Curr Neurobiol 2016; 7 (2): 56-58 *ISSN 0975-9042*

Proposed methods for neuroprotection during human head transplantation: A critical review of HEAVEN.

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Accepted July 20, 2016

Introduction

Recently, plans have been announced to perform the first human head transplantation within the next few years [1-5]. Known as the head anastomosis venture (HEAVEN) protocol, details of this project have been outlined primarily from existing literature with supplementary basic science animal model data [1-6]. In this brief review, I analyze the literature of the two methodologies proposed by HEAVEN investigators to achieve neuroprotection during vascular reconnection of the head and new body. Specifically, the neurobiological benefits and potential adverse effects of hypothermia on the brain and body as well as neuroprotective pharmacologic candidates will be discussed.

Hypothermic Effects on the Brain and Body

As per HEAVEN protocol, the time for vascular reconnection between the head and new body is estimated to take 30 min [1]. However, the brain parenchyma must be protected during this period of ischemia in order to prevent stroke and neuronal degradation. Recently, Ren et al. [1] proposed two methodologies to protect brain tissue from ischemia during vascular reconnection including (i) induced-hypothermia of the head and (ii) specific neuroprotective pharmacologic agents.

In the absence of cerebral blood flow, hypothermia has been demonstrated to suppress cerebral metabolism thereby decreasing oxygen demand and the development of acidosis [7-10]. Furthermore, hypothermia has been shown to diminish or modulate numerous molecular responses including the release of inflammatory intermediaries, cytokines, free radicals, and excitatory amino acids [7]. Importantly, diminishing the release of inflammatory mediators results in suppression of neuroinflammation, preservation of the integrity of the blood-brain barrier, as well as the preclusion of secondary brain edema [7,11,12].

As mentioned in prior, there are numerous therapeutic effects of hypothermia; however, the literature also reports potential adverse effects of this procedure [13-20]. Cardiovascular effects of induced-hypothermia include various electrocardiogram changes, increased risk of arrhythmias below 30ºC and coronary vasoconstriction [7]. Hypothermia has been shown to increase the risk of infection through multiple mechanisms such as inhibition of pro-inflammatory cytokine release and suppression of leukocyte migration and phagocytosis [13-15]. Hypothermia-induced diuresis is also a consideration, albeit it is more commonly observed in patients with traumatic brain injury [16-19]. There are also various detrimental metabolic effects of decreasing body temperature such as causing a decrease in insulin sensitivity. Insulin resistance can cause hyperglycemia, which can increase the risk for development of critical illness neuropathy, infection and renal failure [7,20].

Ren et al. [3,6] indicated that hypothermia-induced adverse effects are not expected in the body because only the head/brain will be subject to hypothermia protocol. However, the absence of such adverse effects on the brain parenchyma cannot be ruled as absolute until the first human head transplantation procedure takes place. For example, as discussed previously, hypothermia can cause immunosuppression, infection, and the various sequelae associated with hyperglycemia. All of these adverse effects may jeopardize the integrity of the brain parenchyma [7,13-15,20]. Furthermore, although hypothermia of the new body is currently not indicated in protocol methodology, it may become a consideration in the future. The adverse effects of hypothermia on the body should be contemplated prior to advising hypothermic-induction of the body in HEAVEN protocol.

Pharmacologic Neuroprotection

A second mechanism proposed by Ren et al. [1] to achieve neuroprotection during the 30 min window for vascular reconnection is that of administration of neuroprotective pharmacologic agents. Various experimental pharmacologic agents, such as opioid receptor agonists,

neurotensin analogs, cannabinoid 1 receptor agonists, transient receptor potential vanilloid 1 agonists, dopamine receptor activators, thyroxine derivatives and adenosine, may exhibit neuroprotective effects; however, Ren et al. [1] indicated that such agents will not be included in HEAVEN due to a lack of clinical studies. Similarly, gas-mediated compounds such as sodium sulfide, molecular hydrogen and hyperbaric oxygen have shown promising results with respect to neuroprotective efficacy, yet these agents have also not been studied in a clinical setting and, thus, will not be incorporated into the protocol [1]. Nevertheless, one gas-mediated agent, hydrogen sulfide, is being considered as a possible neuroprotective agent despite numerous adverse effects reported in the literature [1,21].

It is important to note that the adverse effects of hydrogen sulfide will initially be constrained to the brain parenchyma prior to vascular reconnection between the head and new body; however, systemic effects may ensue upon vascular reconnection, as hydrogen sulfide will then gain access to systemic vasculature. The clinical effect of hydrogen sulfide is dependent upon the concentration as well as duration of exposure [21]. Exposure to concentrations between 10-500 parts per million (ppm) can cause numerous respiratory symptoms ranging from rhinitis to respiratory failure [21]. Furthermore, hydrogen sulfide affects several organs causing transient or perpetual damage to the cardiovascular, hepatic, renal, hematologic and nervous system [21]. Exposure to higher concentrations between 500-1000 ppm is immediately fatal [21]. Neuroprotective effects of hydrogen sulfide have been demonstrated with concentrations of 40-80 ppm, yet such concentrations have been demonstrated to cause significant adverse effects as discussed [21-23]. If hydrogen sulfide is to be considered in the HEAVEN protocol, the benefits ought to be carefully weighed against the adverse effects.

Conclusion

Although there is literature that supports a scientific basis for neuroprotection during vascular reconnection, such evidence is not without significant concerns with respect to adverse effects. Undoubtedly, HEAVEN pushes our scientific capabilities and ethics to the limit; nevertheless, the scientific community ought to be cautious in supporting the first human head transplantation as such a procedure may be subject to unwelcome slipper slope argumentation in near future [24-26].

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