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Role of vasopressin antagonism in treatment of brain edema after middle cerebral artery occlusion in mice

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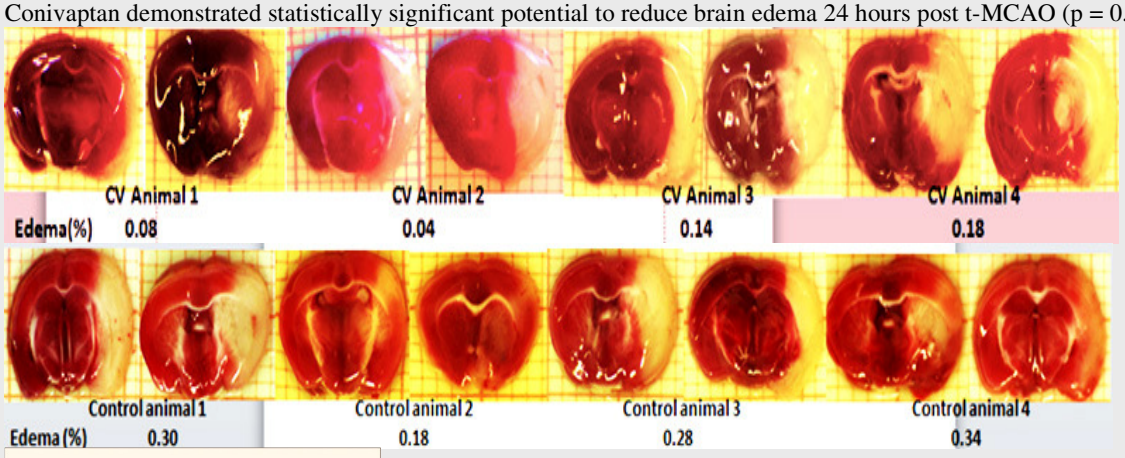
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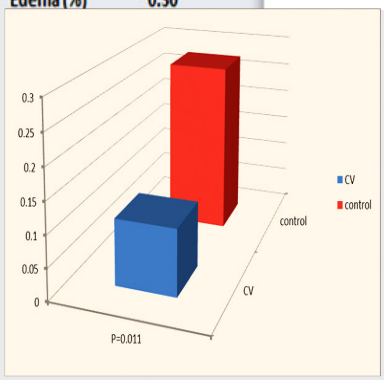
Abstract

Introduction: Middle cerebral artery (MCA) occlusion is the leading cause of ischemic stroke worldwide. "Malignant MCA stroke" (MMS), which denotes a large infarction of the MCA territory with associated cytotoxic edema, has a mortality nearing 80%. Current treatments such as osmo-therapy and hemicraniectomy are designed to reduce post-stroke cytotoxic edema, but have substantial limitations and fail to significantly decrease morbidity and/or mortality. The current studyproposes a non-surgical alternative by using a mixed arginine vasopressin receptor antagonist as an efficient modality to prevent and treat MMS by influencing cerebral water homeostasis through modulating BBB permeability. Conivaptan (mixed V1a/V2 vasopressin receptor antagonist), which is currently FDA approved to treat euvolemichyponatremia, was investigated and showed promising results to reduce cerebral edema on post-ischemic stroke in a murine model.

Methods: Temporary intraluminal MCA occlusion model (t-MCAO) was performed in two experimental groups of male C57BL/6 mice aged between 8 to 12 weeks. Single dose of intraperitoneal (IP) Conivaptan 10mg/kg (1.2ml) premixed with 5% dextrose (5D) was administered in the treatment group (n=6). The control group (n=6) received 1.2ml of intraperitoneal 5% dextrose (single dose). Both treatments were administered at 30 minutes of MCA occlusion. Brain sections were stained with 1% TTC 24 hours after t-MCAO to measure brain edema via calculation.

Results: Brain edema average in Conivaptan group was 0.105±0.066mm^3 and in control group was 0.275±0.068mm^3. Conivaptan demonstrated statistically significant potential to reduce brain edema 24 hours post t-MCAO (p = 0.011).





Conclusion: Conivaptan significantly reduced cerebral edema in the murine MCA occlusion model. These encouraging results support the effectiveness of Conivaptan in brain edema and neuroprotection in the setting of MMS.