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Improved survival following cerebral edema using a novel hollow fiber-hydrogel device

Laboratory investigation

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Object. Cerebral edema is a significant cause of morbidity and mortality in many disease states. Current therapies of cerebral edema are often ineffective in treating severe edema. Here, the authors develop a hollow fiber-hydrogel device (HFHD) for direct surface contact–based treatment of severe cerebral edema.

Methods. Brain edema was induced in adult mice via water intoxication by intraperitoneal water administration (30% body weight). Control mice received no treatment. A distinct group of mice was treated with craniectomy but no device application (craniectomy only). A third experimental group was treated with craniectomy and HFHD application. The HFHD contained a lumen solution of 350 g/L bovine serum albumin in room-temperature artificial CSF at pH 7.4. Survival and brain water content were assessed as end points.

Results. Craniectomy and application of the HFHD enhanced survival in animals with severe cerebral edema. Animals treated with a craniectomy and HFHD (n = 5) survived up to 5 hours longer than animals treated with craniectomy only (n = 5) ($p < 0.001$) or no treatment (n = 5) ($p < 0.001$). Animals treated with craniectomy and HFHD (n = 5) had a survival rate of 80% within the observation period (360 minutes), whereas no animal treated with craniectomy only (n = 5) or no treatment (n = 5) survived longer than 50 and 33 minutes, respectively. Statistical significance was observed for the survival rate between the animals treated with a craniectomy + HFHD (n = 5) versus those treated with craniectomy only (n = 5) ($p < 0.001$), and craniectomy + HFHD versus no treatment (n = 5) ($p < 0.001$). Histological analysis demonstrated no significant cell loss in the cortex subjacent to HFHD application.

Conclusions. Here, the authors demonstrate the feasibility of their HFHD to treat cerebral edema in this model. These results indicate that controlled water extraction from edematous brain tissue can be performed and can lead to increased survival compared with craniectomy only. Further studies remain to be performed to further optimize the HFHD and to test it in more clinically relevant models, such as traumatic brain injury.
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Key Words • **cytotoxic edema** • **vasogenic edema** • **hollow fiber-hydrogel device** • **mouse**

Cerebral edema, an increase in brain tissue water content, is responsible for significant morbidity and mortality in many disease states, including TBI, stroke, infection, tumor, and chemical and metabolic intoxications. Traumatic brain injury is particularly important from a public health standpoint since it is the foremost cause of morbidity and mortality in persons younger than 45 years of age worldwide. In the US, about 200,000 victims of TBI need hospitalization annually, and approximately 52,000 deaths per year in the US result from TBI. Affected individuals experience delayed onset of cerebral edema after head injury, which can lead to raised ICP, brain herniation, and death.[9]

There are 2 major types of cerebral edema: vasogenic and cytotoxic (cellular). Vasogenic edema is characterized by the disruption of the BBB and may be caused by direct injury or by breakdown of the BBB (for example, by tumors). Disruption of the BBB leads to the accumulation of blood components in the brain, and an influx of water into the interstitial space between cells follows, causing swelling of the tissue. Cytotoxic edema is characterized by the flux of water into brain cells (predominantly brain glial cells [astrocytes]) and is associated with trauma, ischemia, and toxins.[7,9]

Significant secondary injury to the brain could be avoided if cerebral edema could be treated early.[9] The

Abbreviations used in this paper: BBB = blood-brain barrier; BSA = bovine serum albumin; HFHD = hollow fiber-hydrogel device; ICP = intracranial pressure; TBI = traumatic brain injury.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

most widely used current treatments of cerebral edema are osmotherapy, ventriculostomy, and craniectomy. While often effective, even combinations of these therapies may have limited success in treating severe edema.[3,10,13]

