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Neuroprotective Effect of Dexmeditomidinein Patients with TraumaticBrain Injury Using Interleukin-6 As Inflammatory Marker: Review Article

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ABSTRACT
Synopsis: Research on the role of dexmedetomidine in neonatology and anesthesia has been particularly interesting since the drug's many benefits were reported (1). These benefits include improving post-operative recovery, lowering the need for opioids, lowering sympathetic tone, preventing inflammatory reactions, and safeguarding organs (1). This review article aims to evaluate the effectiveness of dexmedetomidine in causing neuroprotection in individuals with head trauma

Keywords: dexmedetomedine, traumatic brain injury, neuroprotection, IL-6

1. INTRODUCTION

Any hit to the brain that may cause a person's mental state to change is referred to as a traumatic brain injury (TBI). When the brain is injured by an outside force, it is sometimes referred to as intracranial damage (2).
For those under 40, traumatic brain injury (TBI) is one of the leading causes of mortality and disability. Approximately 6.2 million people worldwide are at risk of TBI each (2). In addition to physical dysfunction, survivors experience neurobehavioral impairments and a heightened risk of developing neurodegenerative illnesses including Parkinson's and Alzheimer's (3).

2. Brain injury

Traumatic brain damage comes from two different kinds of injuries: initial brain damage It happens when there is trauma (brainstem contusion, diffuse axonal injury, lacerations, cortical contusions, and bone fragmentation) (4). supplementary harm It occurs after the initial injury and includes vasospasm, ischemia (mostly from raised ICP and/or shock), edema, hypoxemia, and cerebral hematomas. Surgery is typically necessary for these patient groups (5).

3. Pathogenesis of brain injury

One of the most prevalent reactions to traumatic brain injury is inflammation. In the central nervous system, T cells, monocytes, microglia, and other immune cells such macrophages produce inflammation when traumatic brain injury (TBI) (6).
Of these events, post-traumatic neuroinflammation—which is characterized by glial activation, peripheral inflammatory cell infiltration, and the release of inflammatory mediators—is thought to be a major contributor to secondary brain cascades (7).
To put it succinctly, upon injury, macrophages and microglia promptly initiate the release of damage-associated molecular patterns, which in turn trigger the local release of chemokines and cytokines (8). Following their recruitment by these cytokines and chemokines, immune cells like neutrophils penetrate damaged brain regions, encourage the release of further cytokines, and ultimately result in oxidative stress (9).

4. Inflammatory markers

While a moderate level of inflammation is necessary for the processes of repair and remodeling, prolonged and excessive inflammation can worsen these conditions by releasing pro-inflammatory mediators like interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 (10), which can worsen brain edema, blood-brain barrier (BBB) damage, secondary neuronal injury, and subsequent neurological impairment, episodes of cortical-spreading depression, and impairment of mitochondria and subsequent cell death in the brain (1).
Interleukin (IL)-6 is a prominent member of the broad family of cytokines that aids in regulating this communication and plays a significant role in the immune response to acute neurological damage (11).

It is a recognized therapeutic target in numerous other illness situations as well (12). Serum interleukin-6 (IL-6) shows a negative correlation with overall cognitive functioning and has been linked to compromised executive function after stroke and Alzheimer's disease (13).
Although higher IL-6 levels are linked to worse outcomes in TBI, IL-6 has a dual function in the body's reaction to injury. In animal models of traumatic brain injury, IL-6 stimulates neurogenesis and wound repair, but it may also be involved in BBB disruptions and the development of cerebral edema (12).

5. Dexmedetomidine

One powerful and extremely selective α-2 adrenoceptor agonist that has sedative, analgesic, anxiolytic, sympatholytic, and opioid-sparing qualities is dexmedetomidine. When a patient is stimulated, dexmedetomidine produces a distinct sedative reaction that facilitates a smooth transition from sleep to waking, enabling them to be cooperative and talkative (14; 15). It is medetomidine's dextroenantiomer. Decemedetomidine has been used more often in the perioperative context since it was approved in 1999 for use as a sedative in intensive care units (16). In the intensive care unit, dexmedetomidine is frequently used to sedate patients (ICU). The sedative effect could be facilitated by activating α2 adrenoceptors in the locus ceruleus (17). After four different circumstances, including surgery (19), systemic dexmedetomidine treatment can reduce neuroinflammation and enhance neurocognitive skills (18). But the process underlying this phenomenon remains unclear.

