Protocol

CONIVAPTAN FOR THE REDUCTION OF CEREBRAL EDEMA IN INTRACEREBRAL HEMORRHAGE – A Safety and Tolerability Study

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Principal Investigator: Jesse J. Corry, MD

Co-Investigators: Ganesh Asaithambi, MD
Arif Shaik, MD
Jeff Lassig, MD

Research Nurse: Amy Castle, RN

Study Coordinator: Emily Marino, BS
Bridget Ho, BA, CCRC

United Hospital, part of Allina Health
John Nasseff Neuroscience Institute, part of Allina Health
333 North Smith Avenue
St. Paul, MN 55102
651-241-6550

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1. Research Goal

The goal of this study is to preliminarily determine/estimate feasibility and whether frequent and early conivaptan use, at a dose currently determined to be safe (i.e., 40mg/day), is safe and well-tolerated in patients with cerebral edema from intracerebral hemorrhage (ICH) and pressure (ICP). A further goal is to preliminarily estimate whether conivaptan at this same dose can reduce cerebral edema (CE) in these same patients. This study is also an essential first step in understanding the role of conivaptan in CE management.

Hypothesis: The frequent and early use of conivaptan at 40mg/day will be safe and well-tolerated, and also reduce cerebral edema, in patients with intracerebral hemorrhage and pressure.

2. Specific Aims

Aim 1: Evaluate the feasibility of the proposed study methods.

Subaim 1: Determine the efficiency of enrolling patients into the study. [Accomplished by tracking the number of patients asked to participate compared to the number of subjects enrolled into the study.]
Subaim 2: Determine the efficiency of obtaining all the study required data and information.

Aim 2: Estimate trends in the safety, tolerability, and efficacy of frequent and early conivaptan use (started within the first 48 hours from ICH symptom onset).

Subaim 1: Estimate if frequent and early use of conivaptan is safe and well-tolerated. [Based on previous work demonstrating conivaptan safety in other models, the working hypothesis is that early and frequent use will be well-tolerated, with few, if any, adverse events.]
Subaim 2: Evaluate the amount of adjunct osmotic therapy (i.e., mannitol, hypertonic saline) given throughout study period.
Subaim 3: Evaluate whether conivaptan reduces the extent of cerebral edema. [The working hypothesis is that early conivaptan use will reduce the presence of AQP4 and limit the development, and thus consequences, of CE.]

3. Background

Intracerebral hemorrhage (ICH) represents ~10-15% of all strokes in the United States (U.S.), numbering 50-70,000 cases per year, twice as common as subarachnoid hemorrhage (SAH), the 30 day mortality is ~40%, and greatest among the poor, elderly, black and Asian (Adams, 2005; Thomas et al., 1996). Only 20% of ICH patients are independent at 6 months. Only admission to a neuro-ICU, and the use of a CT scanner, have been shown to improve outcome from ICH (Thomas et al., 1996; Diringer & Edwards, 2001). With respect to cost, ICH represents 34% of years of potential life lost to stroke (Thomas et al., 1996). Per case, the cost is ~$124,000, and the total lifetime cost for annual US cases >$4B (Thomas et al., 1996).

Complicating ICH is the development of cerebral edema (CE). Worsening CE has been implicated in delayed neurological deterioration, and worse outcome, through the elevation of intracerebral pressure (ICP) (Mayer & Sacco, 1994). Elevations in ICP reduce the ability of blood to reach the

brain, exacerbating the injury and producing ischemia. The formation of peri-hematomal edema contributes to an increased volume of ~75% (Gebel et al., 2002). Animal models of ICH demonstrate a large peri-hematomal area that undergoes neuronal death characterized by increased water content and inflammation (Theix & Tsirka, 2007). Reduction of this edema may reduce the degree of neuronal death, decreasing hospital length-of-stay (LOS), and improving short-term outcome (Volbers et al., 2016).