While usually effective in acutely reducing ICP, osmolar therapy may have significant disadvantages including clinical variability, temporary duration of effect, and potential deleterious systemic consequences on the cardiovascular and renal physiological systems.[2,8] In addition, these medications are nonspecific in that they remove water from all tissues and can lead to significant volume and electrolyte imbalances. Furthermore, even maximum concentrations of these medications can be ineffective at treating severe cerebral edema and, in some cases, even exacerbate the edema.[1,6,8,11,12]

Surgical treatment of cerebral edema involves ventriculostomy and/or craniectomy. Ventriculostomy alone is often not effective in treating severe edema, as the total CSF volume (approximately 150 ml for adults) is only approximately 10% of the brain volume. Decompressive craniectomy, while often used for severe edema, is really more a treatment for ICP reduction and to prevent transtentorial herniation than a direct treatment for cerebral edema. After craniectomy, external brain herniation can lead to venous compression, ischemia, and further secondary damage. Interestingly, recently reported results from the DECRA trial have indicated no significant improvement in outcome following decompressive craniectomy after diffuse TBI.[3]

A new method of directly removing water from brain tissue would potentially circumvent some limitations of current therapies. For therapeutic benefit in treatment of cerebral edema, the ideal medical device would have the capacity to remove water from brain tissue in a controlled fashion, have the flexibility for deployment on the surface of the brain, not require brain tissue penetration, and not do any harm to the underlying brain. Here, we have developed a direct surface contact–based treatment using a novel HFHD, and we successfully enhanced survival in mice with severe cerebral edema.

Methods

Hollow Fiber-Hydrogel Device

The HFHD consists of a hollow fiber semipermeable membrane system embedded in a moldable, soft hydrogel that is placed directly on the exposed injured tissue and will conform to the injured area to maximize the contact area (Fig. 1). The hydrogel will ensure that the contact between the hollow fiber and tissue is maintained. An aqueous fluid containing concentrated, fully rejected species (such as proteins) is passed through the lumen of the fibers. The aqueous solution contact is continuous through the moldable gel and the tissue, resulting in an inevitable osmotic pressure. This pressure gradient will gently remove fluid from the tissue through the gel and ultimately through the fibers and away from the patient.

A major advantage of using the HFHD lies in its intrinsic nature. The water removal rate can be controlled and modified as treatment requires based on alterations in the properties of the lumen solution. A few of the possibilities are changes in the impermeable solute concentration to alter the osmotic pressure of the lumen solution, altering the flow properties (for example, flow rate or viscosity), and increasing the number of hollow fibers or treatment contact area.

The choice of hollow fibers requires flexibility and knowledge of the lumen solution properties. The smaller the hollow fiber outer diameter is, as well as the hollow fiber material, will determine the flexibility and, more importantly, the range of surface area that can be treated. Flexible hollow fibers with a relatively small outer diameter (200 μm) will be able to mold to brain gyrations while the hydrogel ensures that fiber-tissue contact is maintained.

In this study, the HFHD was developed using regenerated cellulose fibers with a molecular weight cutoff of 13 kD (model 132294, Spectrum Laboratories, Inc.). The contact area between the hollow fibers and the cerebral cortex was 17.8 ± 2.2 mm^2 (± SEM). The solution passing through the hollow fibers (lumen solution) operated at a flow rate with a Reynolds number *(Re)* between 50 and 100.

Treatment with the HFHD consisted of the fibers being placed directly onto the mouse cerebral cortex after craniectomy, with a hydrogel covering the fibers and the exposed tissue (Fig. 2). The hydrogel was created by dissolving agar into the same solution properties as the lumen solution without the impermeable solute (0.3% agar, artificial CSF, pH 7.4 gel).

