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The protective effects of dexmedetomidine on ischemic brain injury: A meta-analysis

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ABSTRACT

Background: Intracranial lesions, trauma or surgery-related damage activate immune inflammation and neuroendocrine responses, causing ischemic brain injury. Studies have shown that inflammatory cascade mediated by neuroendocrine hormones and proinflammatory mediators is implicated in the pathophysiology of ischemic brain injury. Alpha2-adrenoceptor agonists, dexmedetomidine, is widely used as neuroprotectants in anesthesia practice. However, it is still lack of a comprehensive meta-analysis to evaluate the neuroprotection of dexmedetomidine against ischemic brain injury via suppressing these two physiological responses.

Method: Searched the Cochrane Library, Pub-Med, EMBASE, EBSCO, Ovid, Chinese biological and medical database (CBM). Related literatures published in English or Chinese before January 2017 were enrolled. We assessed the quality of eligible studies and synthesized predefined outcomes with a random-effects model or fixed-effects model.

Result: Nineteen Randomized Controlled Trials including 879 patients were included. Findings for meta-analysis of various outcomes were summarised. Primary results shown that compared with placebo, dexmedetomidine reduced a surge of TNF-α [SMD = −2.34, 95%CI (−3.25, −1.44)], IL-6 [SMD = −2.44, 95%CI (−3.40, −1.47)], S100-β [SMD = −2.73, 95%CI (−3.65, −1.82)], NSE [SMD = −1.69, 95%CI (−2.77, −0.61)], cortisol [SMD = −2.48, 95%CI (−3.38, −1.58)] and glucose [SMD = −1.44, 95%CI (−1.85, −1.04)]; maintained the level of SOD [SMD = 1.36, 95%CI (0.62, 2.10)]; decreased the rise in CRP level at postoperative one day. In response to stress reaction, dexmedetomidine attenuated the stress-related increasing of MAP, HR and intracranial pressure without significant effects on cerebral oxygen metabolism.

Conclusion: Alpha2-adrenoceptor agonists, dexmedetomidine, could reduce the release of inflammatory mediators and neuroendocrine hormones as well as maintain intracranial homoeostasis, alleviating ischemic brain injury and exerting an effect on brain protection.

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1. Introduction

It is important to achieve hemodynamic stability, intracranial homoeostasis and weaker stimuli during neurosurgery. Disordered hemodynamics or adverse stress may activate the immune inflammation or neuroendocrine responses and lead to a surge of inflammatory mediators and stress hormones [1]. Studies have shown that inflammatory cascade mediated by neuroendocrine hormones and proinflammatory mediators is implicated in the pathophysiology of ischemic brain injury [2–4], and becomes a potential new strategy for ischemic stroke therapy [5]. During the craniotomy, these adverse physiological responses caused by increased intracranial pressure, lower perfusion pressure, pain stimuli or surgery-related damage, may lead to some secondary ischemic brain injury (such as cerebral edema, cerebral hemorrhage, stroke), aggravating damage to brain tissue and affecting the recovery from anesthesia, cognition and prognosis in patients [6–12]. Therefore, it's necessary to take anesthesia management to modulate the balance of inflammatory and neuroendocrine responses, reducing the incidence of postoperative complications and preventing from ischemic brain injury.

Alpha2-adrenoceptor agonists have been widely used for sedation, analgesia and anti-sympathetic actions for many years, but the definite evidence of their potential use as neuroprotectants has so far been confined to animal studies. Sometimes these results are also not completely consistent. For example, some studies reported that α_2 -agonists do not suppress elevation in brain norepinephrine and glutamate concentration associated with cerebral ischemia [13], not improve neuronal damage caused by cerebral ischemia [14,15], and not affect brain edema and neurological outcome in surgical brain injury, but elevate blood glucose levels [16]. In recent years, especially emergence of dexmedetomidine (DEX), more clinical studies found that α_2-agonists have played important roles in inhibiting inflammatory and neuroendocrine responses. Although most results of these researches tend to neuroprotection, it's still lack of a comprehensive meta-analysis to estimate neuroprotection of α_2-agonists via suppressing these two physiological responses.

A Meta conducted by Wang [17] shown that DEX could decrease heart rate and blood pressure in stress, and concluded that DEX play a role in brain protection. However, whether it is persuasive enough to evaluate the protective effect of α_2-agonists on brain just from results of hemodynamic parameters is in dispute.

Thus, literatures of Randomized Controlled Trials (RCT) conducted to compare effects of DEX on brain protection with placebo were enrolled. We attempted a meta-analysis to systematically evaluate the protection of DEX against ischemic brain injury from immune inflammation and neuroendocrine responses, in order to inform guidance for clinical treatment and prognosis.

2. Method

2.1. Outcomes

Outcomes measured to evaluate neuroprotection of DEX against ischemic brain injury, were selected. Primary outcomes: S100-β, neuron-specific enolase (NSE), inflammatory mediators [tumor necrosis factor-α (TNF-α), interleukin (IL)], neuroendocrine hormones [cortisol, C-reactive protein (CRP), and superoxide dismutase (SOD)]. Secondary outcomes included the average arterial pressure (MAP), heart rate (HR), cerebral hemodynamics and cerebral oxygen metabolism parameters [intracranial pressure (ICP), cerebral perfusion pressure (CPP), arterial oxygen (CaO_2), internal jugular venous oxygen ($CjvO_2$), arteriovenous oxygen content difference ($Da\text{-}jvO_2$) and cerebral oxygen uptake rates ($CERO_2$)].

2.2. Search strategy

We searched Pub-med, Embase, the Cochrane Library, EBSCO, Ovid, Chinese biological and medical database (CBM). Reviews, meetings, reports and related references in eligible literatures were also reviewed. Limits were set to literatures published in English or Chinese before January 2017. According to search strategy, we searched literatures about association between DEX and brain protection, inflammatory and neuroendocrine markers. Search words included: “Adrenergic alpha-2 Receptor Agonists”, “α_2-agonists”, “Dexmedetomidine”, “CRP”, “SOD” “ischemic brain injury”, “neuroendocrine”, “inflammation”, “S100β” and “NSE”. If necessary, we even only searched literatures about DEX to increase the recall ratio of literature, although raising search workload.

2.3. Inclusion and exclusion criteria

RCTs conducted to compare α_2-agonists, DEX, with placebo on brain protection were all enrolled. We also included the studies undergoing non-craniotomy, but they must presented original data for NSE, S100-β, IL-6, TNF-α, CRP, SOD, ICP, CPP and other indicator for brain protection. Exclusion criteria as follows: 1) patients with accompanying serious systematic diseases and cognitive impairment; 2) patients with chronic use of antipsychotic medications; 2) pediatric patients; 4) emergency surgery; 5) study is at high risk of bias (≤1 point according to Oxford scale [18]; 6) not intravenous administration; 7) data was unable to obtain or repeated publication.

2.4. Data extraction and management

Two authors (Hu and Lu) independently screened the titles and abstracts identified by search and excluded those for which title and abstract indicated clear ineligibility. For preliminary eligible literatures, two authors read the full text and enrolled the literatures met the inclusion criteria together after discussing the discrepancies. Data were extracted by another two authors (Cao and Chang). One author then entered those into the table and a second author checked entries for accuracy. Different opinions were resolved through discussion.

2.5. Assessment of quality of studies

Refer to the Cochrane Collaboration's Risk of Bias tool, we used a modified 7 point, 4 item Oxford scale to assess the enrolled studies from the following four domains: reporting and adequacy of randomization (2 points), allocation concealment (1 point), double blinding (2 points), and description of drop-outs (2 points) [18].