Wide variability exists in the treatment of ICP and CE among intensivists (Hays et al., 2010). In part, this may be the function of training and/or experience. The use of mannitol, which elevates the osmolarity within the cerebral vasculature, promoting water movement across the blood-brain barrier and into the capillary system (Galton et al., 2011), is common, but is limited by its deleterious effects on renal function, fluctuations in intravascular volume, and pH. Most concerning is the slow elimination of mannitol from the cerebrospinal fluid (CSF) which may potentially require progressively higher doses, over time, to control ICP, and may result in rebound CE (Nau et al., 1997; McGraw & Howard, 1983). Increasingly, hypertonic saline (HS), which acts similar to mannitol, is being used to abate CE. However, this therapy has not demonstrated any survival or outcome benefit despite reductions in ICP (Bulger et al., 2010; Strandvik, 2009). And, currently, there is a national shortage of HS (FDA, 2010). A retrospective review of available data at Henry Ford Health System preliminarily demonstrates adverse effects on renal function with the use of HS (Corry et al, 2014). Further, anecdotal observations have noted changes in renal function and difficulty replacing free-water deficits (FWD) following aggressive antecedent use of HS. A known side-effect of HS therapy is hyperchloremia (HC). Chlorine is a potent renal vasoconstrictor potentially reducing blood flow, precipitating renal ischemia and reducing glomerular filtration rate (Wilcox, 1983; Gazitua et al., 1969). Finally, the use of HS may be associated with increased risk of blood-stream infections (BSI), and trends to increased risk of nosocomial and urinary tract infections (Bulger et al., 2010).

In sum, neurocritical care needs a therapy that can reduce the development of CE, potentially decreasing ICU LOS and possibly improving outcome. Could a single medication reduce the CE in ICH and improve the treatment variability found in this disease process? Conivaptan, a non-selective Arginine-Vasopressin (AVP) V_{1A}/V_2 antagonist that reduces aquaporin 4 production, thus promoting aqueresis, is approved for the treatment of euvolemic and hypervolemic hyponatremia (Cumberland Pharmaceuticals, 2014). The early use of conivaptan could potentially be used clinically to reduce CE by these means. Current clinical data in traumatic brain injury patients demonstrate conivaptan is safe and well tolerated using a single dose (20mg) to increase Na^+ in a controlled fashion to reduce ICP (Galton et al., 2011; Dhar & Murphy-Human, 2011). Further, additional work has demonstrated the safety and tolerability of conivaptan, in doses ranging from 10-80mg/day, in the neurocritical care population (Ghali et al., 2006; Zeltser et al., 2007; Verbalis et al., 2008; Annane et al., 2009; Murphy et al., 2009; Wright et al., 2009; Naidech et al., 2010; Human et al, 2012; Marik & Rivera, 2013).

AVP V(1) receptor antagonism significantly reduces hemorrhagic brain edema in rat models (Rosenberg et al., 1992). Traumatic brain injury (TBI) research, using animal models, has demonstrated V1 expression is increase in astrocytes and blood vessel endothelium during the first week following injury (Szmydynger-Chodobska et al., 2004). Experimental models have demonstrated AVP V(1) receptor antagonism attenuates injury volume, and CE, through changes in aquaporin-4 (AQP4) expression (Liu et al., 2010). Although not the exclusive means for water flux in the brain, AQP4 is the predominant class of water channel in the brain (Yool et al., 2010; Zeynalov et al., 2008). For edema to occur, water must enter the astrocyte compartment. Water must pass from the capillary lumen and through the luminal, abluminal, and luminal perivascular endothelium. The perivascular pool appears, in both the influx and efflux of water, to be the rate limiting step (Zeynalov et al., 2008). Inhibition of water permeability, via reductions in AQP4, decreases ipsilateral hemispheric water content and may have therapeutic potential for CE in the clinical setting (Migliati et al., 2010; Rosenberg et al., 1992).