Lumen Solution

The lumen solution consisted of concentrated BSA (impermeable solute) in a saline solution at pH 7.4. Bovine serum albumin was used because the osmotic pressure of concentrated BSA solutions has been extensively studied for various solution properties[15,16] and because it is completely rejected by the hollow fiber membrane. The BSA solution was made by dissolving BSA into the saline solution. The BSA was mixed using a stir-plate at room temperature, and the pH was adjusted using 1 M NaOH or 1 M HCl. In these experiments, a BSA concentration of 350 g/L in artificial CSF at pH 7.4 was used. This BSA concentration has an osmotic pressure of approximately 28 psi.[15]

The saline solution used in this study was isotonic saline mimicking the CSF (artificial CSF). The artificial CSF was prepared by dissolving the salts in nanopure (ddH_2O) water following the protocol described for artificial CSF.[4]

Animals

All experiments were conducted under protocols (A-20100018) approved by the University of California, Riverside Institutional Animal Care and Use Committee. Adult female 10- to 12-week-old mice were used in all experiments.

Surgical Technique

Prior to induction of water intoxication, the mice

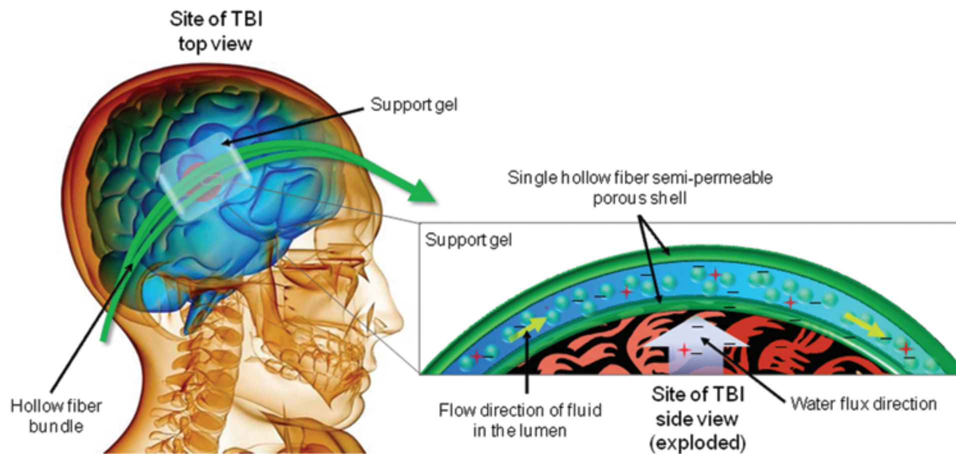

Fig. 1. Concept of the HFHD for treating cerebral edema. Aqueous proteinaceous solution is pumped across the injured surface area through the semipermeable hollow fiber membrane lumen. The membrane is selected such that it completely rejects the solute but allows easy passage of ions and water. The lumen solution induces an osmotic pressure driving force for water removal. The rate of pumping is controlled to allow fluid from the tissue to flow up to the membrane device due to osmotic pressure. A hydrogel with significantly large permeability is used to maintain membrane-tissue contact. Printed with permission from Victor G. J. Rodgers.

were anesthetized with a mixture of 80 mg/kg ketamine and 10 mg/kg xylazine. Surgical procedures began only after determining that an adequate plane of anesthesia had been reached with the loss of paw pinch reflex. Reflex activity was continuously monitored throughout the procedure and supplemental doses of half of the initial dose were provided as needed.

After anesthesia, the animals were placed into a standard rodent stereotactic frame. A midline skin incision was made and reflected. A right-sided craniectomy was performed (anterior border, coronal suture; posterior border, lambdoid suture; medial border, midline; and lateral border, temporalis attachment). The dura was carefully and atraumatically opened with microdissection.

Water Intoxication Model

Cytotoxic cerebral edema from water intoxication was induced as previously described.[5] The mice were injected with distilled water (30% body weight, intraperitoneally). Approximately 5 minutes postinjury, treatment began. The 3 experimental groups were as follows: no treatment (water intoxication only), craniectomy only, and craniectomy + HFHD.

