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Research Report

Effects of propofol and sevoflurane on aquaporin-4 and aquaporin-9 expression in patients performed gliomas resection

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ABSTRACT

Post-operative cerebral edema is a threat for patients performed gliomas resection. Some studies have shown that general anesthesia drugs, such as, propofol had neuroprotective effect. Aquaporin-4 (AQP4) and Aquaporin-9 (AQP9) play an important role in maintaining brain water homeostasis under various conditions. The aim of this study was to compare the effect of propofol or sevoflurane on expression of AQP4 and AQP9 in patients performed gliomas resection. 30 patients performed gliomas resection were included in this study. The patients were randomly divided into two groups: propofol group and sevoflurane group. Fresh human gliomas specimens were obtained and hematoxylin eosin (HE) staining, immunohistochemical staining and Western blot analysis were used for observation of the expression of AQP4 and AQP9. The immunohistochemical staining of the sections showed that the percentage of AQP4 positive cells in the propofol group (14.3±4.61%) was significantly lower than that in sevoflurane group (37.3±10.01%) ($n=15$, $P<0.05$). There was no significant difference in the percentage of AQP9 positive cells in propofol group and sevoflurane group (25.8±2.67 versus 28.1±7.81%, $n=15$, $P>0.05$). Western blot analysis confirmed the immunohistochemistry results. AQP4 protein level in propofol group was significantly lower than that in sevoflurane group (1.4±0.13 versus 1.7±0.12, $P<0.05$). Western blot analysis did not show any difference of expression of AQP9 protein between the propofol group and sevoflurane group (2.0±0.13 versus 2.1±0.13, $P>0.05$, $n=6$). AQP4 expression was lower in patients of propofol group than that in sevoflurane group. Our results suggested that propofol could inhibit the expression of AQP4.

Abbreviations: AQP4, aquaporin-4; AQP9, aquaporin-9; BBB, blood–brain barrier; ECG, electrocardiograph; EDTA, ethylene diamine tetraacetic acid; BIS, Bispectral Index of the electroencephalogram; $ETCO_2$, end tidal carbon dioxide; HE, hematoxylin eosin; HRP, horseradish-peroxidase; I/R, ischemia reperfusion; PBS, phosphate buffered saline; PKC, protein kinase C; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis

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1. Introduction

One of the most serious consequences of gliomas resection is post-operative brain edema, which could lead to a lot of deleterious effects. The expansion of brain volume could lead to increased intracranial pressure, which can cause some consequences, such as, brain herniation, coma, and failure of the respiratory and cardiovascular systems, not only aggravating neurologic outcome but also threatening life (Sorani et al., 2008). Although the post-operative edema could be treated with sedation, osmotic agents, and corticosteroids, the occasionally malignant post-operative edema occurs and worsening post-operative edema is never desirable (Papadopoulos and Verkman, 2007).

Recent studies have elucidated the role of AQPs in inducing brain edema. Aquaporins are water-selective, plasma membrane channels that increase water permeability in cells (Unterberg et al., 2004). One of the most important aquaporins is AQP4 which is primarily expressed in ependymal cells and astrocytes, both of which play an important role in maintenance of the blood–brain barrier (BBB) (Sun et al., 2003). Another important aquaporin is AQP9 which has also been shown to be expressed in the BBB. The high level expressions of AQP4 and AQP9 could increase the permeability of BBB and lead to cerebral edema (Higashida et al., 2011).

Propofol (2, 6-dilsopropylphenol) is an IV anesthetic commonly used in clinical practice and characterized by rapid induction and quick recovery from its anesthetic effects. In addition, propofol is also used as a sedative for intensive care unit (ICU). Some studies have shown that propofol had neuroprotective activities and possible mechanisms of action may include reduction in cerebral metabolism (Kochs et al., 1992), antioxidant activity (Ergun et al., 2002), anti-excitotoxic properties (Hans et al., 1994), modulation of inhibitory neurotransmitter action and excitatory neurotransmitters (Wang et al., 2002), or influence on neuronal apoptosis (Xi et al., 2011).

Propofol was found to reduce AQPs expression and brain edema in animal models (Lee et al., 2013). But, there was seldom study about the effect of propofol or sevoflurane on AQP4 and AQP9 in human. The present study was designed to compare the effect of propofol with sevoflurane on AQP4 and AQP9 expression levels in patients performed gliomas resection.

2. Results

2.1. Physiological parameters

In this study, 30 patients diagnosed as glioma by MRI scan and post-operative histopathological examinations were included. 30 patients were randomly divided into propofol group and sevoflurane group. Demographic data of the patients, including age, duration of surgery, and body weight were comparable (Table 1). There was no difference in mean artery pressure (MAP), heart rate (HR), SPO_2, end tidal carbon dioxide ($ETCO_2$) and Bispectral Index of the electroencephalogram (BIS) during operation between the two groups (Table 2).

Table 1 – Demographic data of 30 patients ($n=15$ in each group; mean ± SEM).

	Propofol	Sevoflurane
Age (years)	50.4±4.9	49.2±4.1
Male/female	10/5	7/8
Weight (Kg)	67.9±3.6	64.9±3.7
Duration of operation (min)	94.7±6.1	96.7±10.1

2.2. Immunohistochemical staining of AQP4 and AQP9

In this study, immunohistochemical staining was performed in surgically abandoned glioma specimens. The percentage of AQP4 and AQP9 positive neurons was calculated in the sections in the two groups. The immunohistochemical staining of the sections showed that the percentage of AQP4 positive cells in the propofol group (14.3±4.61%) was significantly lower than that in the sevoflurane group (37.3±10.01%) ($n=15$ in each group, $P<0.05$). There was no significant difference in the percentage of AQP9 positive cells in propofol group and sevoflurane group (25.8±2.67% versus 28.1±7.81%, $n=15$ in each group, $P>0.05$, shown in Fig. 1A–E).

2.3. Western blot of AQP4 and AQP9 protein expression

Western blot analysis confirmed the immunohistochemistry results. Propofol group reduced AQP4 expression compared with sevoflurane group. Western blot analysis revealed that the AQP4 protein level in propofol group was significantly lower in propofol group than that in sevoflurane group (1.4±0.13 versus 1.7±0.12, $P<0.05$). Western blot analysis did not show any difference of expression of AQP9 protein between the propofol group and sevoflurane group (2.0±0.13 versus 2.1±0.13, $P>0.05$, $n=6$ in each group, as shown in Fig. 2A–C).

3. Discussion

In our study, our results showed that propofol could decrease expression of AQP4 than sevoflurane in patients performed gliomas resection. The results of this study, for the first time to our knowledge, compared the effect of propofol and sevoflurane on the expression of AQP4 and AQP9 in patients performed glioma resection. These findings support the notion that neuroprotective effect of propofol has a relationship with the suppression of AQP4.

The mechanisms for neuroprotective effect of propofol were very complicated, and had not yet been clear. The mechanisms may include reduction in cerebral metabolism; the redistribution of cerebral blood flow; anti-oxidant properties; the elimination of free radicals and the anti-apoptotic effects (Daskalopoulos et al., 2001; Hans et al., 1996; Kokita and Hara, 1996). Our previous study showed that the protective effect of propofol was related to its anti-apoptotic effects and protective effect of mtDNA (Yue et al., 2015). It remains