The Role of Mixed V1a/V2 Vasopressin Receptor Antagonist (Conivaptan) in Prevention and Treatment of Brain Edema After Middle Cerebral Artery Occlusion in Mice

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Introduction

Middle cerebral artery (MCA) occlusion is the leading cause of ischemic stroke worldwide. "Malignant MCA stroke" (MMS), a large infarction of the MCA territory with associated cytotoxic edema, has a mortality nearing 80% [1]. Current treatments have substantial limitations and fail to significantly decrease morbidity and/or mortality.

Vasopressin plays a significant role in ischemic stroke through V1a, V1b, and V2 receptors [2-6]:

- V1a antagonism - platelet inhibition, aquaporin channel modulation, vasodilatation, and reduction in infarct size
- V2 antagonism - ameliorated cerebral edema, modulated aquaporin-4 (AQP-4), and decreased GFAP in astrocytes accompanied by aquaresis

Conivaptan (mixed V1a/V2 receptor antagonist) is FDA approved to treat euvolemic hyponatremia [7-9].

Hypothesis: Conivaptan (CV) is an effective treatment for brain edema in murine ischemic stroke model.

Methods

Male C57BL/6 mice aged (2 to 3 months-old) were used:

- Treatment group (n=10) - single dose intraperitoneal 1.2 ml Conivaptan (10mg/kg) premixed with 5% dextrose at 30 minutes post MCA occlusion
- Control group (n=10) - single dose intraperitoneal 1.2 ml 5% dextrose at 30 minutes post MCA occlusion

Temporary intraluminal middle cerebral artery occlusion (tMCAO) was performed with a 45 minute occlusion period followed by reperfusion by removing the filament. Laser-Doppler was used to monitor cerebral blood flow (CBF). Core temperature and body weight were also monitored. Brain edema (BE) and corrected infarct volume (CIV%) was measured 12 hours (n=6 in each group) or 24 hours (n=4 in each group) post tMCAO.

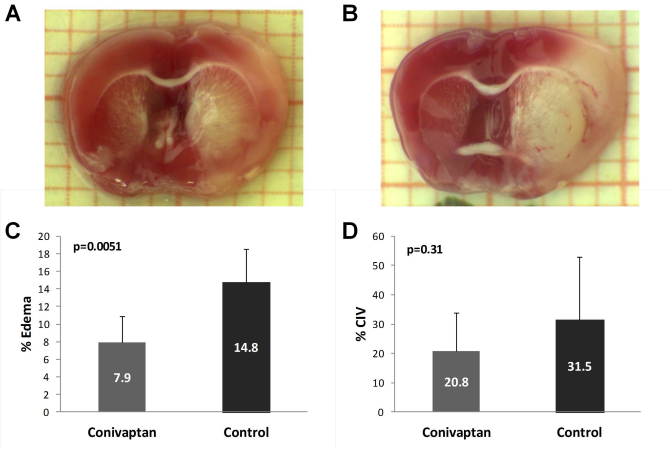
The study protocol was approved by the IACUC at University of Florida and fulfilled the National Institutes of Health's guidelines for the care and use of animals in research.

Results

At 12h, ipsilateral average hemispheric edema (HE%) in the CV-treated group was 7.8±2.9% versus 14.8±3.7% in controls (p=0.0051). Average corrected infarct volume (CIV%) in CV-treated animals was 20.8±13.0% compared to 31.5±21.5% in controls (p=0.31) in 12h timepoint. Moreover, the CV-treated animals showed improved NDS in comparison to control animals at 12h. In addition, more CV-treated animals were in the mild deficit category (NDS=1) while more control animals were in the moderate deficit category (NDS=2).

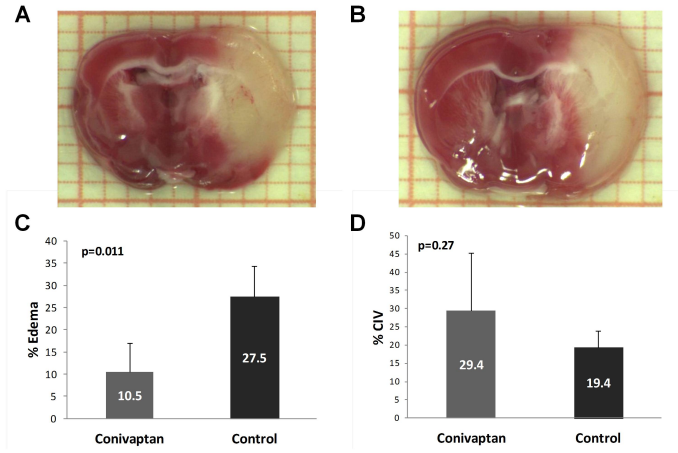
At 24h, HE% in the CV-treated group was 10.5±0.1% in comparison to 27.5±0.1% in the control group (p=0.011). Infarct volume (CIV%) in the CV-treated group was slightly worse at 29.4±16.0% compared to 19.4±4.5% in the control group (p=0.27) at 24h timepoint. CV-treated animals demonstrated significantly increased weight loss after treatment due to dehydration and this might caused increased infarct volume at the later timepoint. The NDS at 24h category showed a similar trend as 12h timepoint.

Hemispheric edema and infarct volume in the conivaptan (n=6) and control (n=6) animals at 12h



TTC-stained sections of CV-treated animals (A) in comparison to controls (B). Also shown is the average brain edema (C) and CIV% (D) values.

Hemispheric edema and infarct volume in the conivaptan (n=4) and control (n=4) animals at 24h



TTC-stained sections of CV-treated animals (A) in comparison to controls (B). Also shown is the average brain edema (C) and CIV% (D) values.

Conclusion

These results support the possibility of conivaptan as a non-surgical approach to neuro-protection and treatment of brain edema in the setting of MMS.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Know about the early measures facing malignant MCA stroke, 2) The role of vasopressin receptor antagonists, specifically Conivaptan, in prevention and treatment of brain edema in ischemic stroke.

References

[1] Hacke W, et al. (1996) [2] Joynt RJ, et al. (1981) [3] Barreca T, et al. (2001) [4] Shuaib A, et al. (2002) [5] Liu X, et al. (2010) [6] Rosenberg GA, et al. (1990) [7] Potts MB, et al. (2011) [8] Walter KA (2007) [9] Dhar R, et al. (2011)