End points included survival time and brain water content analysis. Survival was assessed over the course of 360 minutes after water intoxication in all animals. After the treatment procedure, the brains were dissected out postmortem and subjected to wet-dry weight comparisons to determine the percentage water content as previously described.[5,17]

Histology After HFHD Application

To examine any histological changes following HFHD application, HFHD was applied directly to the cortex for 3 hours in a subset of mice (n = 3). The animals were deeply anesthetized, brains were dissected and frozen, and 50-μm coronal cryostat sections were prepared and subjected to Nissl staining.

Data Analysis

Intergroup comparisons of survival times and brain tissue water content were done using 1-way ANOVAs and post hoc Bonferroni tests. Mean values are presented as the mean ± SEM.

Results

Improved Survival After Treatment With the HFHD

The mean survival times after water intoxication were determined for untreated, craniectomy-only treated, and craniectomy + HFHD-treated mice (Fig. 3 upper). Survival time for the untreated group was 31 ± 1.4 minutes (n = 5). Treatment with craniectomy only slightly increased survival time to 48 ± 1.8 minutes (n = 5). Treatment with craniectomy + HFHD markedly improved survival time to 333 ± 12.7 minutes (n = 5). Four (80%) of 5 of the

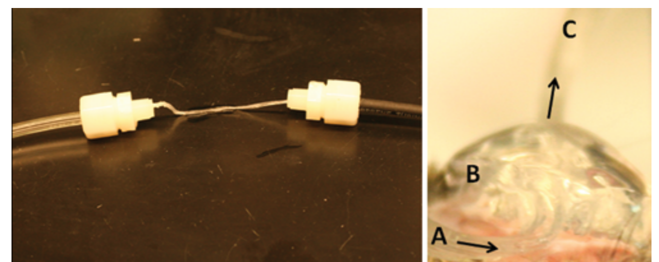

Fig. 2. Application of the HFHD. **Left:** Sample hollow fiber attached to inlet and outlet ports. **Right:** Application of the HFHD with multiple parallel hollow fibers embedded in a hydrogel to brain surface. Point A is the inlet of the hollow fiber bundle. Point B is the hydrogel that is placed directly on the tissue surface at the injury location. As can be seen, the hydrogel also molds around the hollow fiber bundle. Point C is the outlet for the hollow fiber bundle. Fluid passing through the hollow fibers at Point A osmotically drives excess fluid from the tissue under the hydrogel at Point B into the walls of the hollow fibers. The excess fluid associated with edema is subsequently carried away from the brain at Point C.

HFHD-treated animals actually survived throughout the entire 360-minute observation period (and then were euthanized to obtain brain water content data). Thus, animals treated with a craniectomy + HFHD survived approximately 5 hours longer before termination than animals receiving no treatment or craniectomy only (Fig. 3 lower). Significant differences in survival were observed statistically between the craniectomy + HFHD and craniectomy-only groups ($p < 0.001$), and significant differences in survival were observed between the craniectomy + HFHD and no-treatment groups ($p < 0.001$).

Brain Water Content Analysis

Brain water contents for water-intoxicated animals (79.0% ± 0.09%; n = 5), water-intoxicated animals treated with a craniectomy only (79.1% ± 0.21%; n = 4), and water-intoxicated animals treated with craniectomy + HFHD (80.1% ± 0.34%; n = 5) were significantly higher than brain water content for untreated control animals (77.0% ± 0.13%; n = 5) ($p < 0.001$) (Fig. 4). No significant difference in water content was observed among any of the treatment groups ($p > 0.05$). In addition, no significant differences were found in brain water content between hemispheres ipsilateral and contralateral to HFHD application in any treatment group (Table 1). While the brain water content of all treatment groups involving water intoxication was significantly higher than untreated control animals ($p < 0.001$), the brain water content of non–water intoxicated animals receiving either craniectomy only or craniectomy + HFHD treatment was not significantly different from untreated control animals ($p > 0.05$) (Table 1).