a. Structure of Dexmedetomidine

Dexmedetomidine, also known as 4-[(1R)-1-(2,3-dimethylphenyl) ethyl]-3H-imidazole hydrochloride (20), is a recently produced α2 adrenergic receptor agonist and imidazole derivative.
With a receptor selectivity (α2/α1) of 1,620:1, dexmedetomidine is a very strong and selective α2 adrenergic receptor agonist; in contrast, clonidine has a receptor selectivity of 220:1 (21). Additionally, dexmedetomidine has a higher intrinsic activity than clonidine (3:1) (22). Dexmedetomidine has an elimination half-life of roughly two hours, whereas clonidine has an elimination half-life of 8.6 ± 1.5 hours. Consequently, dexmedetomidine offers a wide range of potential applications in clinical anesthesia because of its distinct receptor activation, brief half-life, and distinctive pharmacological properties (20).

B. Mechanism of action

When agonists bind to G-Protein-coupled α2-AR, which has three subtypes (α2A, α2B, and α2C) with varying physiological functions and pharmacological activity, α2-AR can generate clinical consequences. The central, peripheral, and autonomic nervous systems, as well as critical organs and blood arteries, are all populated by these receptor subtypes (22). The major sites for the sedative and analgesic effects, which both work through α2A-AR, are the brain stem's locus ceruleus and the spinal cord, respectively. The main effects of α2-AR agonists on the heart are a reduction in bradycardia via α2A-AR (by a vagomimetic action) and tachycardia (by inhibiting the cardiac accelerator nerve). Both smooth muscle cell receptor-mediated vasoconstriction and sympatholysis-mediated vasodilatation occur in the peripheral vasculature (23).
The primary presynaptic inhibitory feedback receptor that regulates the exocytosis of adrenergic neurons is thought to be the α2A receptor (25). Therefore, the absence of a gene that codes for the α2A receptor leads to high blood pressure, a faster heartbeat, and a smoother development of cardiac hypertrophy and heart failure. Furthermore, the regulation of epilepsy, analgesia, sedation, and platelet aggregation all depend on the α2A receptor or α2 receptor agonist (25). Peripheral vascular smooth muscle contains the majority of α2B receptors, which when activated can result in a brief hypertensive reaction (26). A fundamental element in the control of descending noradrenergic neurons' nitrogen monoxide analgesia is the spinal cord's α2B receptor (27).
The α2C receptor is primarily found in the cerebral cortex, olfactory bulb system, hippocampus, and basal ganglia and regulates a number of intricate behavioral and memory processes (22). Dexmedetomidine functions as a highly selective activator of the α2A receptor, acting on the nucleolus of the nucleus. Its actions on the spinal cord can produce analgesic effects, and its actions on the peripheral and central nervous system can contribute to the inhibition of sympathetic excitation (28).

c. Adverse effects of dexmedetomidine

The three side effects of dexmedetomidine that occur most frequently are bradycardia, hypertension, and hypotension. Stimulation of alpha subtypes of receptors in vascular smooth muscles can lead to hypertension. Treatment for hypertension is usually not necessary, and it can be prevented by administering the loading dose gradually or not at all. In addition to the reduction in central sympathetic outflow, stimulation of presynaptic alpha-receptors results in a decreased release of norepinephrine, hypotension, and bradycardia. Regardless of the administration route, these are concerns (29). Among the more severe side effects of dexmedetomidine include xerostomia, vomiting, and nausea (30).

6. Studies

According to Tanabe et al. (31) dexmedetomidine inhibits the production of IL-6 in rat glial cells, hence averting the inflammatory-induced death of neurons.

Furthermore, Zhang et al. (32) discovered that the use of Dex following a TBI may enhance clinical results by lowering brain edema and neurological functional impairment through anti-apoptotic processes involving the alteration of expression levels of the apoptosis-associated proteins Bax, Bcl-2, and HSP70.

This could be a crucial mechanism via which Dex offers a significant neuroprotective benefit after traumatic brain injury.

Ding et al. (33) noted that patients with TBI had lower levels of inflammatory cytokines after receiving dexmedetomidine due to inflammatory cytokine downregulation.

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