Effect of Dexmedetomedine on Oxidative Stress Accompanying Trumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a leading cause of death and disability allover the world. It is caused by a blow to the head from blunt or penetrating trauma (1). The burden of TBI is more prominent in Developing Countries which face a higher prevelance of risk factors for causes of TBI and have inadequately prepared health systems (2).

The major goals of anesthesia during craniotomy in patients with traumatic brain injury (TBI) are maintenance of hemodynamic stability, optimal cerebral perfusion pressure, lowering of ICP, and providing a relaxed brain (3). Although both inhalational and intravenous anesthetics are commonly employed, there is no clear consensus on which technique is better for the anesthetic management TBI (3).

Oxidative stress is a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses (4). Oxidative stress may contribute to many pathophysiological changes that occur after traumatic brain injury (4).

KeyWords: Oxidative Stress, Dexmedetomedine, Traumatic Brain Injury.

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Introduction

Traumatic brain injury (TBI) is defined as a disturbance in brain function or evidence of brain pathology caused by blunt or sharp injury to the head (5).

The annual incidence of traumatic brain injury is estimated to be around 69 million cases worldwide, thus approximately affecting half of the population once during their lifetime. In low and middle income countries, traumatic brain injury is the most leading cause of morbidity and mortality in the population below 40 years of age (6).

Classification of TBI

Traumatic brain injury is usually classified according to severity, anatomical features of the injury and the mechanism (the causative forces) (7).According to the mechanism, TBI is classified into closed and penetrating head injury. The closed or nonpenetrating injury occurs when the brain is not exposed. The penetrating or open head injury occurs when an object pierces the skull and breaches the dura mater (7).

Severity

Table 1. Severity of traumatic brain injury (8)

Severity of traumatic brain injury			
	GCS	**PTA**	**LOC**
Mild	13–15	<1 day	0–30 minutes
Moderate	9–12	>1 to <7 days	>30 min to <24 hours
Severe	3–8	>7 days	>24 hours

Traumatic brain injuries can be classified into mild, moderate and severe categories.

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The Glasgow Coma Scale (GCS) is the most commonly used system for classifying TBI severity, grades the level of consciousness on a scale of 3–15 based on verbal, motor and eye-opening reactions to stimuli. In general, TBI with a GCS of 13 or above is mild, 9–12 is moderate and 8 or below is severe. However, the GCS grading system cannot predict outcomes. So, other classification systems are also used to help determine severity (8). A current model developed by the Department of Defense and Department of Veterans Affairs in U.S.A uses the three criteria of GCS after resuscitation, duration of post-traumatic amnesia (PTA) and loss of consciousness (LOC). It also use changes that are visible on neuroimaging such as swelling, focal lesions or diffuse injury as method of classification (8).

Pathological Features

Traumatic brain injury can be also classified according to thepathological features. Lesions may be extra-axial (occurring within the skull but outside of the brain) or intra-axial (occurring within the brain tissue). Damage from TBI can be focal (confined to specific areas) or diffuse (distributed in a more general manner).However, both types of injury may be exist in one case (9).

Clinical Picture of TBI

Symptoms of TBI depend on severity, type of injury (focal or diffuse) and the parts of the brain that are affected (10). With mild TBI, the patientsmay suffer from unconsciousness for a few seconds or minutes, headache, nausea, vomiting, lack of motor coordination, difficulty balancing, dizziness, blurred vision, fatigue and changes in sleep patterns. Also, emotional andcognitive symptoms include moodand behavioral changes, confusion, and troubles with attention,memory, concentration or thinking (10). These symptoms ofmild TBI may also be present in moderate and severe injuries (11).

In patients withmoderate or severe TBI, they may have a severe headache that does not go away, nausea, repeated vomiting, convulsions, an inability to awaken, slurred speech, aphasia, dysarthria,dilation of one or both pupils, weakness and numbness in the limbs, restlessness, confusion or agitation (11). with long run, they may suffer from abnormal social behavior and cognitive changes, especially problems with sustained attention and executive functioning (11).

Patients with increased intracranial pressure (ICP) presented withheadache, projectile vomiting, disturbed conscious level, paralysis or weakness on one side of the bodyand pupillary dilatation or sluggish reactive pupil (12). Cushing's triad, bradycardia with elevated blood pressure and respiratory depression is a classic presentation of significantly raised ICP. Also, unequal pupil size (anisocoria) is considered as a sign of serious TBI (12).

Oxidative Stress

Oxidative stress is defined as an imbalance between oxidants and antioxidants in favor of the oxidants resulting in disturbance in normal redox state with subsequence toxic effectsthrough the production of peroxides and free radicals that damage all components of the cell (13).

Reactive oxygen species (ROS) are oxygen containing reactive species.they include superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^\cdot$), singlet oxygen ($^1O_2$), peroxyl radical ($LOO^\cdot$), alkoxyl radical ($LO^\cdot$), lipid hydroperoxide (LOOH), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), and ozone (O_3) (14).

Reactive oxygen species (ROS) are formed from various endogenous sources including mitochondrial electron transport chain and NAD(P)H oxidases. They are also formed from exogenous sources as radiation, air pollutants and certain xenobiotics that undergo continuous reduction and oxidation cycles. The levels of ROS in a biological system are determined by the rates of their production and activities of cellular antioxidant defenses (15).

Dexmedetomedine

Dexmedetomidine is a new generation highly selective α2-adrenergic receptor agonist that is associated with sedative and analgesic sparing effects, perioperative sympatholysis, reduced delirium and agitation, cardiovascular stabilizing effects and preservation of respiratory function (16).

Dexmedetomidine is approved at the end of 1999 by the Food and Drug Administration (FDA) for humans use for short term sedation and analgesia (less than 24 hours) in the intensive care unit. It facilitate early weaning from mechanical ventilation in ICU as it does not cause respiratory depression (17).

Alpha-2 adrenoceptor (α2-AR) agonists produce clinical effects after binding to G-Protein-coupled

α2-AR. There are three subtypes of α2-AR (α2A, α2B, and α2C) with each having different physiological functions and pharmacological activities. These receptor subtypes are found in theautonomic, central and peripheral nervous systems, as well as in vital organs and blood vessels. Dexmedetomidine is more selective towards α2-AR than clonidine. Dexmedetomidine seems to have higher α2A-AR and α2C-AR affinity than clonidine (18).

The principal site for the sedative action of α2-AR agonists is the Locus ceruleus of the brain stemwhile the spinal cord is the principal site for the analgesic action. In the heart, the main action of α2-AR agonists is a decrease in tachycardia through blocking cardioaccelerator nerve and bradycardia via α2A-AR through a vagomimetic action. In the peripheral vasculature, they producesympatholysis-mediated vasodilatation and smooth muscle cells receptor-mediated vasoconstriction. Also they have antishivering and diuretic actions (19).

The protective effects of dexmedetomidine against oxidative damage under both in vitro and in vivo conditions have been demonstrated.Dexmedetomidine inhibite production of ROS and ROS induced apoptosis through inhibition of certain gene involved in mitochondrialbiosynyhesis (20). Also, It could inhibite inflammation through direct inhibition of inflammatory factors and activation of the cholinergic anti-inflammation pathway (20).

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