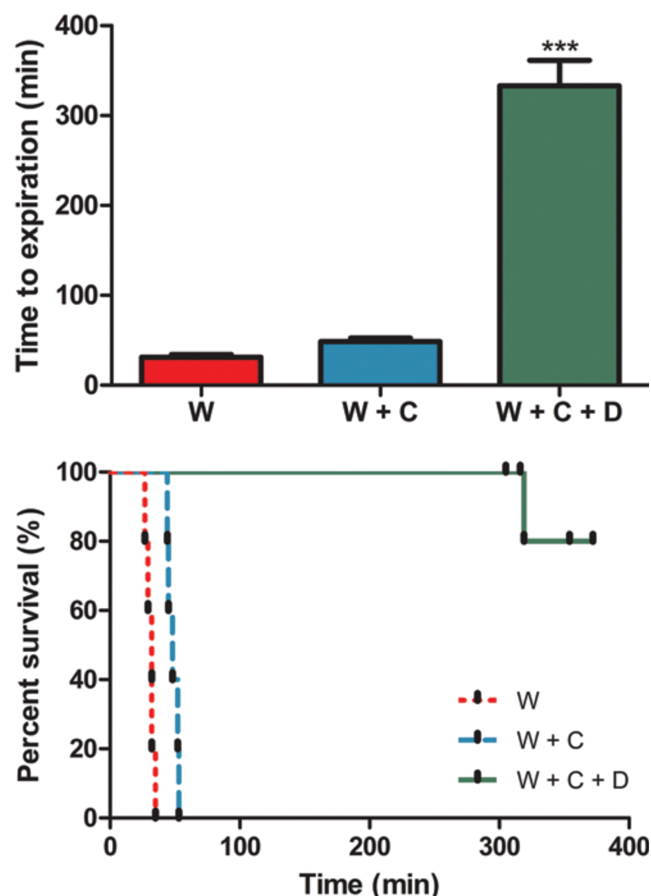

Fig. 3. The HFHD improves survival in a mouse model of cytotoxic cerebral edema. **Upper:** Mean time to death for 3 treatment groups as follows: untreated water-intoxicated animals (W), 31 ± 1.4 minutes; water-intoxicated animals treated with craniectomy only (W + C), 48 ± 1.8 minutes; and water-intoxicated animals treated with craniectomy + HFHD (W + C + D), 333 ± 12.7 minutes. A significant increase in time to death was seen in the animals treated with craniectomy + HFHD (***$p < 0.001$ vs W or W + C groups). **Lower:** Kaplan-Meier survival curve. Comparison of the survival curves for W, W + C, and W + C + D groups. Individual animals are depicted as *closed ovals*.

Histology Following HFHD Treatment

To examine whether the usage of the HFHD was associated with any histological changes in tissue underneath the device, Nissl staining of the brain for non–water intoxicated animals treated with a craniectomy + HFHD was performed. Nissl-stained histological sections (n = 3) demonstrated that there was minimal histological damage ipsilateral (Fig. 5 upper) and contralateral (Fig. 5 lower) to HFHD application.

Discussion

We have developed a novel device to directly remove water from brain tissue in a controlled fashion to treat cerebral edema. First, in extensive preliminary experiments (not shown), we developed and tested an HFHD for removing water from ex vivo tissue samples. Second, in the studies reported here, we validated the use of the HFHD, with the correct lumen solution properties, in conjunction with a craniectomy to apply the device to the brain in vivo. We demonstrate, in the water intoxication model, that application of the HFHD is associated with significantly enhanced survival.