Animal models have demonstrated AQP4 expression increases within 6 hours from injury, peaks between 48-72 hours, and remains elevated over the first week (Li & Sun, 2003; Sun et al., 2009). This increased expression parallels brain water content (BWC) in hemorrhagic animal models. Antagonism of AVP V(1), in animal models of TBI and both hemorrhagic and ischemic stroke, is associated with parallel reductions of AQP4 expression and CE as measured by BWC (Liu et al., 2010; Taya et al., 2008; Trabold et al., 2008; Rosenberg et al., 1992).

Recently, bolusing of conivaptan (20mg) has been shown to lower ICP in hyponatremia following TBI and cerebral ischemia (Dhar & Murphy-Human, 2011; Galton et al., 2011). The authors reported improvements in cerebral perfusion pressure (CPP) and stable blood pressure, and a prolonged reduction in ICP. They theorize the V2 antagonism of conivaptan promotes free water loss to reduce BWC, and the V1 antagonism may improve cerebral blood flow (CBF) and reduce blood brain barrier permeability (Taya et al., 2008; Trabold et al., 2008; Dhar & Murphy-Human, 2011; Vakili et al., 2005; Kleindienst et al., 2006; Fernandez et al., 2001).

Given the enormous costs of ICH, problems with current therapies, and variability in treatment, there is an urgent need to identify a therapy that has a better safety and effectiveness profile compared to the currently used agents. Our central hypothesis is that through reductions in AQP4 expression, the early use of conivaptan will reduce CE while also being safe to the patient. Our long term goal is to show that early use of conivaptan in ICH will reduce CE, thus improving outcome and reducing the need for rescue therapies, ICU length of stay, and overall treatment cost. However, more data is needed to evaluate the dosing and amount of drug. With respect to conivaptan's efficacy in the correction of hyponatremia, a direct dose-response relationship exists (Onuoho et al., 2010). Further, this effect was more noted at milder degrees of hyponatremia, suggesting higher doses may be required to achieve a hypernatremic state (Onuoho et al., 2010). However, whether the reduction in CE parallels the relative changes in serum sodium remains to be determined. The objective of this proposal is to first establish whether conivaptan use, at a dose currently determined as safe (i.e., 40mg/day), can reduce CE. This proposed study is an essential first step in understanding the role of conivaptan in CE management. Prior to any mechanistic investigations, a fundamental understanding of dosing and toleration must occur. If this proof-of-concept study demonstrates the desired effect, work can take place identifying the optimal dosing and frequency needed for maximal effect. Later studies could ask questions on efficacy. Further, should such studies prove fruitful, mechanistic investigations using MRI and microdialysis could elucidate effects on membrane integrity, inflammation, and secondary cell injury.

4. Significance

As stated above, there are enormous costs involved with ICH, there is variability in its treatments, and many of the current therapies can cause serious side effects. A new, safe and effective therapy is needed. Conivaptan was approved by the FDA ~11 years ago for the treatment of euvolemic and hypervolemic hyponatremia. Since then, it has been used safely in doses ranging from 10-80 mg/day for this treatment. An additional benefit observed has been the reduction of ICP in a number of patients. However, more work is needed to determine the appropriate amount of drug, dosing schedule, etc. needed for the maximal effect on CE. This proposed study is an essential first step in that direction.

5. Preliminary Studies and/or Data

Dr. Corry received his MD degree from the Medical College of Wisconsin in 2002. Remaining at the Medical College of Wisconsin Affiliated Hospitals, he completed an Internal Medicine Internship in 2003 and a Residency in Neurology in 2006. He went on to complete a Fellowship in Neurocritical Care at Washington University School of Medicine in St. Louis, Missouri, in 2008. He practiced at Henry Ford Hospital in Detroit and at Marshfield Clinic in Wisconsin prior to joining the John Nasseff Neuroscience Specialty Clinic at United Hospital. As neurovascular physician, Dr. Corry is familiar with the physiology and clinical consequences of CE, as well as the limitations of available medical and surgical interventions. On the topic of CE, Dr. Corry has studied the renal effects of HS, and published on methods to mitigate the deleterious effects of CE. Publications include:

Corry JJ, Varelas P, Abdelhak T, Morris S, Hawley M, Hawkins A, Jankowski M. Variable Changes in Renal Function by Hypertonic Saline. *World Journal of Crtical Care Medicine.* 2014 May 4; 3(2): 61-67.

