PERSPECTIVE

Hypertonic saline: a brief overview of hemodynamic response and anti-inflammatory properties in head injury

Hypertonic saline (HS) has been applied in several medical areas such as pneumology (asthma, cystic fibrosis and bronchiolytis), endocrinology (hyponatremia) and especially in emergency medicine, in traumatic and inflammatory/infectious disorders. It may be composed of 3% or 7.5% sodium chlorate. By far, 3% solution is the most widely studied and used solution (Pinto et al., 2006, 2015; Dekker et al., 2014; Gantner et al., 2014; Shein et al., 2014).

Head injury is the main cause of trauma-related deaths in over 60% of cases. Hemorrhage and shock are observed in up to 20% of patients with head injuries. Hypotension, even for very brief periods, is a well-established cause of secondary brain injury, and contributes to worse outcomes (Pinto et al., 2006, 2015).

After the initial trauma, a second phase of brain injury begins. Secondary brain injury is a complex sequence of events that begins just after the initial insult and continues throughout hospitalization. Secondary brain injury involves a diverse host of etiologies, including edema, ischemia, excitotoxicity, and inflammation. Excitotoxicity occurs when a neuron is stimulated with excess amounts of neurotransmitter, especially glutamate. Inflammation has been increasingly recognized to be an important source of secondary brain injury. Additionally, trauma results in a dysregulation of the immune system, predisposing patients to nosocomial infections and worse outcomes (Phillips et al., 2009; Gong et al., 2011; Van Aken et al., 2012; Wang et al., 2014; Coritsidis et al., 2015).

Transcranial doppler (TD) is a widely applied diagnostic tool to access brain hemodynamics. It can measure several parameters related to arterial and venous circulation in anterior and posterior circulation. It is a fast and practical evaluation tool that is used to clarify clinical effects of HS (Pinto et al., 2006, 2015).

Brain injury, inflammation and the role of hypertonic saline: Various mammalian cells and tissues oxidize arachidonic acid from cell membranes into physiologically active components. These components include prostacyclin, thromboxanes, prostaglandins, and leukotrienes. Regardless of its etiology, cerebral ischemia stimulates the synthesis, activation, and release of vasoactive and immunologically active substances (Pinto et al., 2006, 2015).

The biological effects of prostacyclin are opposite to those of thromboxane A2 (TXA2). Prostacyclin is a vasodilator and potent platelet aggregation inhibitor, whereas TXA2 is a vasoconstrictor and platelet aggregation promoter. The physiological balance between the activities of prostacyclin and TXA2 is probably important for maintaining a healthy vascular bed (Pinto et al., 2006, 2015).

Hemorrhagic hypotension associated with intracranial hypertension secondary to head injury causes decreased cerebral blood flow and cerebral ischemia by altering the synthesis, activation, and release of potent vasoactive substances – vasoactive prostanoids, such as prostacyclin (PGI2) and TXA2 – and may interfere with cerebrovascular reactivity (Pinto et al., 2006, 2015).

Widespread cerebral ischemia causes release of TXB2, the principal metabolite of TXA2, an eicosanoid with potent vasoconstrictive and platelet aggregating properties. This increase in TXB2 in the cerebral venous circulation, which persists for up to 2 hours after reperfusion, is associated with cerebral hypoperfusion (Pinto et al., 2006, 2015).

Hemorrhagic shock associated with increased intracranial pressure (20 mmHg) causes decreased cerebral blood flow and a significant increase in the release of TXB2 into the cerebral venous circulation. At this point, ischemic events posterior to trauma may release TXA2 and TXA2 itself promotes vasoconstriction, and then, more ischemia, in a continuous cycle (Pinto et al., 2006, 2015).

It was already demonstrated that plasma concentrations of thromboxane in central blood samples were always higher than those found in cerebral blood, while the opposite pattern was observed for prostaglandin concentrations, which were consistently higher in the cerebral venous circulation. This suggests the existence of a balance between prostaglandin and thromboxane concentrations (Pinto et al., 2006, 2015).

Several studies have pointed that HS is able to improve cerebral and systemic hemodynamic parameters after trauma, with lower resuscitation volume infusion if compared to common saline, lactated ringer and even mannitol. It is associated with lower values of intracranical pressure (ICP) and lower values of systemic and cerebral prostaglandin and thromboxane (Choi et al., 2014; Urbano et al., 2015). HS use after TBI is also associated with higher sodium levels and blood osmolarity. Additionally, it promotes a larger increase in mean arterial pressure (MAP) with less fluid infusion (Pinto et al., 2006).

TD is a widely applied diagnostic tool to access brain hemodynamics. It can measure several parameters related to arterial and venous circulation in anterior and posterior circulation.

In patients with intracranial hypertension secondary to traumatic brain injury (TBI), TD may identify changes in blood flow velocity. When intracranial pressure raises, velocity in intracranial arteries may decrease. Additionally, pulsatility and resistence index reveal lower complacency brain tissue suffering. TD has a decisive role not only diagnosing circulatory collapse, but performing real time evaluation of therapeutic responses to treatment. After HS use in TBI, TD reveals increase in mean velocity in

studied vessels, associated with lower pulsatility and resistence indexes. Additionally, real time evaluation in bedside allow the determination of an optimal mean arterial pressure to brain perfusion (Pinto et al., 2006, 2015).

Imunologic impairments are also a consequence of trauma and inflammation disturbances. T cell suppression following trauma impairs cellular immune defenses, which can lead to posttraumatic infectious complications and sepsis, the leading causes of death in trauma patients. Hypertonic fluids, that modulate immune responses, may be applied as target therapies to reactivate immune defense (Phillips et al., 2009; Gong et al., 2011; Van Aken et al., 2012; Choi et al., 2014; Shein et al., 2014; Wang et al., 2014; Coritsidis et al., 2015; Urbano et al., 2015).

HS treatment enhances cell-mediated immune responses *in vivo*, and elicits immunomodulatory effects that decrease the risk of posttraumatic sepsis. However, the exact mechanisms by which HS treatment increases T cell function remain unclear. There are probably molecular cascades involving ATP release from T cells, Ca^{2+} signaling, interleukin production, and T cell proliferation (Phillips et al., 2009; Gong et al., 2011; Van Aken et al., 2012; Choi et al., 2014; Shein et al., 2014; Wang et al., 2014; Coritsidis et al., 2015; Urbano et al., 2015).

TBI patients receiving HS had lower tumor necrosis factor alpha and interleukin-10 levels than those treated with normal saline (Phillips et al., 2009; Gong et al., 2011; Van Aken et al., 2012; Choi et al., 2014; Dekker et al., 2014; Gantner et al., 2014; Coritsidis et al., 2015; Urbano et al., 2015). This surely correlates with earlier brain injury healing.

In summary, several experimental and clinical data support the use of HS not only for volemic resuscitation but also for addressing inflammatory and immune impairments during acute phase.

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