Device Design

Developing an HFHD to treat cerebral edema pre-

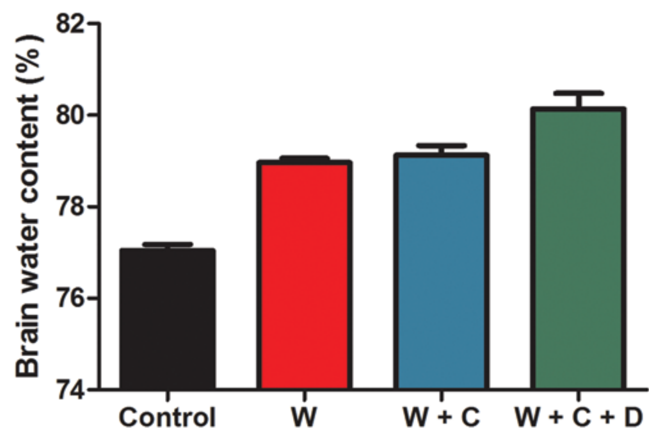

Fig. 4. Brain water content analysis. Brain water content (%) is shown for untreated control animals, water-intoxicated animals with no treatment, water-intoxicated animals treated with craniectomy only, and water-intoxicated animals treated with craniectomy + HFHD.

TABLE 1: Brain water content*

Group	Treatment Time (mins)	Brain Water Content (%) Total	Lt Hemisphere	Rt Hemisphere
control	NA	77.0 ± 0.13	77.0 ± 0.16	77.1 ± 0.11
W	31 ± 1.4	79.0 ± 0.09	79.0 ± 0.04	79.0 ± 0.15
W+C	48 ± 1.8	79.1 ± 0.21	79.1 ± 0.25	79.1 ± 0.17
W+C+D	333 ± 12.7	80.1 ± 0.34	80.0 ± 0.29	80.2 ± 0.41
control+C	180	77.1 ± 0.08	77.0 ± 0.07	77.2 ± 0.11
control+C+D	180	77.1 ± 0.03	77.0 ± 0.12	77.2 ± 0.06

* Note that there were no ipsilateral versus contralateral differences in water content following HFHD application, and the HFHD itself did not dehydrate the brain. Values are presented as the mean ± SEM. Abbreviations: control = untreated control animals; control+C = non–water intoxicated animals treated with craniectomy only; control+C+D = non–water intoxicated animals treated with craniectomy + HFHD; NA = not applicable; W = water-intoxicated animals with no treatment; W+C = water-intoxicated animals treated with craniectomy only; W+C+D = water-intoxicated animals treated with craniectomy + HFHD.

sents several technical challenges. First, lumen solution and concentration need to be selected carefully. Although there are many possibilities for the lumen solution, we chose to use BSA in artificial CSF solution at physiological pH. Bovine serum albumin was chosen because of its physical properties and because at high solution concentrations, its concentration-dependent osmotic pressure range is significantly larger than the proposed physiological application, while having manageable viscosity changes.[15,16] Second, contact with the brain tissue and the liquid-liquid interface, if not maintained, could severely limit the removal of water and success of the treatment. To better maintain the liquid-liquid interface and contact with the brain tissue, we used a hydrogel. One advantage of the hydrogel is that it allows for the HFHD to conform to brain sulci and gyri. This was not specifically tested in this study because mice are lissencephalic, but in further testing with higher mammalian systems, we believe the conformability of the hydrogel will be a significant advantage. Third, another design parameter of importance is the flexibility of the hollow fibers. We carefully chose very flexible hollow fibers so as to allow access through smaller openings in future applications (for example, application through a bur hole and obviating the need for craniectomy).