Corry JJ. The use of targeted temperature management for elevated intracranial pressure. *Curr Neurol Neurosci Rep*. 2014 Jun;14(6):453.

Corry JJ. Use of hypothermia in the intensive care unit. *World J Crit Care Med*. 2012 Aug 4;1(4):106-22.

6. Research Design and Methods

6.1 Study Design: a single-center, open-label, safety and tolerability study.

Based on findings in the literature from both animal research and clinical observations with ICH associated with TBI, this study will begin to look at the safety, tolerability, as well as potential effectiveness, of conivaptan to reduce CE in patients with non-traumatic ICH.

6.2 Subjects and Inclusion/Exclusion Criteria

Patients with non-traumatic ICH admitted to the United Hospital Neurological Intensive Care Unit (Neuro-ICU). The 2016 ICD-10-CM diagnosis code for ICH is 161.9 Non-traumatic ICH generally results from the rupture of blood vessels in the brain, causing blood to collect, form a clot and cause pressure to surrounding tissue. This is most commonly due to hypertension, blood vessel malformation(s), and/or dysfunctional protein(s) leading to weak vessels. The presenting behavior is quite similar with symptoms such as headache, nausea, vomiting, sudden weakness or numbness of the face, arm or leg, temporary loss of vision, seizures, and/or loss of consciousness. Approximately 2/3rds of all ICH's have a volume greater than 20cc.

6.2.1 Major Inclusion Criteria

1. Age ≥18 years old and < 80 years.
2. Diagnosis of primary ICH ≥ 20 cc in volume.
3. Enrollment within 48 hours from initial symptoms.
4. Signed informed consent from the patient or obtained via their legally authorized representative (if the patient is not able to sign the informed consent themselves). The patient's decisional capacity to either provide or refuse consent will be determined using the Glasgow Coma Scale (GCS), which is being assessed at baseline and at 24 hours (+/- 6hrs) after enrollment. A potential study participant with a GCS > 14 will be asked to

provide their own initial study consent. A GCS ≤ 14 would indicate the need to pursue consent via legally authorized representative. Patient and/or LAR must be English speaking.

6.2.2 Major Exclusion Criteria

1. Current need for renal replacement therapy (RRT).
2. GFR of <30 mL/minute at time of admission.
3. Participation in another study for ICH or intraventricular hemorrhage.
4. ICH related to infection, thrombolysis, subarachnoid hemorrhage, trauma or tumor.
5. Presence of HIV or active fungal infection that is known based on information in the EMR.
6. Continued use of digoxin or amlodipine (as recommended by the manufacturer due to CYP3A inhibition).
7. Active hepatic failure as defined by AST >160 units/L and/or ALT >180 units/L, or total bilirubin levels greater than four times normal levels (>4.8mg/dL).
8. Serum $Na^{+} \geq$ 145 mmol/L (admission labs or any time prior to recruitment/enrollment).
9. Unable to receive conivaptan based on contraindications indicated by the manufacturer.
10. Pregnant or lactating females.
11. Not expected to survive within 48 hours of admission, or a presumed diagnosis of brain death.

6.3 Subject Recruitment

The PI, co-investitagors and study team members, will screen and recruit participants from the non-traumatic ICH patient population admitted to the United Hospital Neuro-ICU meeting the study inclusion and exclusion criteria. Investigators will only screen patients seen as part of their normal clnical practice in the Neuro-ICU. Other physicians in Neurology and the Neuro-ICU will be informed of the study by an informational letter sent by the PI, and/or during departmental meetings where the PI will discuss the study. An informational letter, list of inclusion and exclusion criteria and a study binder will also be housed in the Neuro-ICU for reference.

6.4 Sample Size

This study is looking to preliminarily evaluate the safety, tolerability, and efficacy (presence of moderate reduction in CE), and as a ratio of ICH volume to CE volume. Unfortunately, it is not powered to provide robust statistical evaluation of safety and tolerability, nor to detect differences in efficacy, due to time and budgetary limitations.

