, contraindicates its use. Randomized, double-blind, placebo-controlled trials show that dopamine has no benefit when compared with first-line vasopressors, such as norepinephrine and adrenaline and dopamine can increase the risk for cardiac arrhythmias.

Adrenaline at low doses is a potent β-adrenergic agonist, being α-adrenergic at higher doses. The half-life of vasopressin is short (few minutes), with terlipressin (its analogue) being a second option to be considered in neurogenic shock. In patients with signs of cardiac failure associated with shock, inotropic agents can be administered along with first-line drugs. Dobutamine is a potent β- adrenergic agonist with less interference in heart rate compared with isoproterenol (pure β-agonist).

Current management guidelines dictate that mean arterial pressure (MAP) should be maintained above 85–90 mmHg for the first 5–7 days of therapy.[21] A recent study suggests that maintenance of a spinal cord perfusion pressure (mean arterial pressure – cerebral spinal fluid pressure) above 50 mmHg is a stronger predictor of neurologic recovery than systemic MAP.[22]

Persistent bradyarrhythmia, found in neurogenic shock can be reversed with administration of dopamine in continuous infusion (first-line drug), followed by other options such as atropine and transcutaneous pacing, the latter being indicated only in the absence of a response to dopamine. Transvenous pacing is reserved for persistent brady-arrhythmias. Some studies consider the use of aminophylline or any other methylxanthine as good alternatives to episodic bradycardia.

Priorities of the Patient in Shock and Therapeutic Objectives:

In essence, there are four phases in the treatment of the patient in shock:

1. ***Salvage phase:*** the aim is to regularize the patient's blood pressure to the minimum necessary to ensure adequate tissue perfusion associated with the regularization of myocardial function for this minimum perfusion
2. ***Adequacy phase:*** optimized measures for adequate tissue oxygenation; control of inflammatory processes, mitochondrial dysfunctions and activation of Caspases
3. ***Stabilization phase:*** preoccupation with multiple organ dysfunction after hemodynamic stabilization
4. ***Weaning phase:*** general clinical improvement of the patient, with the possibility of gradual and progressive weaning of MV, sedation and vasoactive drugs.[23]

Neurosurgical intervention:

Furlan et al conducted a systematic review of 22 clinical studies evaluating the safety, benefit, viability and efficacy of early neurosurgical intervention in medullary trauma patients to stabilize and align their vertebral columns by spinal cord decompression. Some studies showed no difference between early surgery (up to 72 hours after trauma) and late surgery (after clinical stabilization). However, other series were in favor of early intervention, with less time required for the recovery of spinal functions as well as for hospital stay. Cengiz et al observed in a randomized controlled trial that early surgery significantly improves the ASIA score in the early and late postoperative periods by reducing secondary insults caused by the injury. For patients with evident neurological worsening, immediate neurosurgical decompression is indicated.[24,25]

Therapeutic Perspectives:

Clinical and experimental evidence shows that the mechanism of medullary recovery undergoes neuroplasticity, with dendritic and axonal budding. Physical and electrical stimuli are known to increase the production of brain-derived neurotrophic factor (BDNF) and 3'-5'-cyclic adenosine monophosphate (cAMP), and act directly on the neuroplasticity of the central and peripheral nervous systems.[26,27]

It is currently speculated that chondroitin sulfate proteoglycans (CSPs), the main constituents of the extracellular matrix of the nervous system, would play a key role in the process of spinal regeneration. These matrices of CSPs would act as shrouds for neuronal growth, being inhibitors of the functional restoration of the spinal cord. In this context, Bradbury et al[26] synthesized a bacterial enzyme called chondroitinase ABC (chABC) and administered it intrathecally, observing that the corticospinal pathways no longer presented retraction after the lesions and also facilitated the budding with formations of collateral networks in the lesion area. However, as a side effect, they observed that there was formation of calcium gated related peptide (CGRP)-dependent neural networks, related to hyperalgesia and allodynia. Another experimental line takes into account that NOGO-A glycoprotein blockers would facilitate budding as well as neuronal reconnections after injury.

Neurotrophins like NT3, NGF, BDNF and Peg-BDNF.[27] increase the capacity of neuroplasticity at the site of the lesion, and they are easily administrated through an adenovirus that, by retrograde transport, reaches the lesion site with the least amount of trauma.

Methylprednisolone, which was used in the past 30 years to reduce medullary and cerebral edema, has faded into oblivion. The results of three large prospective, multicenter, randomized, double-blind, placebo-controlled studies—National Acute Spinal Cord Injury Studies (NASCIS) I, II and III—revealed no difference in the long term between groups receiving methylprednisolone and the placebo group, with an aggravating factor: the groups that received methylprednisolone had higher mortality rates due to infections, pulmonary embolisms and severe pneumonia with septicemia.[28]

Some drugs have already been tested and present controversial results in terms of neuroprotection to spinal cord injuries, estrogen and progesterone, magnesium, minocycline, erythropoietin and induced hypothermia, anti-CD11d antibody.[29,30]

A recent study suggests that resuscitative endovascular balloon occlusion of the aorta (REBOA) can be used to maintain central aortic pressure in patient with neurogenic shock. This can prevent prolonged hypotension and secondary spinal cord injury and hypoxic encephalopathy. Further studies are needed to define the optimal use of REBOA in trauma and different shock states.[31]

To conclude, neurogenic shock is a difficult to treat complication of disruption of the sympathetic nervous system which most often occurs in the setting of a spinal cord injury. The diagnosis of neurogenic shock often poses a challenge to the emergency room team. The refractory hypotension and bradycardia may be extremely dangerous for the patient. Beyond the short term, neurogenic shock as well as autonomic dysreflexia, which may commonly accompany spinal injuries at the same level, can complicate the rehabilitation process. Hopefully future prospective studies will adopt standard ways of isolating and confirming neurogenic shock and establish treatment paradigms that improve patient outcomes.

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