Device Efficacy

In the present study, use of the HFHD to treat induced cytotoxic edema resulted in markedly improved survival compared with no treatment or craniectomy only. These results provide proof of principle for direct controlled water extraction as a novel form of treatment for cerebral edema. The device–brain surface contact is gentle, and simple application of the device is not associated with any histological damage. One important finding is that device application to a single small quadrant of the brain over the right hemisphere (based on atlas calculations we estimated contact of the device with approximately 17% of cortical surface area on the right hemisphere only) led to uniform water content throughout the brain and even in the contralateral hemisphere. These results suggest that even for large areas of hemispheric edema, the area of contact may not need to be so extensive to attain adequate water extraction. This interesting result is likely due to rapid osmotic water equilibration via aquaporin-rich astrocyte networks.[14]

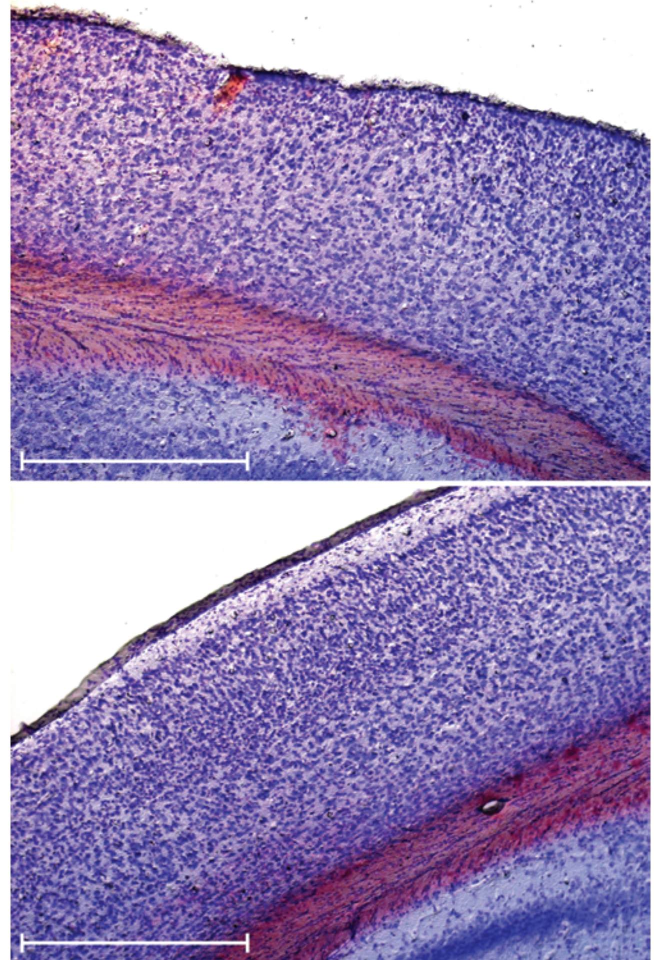

Fig. 5. Photomicrographs obtained after HFHD application. Representative histological sections after 3 hours of HFHD application in non–water intoxicated animals. **Upper:** Cortex ipsilateral to HFHD application (tissue directly under the device). **Lower:** Cortex contralateral to HFHD application. Scale bar = 500 μm.

Implications for Treatment

One limitation of our study is that our results are confined to a model of "pure" cytotoxic edema (water intoxication). Poststroke edema is thought to be largely cytotoxic in nature, whereas brain tumor edema and postinfectious edema are largely vasogenic, and posttraumatic edema is mixed cytotoxic and vasogenic.[9] Therefore, future studies will need to test the device for efficacy in models of vasogenic edema and more clinically relevant models of posttraumatic edema models.

Conclusions

We have validated the use of an HFHD directly applied to the brain surface to enhance survival in a cytotoxic model of cerebral edema. Future studies will need to validate the device in distinct models of cerebral edema such as controlled cortical impact, a model of traumatic brain injury. Conceivably, the HFHD could be used flexibly to treat any anatomical extent and severity of edema given that the appropriate device parameters (lumen solution and concentration, flow rate, contact surface area) are chosen to provide the therapeutically appropriate water removal rate.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Binder, Rodgers. Acquisition of data: McBride, Hsu. Analysis and interpretation of data: all authors. Drafting the article: Binder, McBride. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Binder. Statistical analysis: McBride, Hsu. Administrative/technical/material support: Binder, Hsu. Study supervision: Binder.

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