Seven (7) patients will be treated with conivaptan (40mg/day; four 20mg doses over a 2 day period) in addition to conventional medical means. This number of patients takes into account information in the conivaptan in TBI patients study by Galton et al (2011), use of glyburide in ICH by Sheth et al. (2014), as well as time and budgetary limitations.

The goal is to enroll all seven (7) patients within an 18-month period. This recruitment goal should be achievable since:

1) according to the PI's experience, (based on 2015 data) ~50-70 ICH patients (ICD-10-CM code 161.9) are admitted per year to United Hospital and
2) according to a recent electronic feasibility search, in the year 2015, 55 patients with a diagnosis of ICH were admitted to United Hospital. Of these patients, the PI determined that 9 would have been eligible for the study, based on the study's inclusion and exclusion criteria.

6.5 Study Testing Location

Neurological Intensive Care Unit (Neuro-ICU) at United Hospital, part of Allina Health, 333 North Smith Avenue, Saint Paul, MN 55102.

6.6 Consent and Enrollment Process

Patients meeting inclusion criteria, and not possessing any exclusion criteria, will be approached or will have their healthcare advocate (e.g., legally authorized representative or LAR) approached by a member of the study team (e.g., PI, Co-I, research coordinator).

Consent will need to be obtained within 48 hours of the patient's symptoms onset. This consent can take place at the patient's bedside, in another room in hospital, in a conference room, or over the phone, depending on whether it is with the patient or their LAR. The consent can occur potentially any day of the week; accomplished by the PI, Co-I, and/or RC during the week, and by the PI and/or Co-I on weekends. A consenting schedule will be developed, and training on the consent process will occur, prior to the start of the study.

An explanation of the purpose of the study will follow conformation the subject meets all study criteria listed above. These steps may be performed by the PI, Co-I, and/or the research coordinator.

The consent, along with HIPAA authorizations, will be explained and then signed by the patient or their LAR if they want to participate/want the patient to participate. A copy of the signed consent and the HIPAA authorizations will be given to the patient/participant's LAR. Another copy will be uploaded to the patient's electronic medical record, while the original forms will be kept in a locked file cabinet which is only accessible to study personnel.

The consenting process will take ~ 1 hour.

The patient/their LAR will be able to ask questions at any time during the consenting process and the study procedures.

Those patients who decline enrollment/whose LAR decides to decline their enrollment will be given the standard of care for CE.

If the patient or their LAR consents to the patient's study enrollment, the patient will be assigned a study subject number, such as the patient's day of enrollment and the first 2 letters of their last name (e.g., patient Joe Smith admitted on March 31, 2008 would be subject #033108SM).

The PI will share any new information that could change how the patient feels about continuing in the study.

If during the course of the study a subject regains consciousness and their decisional capacity (i.e., a GCS > 14), especially at any of the study assessment time points, they will be asked if they want to consent to continuing in the research study.

If a patient decides to withdraw for any reason during the study duration or the LAR wants to withdraw a patient for any reason during the study duration, the patient's data collected up to point of withdrawl

will remain in the database and will be analyzed. If the patient/LAR is against any of the data being used, we will grant this request.

The PI may withdraw the subject from the study without patient/LAR consent if considered appropriate. The reason to withdraw would include complications related to the use of conivaptan. For safety, if withdrawn from the study, it would be in the best interest of the patient to allow follow-up outside the study.

The consent will explicitly detail all aspects of the study (the purpose, methods, benefits, risks).

6.7 Why a patient should participate in this trial?

ICH is a devastating disease representing approximately 15% of all strokes in the United States (Adams 2005, Thomas et al 1996). The 30 day mortality is ~ 40% with only admission to a neuro-ICU and the use of a CT scanner demonstrating improved outcomes (Thomas et al., 1996; Diringer & Edwards, 2001). Nearly as great are the costs to society, with the total lifetime cost for annual US cases >$4B and nearly 35% of years of potential life lost because of stroke (Thomas et al., 1996). This devastation is influenced by the dynamic injury processes involved in ICH. Following the initial hemorrhagic injury, CE develops. This peaks between 7-14 days after the initial bleed (Venkatasubramanian 2011). Worsening CE has been implicated in delayed neurological deterioration, and worse outcome, through the elevation of ICP (Mayer & Sacco, 1994). Elevations in ICP reduce the ability of blood to reach the brain, exacerbating the injury and producing ischemia. The formation of peri-hematomal edema contributes to an increased volume of ~75% (Gebel et al., 2002). Animal models of ICH demonstrate a large peri-hematomal area that undergoes neuronal death characterized by increased water content and inflammation (Theix & Tsirka, 2007). Reduction of this edema may reduce the degree of neuronal death, potentially improving outcome and decreasing hospital LOS. Further, a shorter time in the neuro-ICU, much of which is focused on management of CE, would mean decreased hospital costs in the form of less nosocomial infections.

Studies in neurocritical care are often limited in their design and scope because many of the common therapies, despite a paucity of clinical evidence, are considered “standard of care.” (Chesnut, 2012). This holds true in the management of CE and ICP, where a wide variability in treatment exists among intensivists (Hays et al., 2010). The two most commonly used agents for the medical management of CE and elevated ICP, mannitol and hypertonic saline, do not demonstrate any evidence of improving clinical outcome (Grande, 2012). Mannitol use is common, but is limited by its deleterious effects on renal function, and fluctuations in intravascular volume and pH. Most concerning is the slow elimination of mannitol from the CSF which may potentially require progressively higher doses, over time, to control ICP, and may result in rebound CE (Nau et al., 1997; McGraw & Howard, 1983). Increasingly, HS is being used to abate CE. However, this therapy has not demonstrated any survival or outcome benefit despite reductions in ICP (Bulger et al., 2010; Strandvik, 2009). The use of hypertonic saline may be associated with increased risk of BSI, and trends to increased risk of nosocomial and urinary tract infections (Bulger et al., 2010). Recently, a retrospective review of patients receiving HS in a single center’s neurocritical care unit demonstrated a correlation between the degree of hypernatremia and hyperchloremia induced by HS and changes in renal function heralding the development of acute kidney injury (Corry et al., 2014). Therefore, any new therapy for CE in ICH should have less or equivalent side effects to mannitol and HS.

It is with this balance in mind, the need for effective therapies in a devastating disease and the continued use of historically approved therapies, that this study is proposed. The welfare of our patients is the primary goal of this trial. Our first goal *Primum non nocere*, to do no harm, is central to this study (Ross, 1988). All patients will receive the standard of care as outlined by the most recent

American Heart Association and Neurocritical Care Society Guidelines for the management of ICH. This will include, but not be limited to, serial clinical and paraclinical evaluations including CT scans, metabolic profile, echocardiography, etc. Current standards-of-practice, including euvolemia targets, electrolyte replacement, venous thrombosis prophylaxis, normoglycemia, etc. will be maintained in this population. The risks most commonly seen with conivaptan use are hypotension (associated with volume loss), site reactions, and electrolyte abnormalities including hypokalemia and hypomagnesemia that may result in dysrhythmia. Thus, patients will be closely monitored for these and other problems. Finally, to evaluate for any unforeseen problems with the use of this medication, these patients will receive standard of care practice, including neuroimaging and outpatient clinic follow-up.

The seven patients in this study will receive 40mg/day of the study medication conivaptan. In this early phase study, our focus will be to assess the safety and tolerability of this medication. The available clinical data on conivaptan in the neurocritical care population suggest the potential harm is negligible. Data in TBI patients demonstrate conivaptan is safe and well tolerated using a single dose (20mg) to increase Na^+ in a controlled fashion to reduce ICP (Galton et al., 2011). Previous work has demonstrated the safety and tolerability of conivaptan, in doses ranging from 20-80mg/day, in the neurocritical care population (Murphy et al., 2009; Wright et al., 2009; Naidech et al., 2010; Dhar & Murphy-Human, 2011). Conivaptan has been demonstrated to be safe and effective in lowering ICP, and increasing serum sodium, in the neurocritical care population (Murphy NCC ’09, Wright *NCC* ’09, Dhar NCC ’11, Galton *NCC* ’11). Also noted have been improvements in CPP and stable blood pressure, and a prolonged reduction in ICP. Finally, the method of intermittent bolus dosing of conivaptan is equally effective in raising and maintaining serum sodium in the neurocritical care population as continuous infusion, with potentially less risk of adverse reactions including phlebitis (Murphy *NCC* ’09, Wright *NCC* ’09).

Conivaptan, a non-selective Arginine-Vasopressin (AVP) V_{1A}/V_2 antagonist that reduces aquaporin 4 production and promotes aqueresis, is approved for the treatment of euvolemic and hypervolemic hyponatremia (Cumberland Pharmaceuticals, 2014). The exact cause of the observed reduction in ICP with conivaptan is uncertain. However, the mechanism most likely represents a combination of an acute pure aquaresis, removing free water from brain tissue, and a sustained down regulation of aquaporin 4 to abate/slow development of CE (Dhar *NCC* ’11, Liu X *NCC* ’10, Zandor Handb Exp Pharmacol. 2009). The V2 antagonism of conivaptan promotes free water loss, and the V1 antagonism may improve CBF and reduce blood brain barrier permeability (Taya et al., 2008; Trabold et al., 2008; Dhar & Murphy-Human, 2011; Vakili et al., 2005; Kleindienst et al., 2006; Fernandez et al., 2001). Notably, serum sodium tends to correlate inversely with both ICP and CE (Nathan *NCC* ’07). The early use of conivaptan could potentially be used clinically to reduce CE by these means.

It is with this in mind, the research team feels justified in pursuing this study with the hopes that the data obtained will lead to potential good and removal of harm in future patients with this devastating disease. Given the enormous costs of ICH, problems with current therapies, and variability in treatment, there is an urgent need to identify a therapy that has a better safety and effectiveness profile compared to the currently used agents. This study will use a dose (40mg/day) currently approved. Further, given that the primary purpose of the use of this medication in this study is not to correct hyponatremia, an IND from the FDA was sought and determined exempt (FDA IND submission/exemption # 119424).

Our central hypothesis is that through reductions in AQP4 expression, the early use of conivaptan will reduce CE while also being safe to the patient. Our long term goal is to show that early use of conivaptan in ICH will reduce CE. If this reduction is possible, we hypothesize improved outcome and reducing the need for rescue therapies, ICU length of stay, and overall treatment cost will follow. However, more data is needed to evaluate the dosing and amount of drug. With respect to

conivaptan's efficacy in correction of hyponatremia, a direct dose-response relationship exists (Onuoho et al., 2010). Further, this effect was more noted at milder degrees of hyponatremia, suggesting higher doses may be required to achieve a hypernatremic state (Onuoho et al., 2010). This proposed study is an essential first step in understanding the role of conivaptan in CE management. Prior to any mechanistic investigations, a fundamental understanding of dosing and toleration must occur. If this study demonstrates the desired effect, work can take place identifying the optimal dosing and frequency needed for maximal effect. Later studies could ask questions on efficacy. Should such studies prove fruitful, mechanistic investigations using MRI and microdialysis could elucidate effects on membrane integrity, inflammation, and secondary cell injury.

Prior clinical experience suggests patients enrolled in this study will not be harmed. However, patients enrolled may not be helped by participating in this study either; others may be helped by what is learned from this research. Patients initially enrolled, or their LAR, may stop participation at any time. If this happens, they will still be followed-up for safety reasons. Patients will receive the same medical care whether or not they participate in this study. There will be no penalties or loss of benefits if patients choose not to participate. Patients will be told about any significant information that is discovered that could reasonably affect their willingness to continue being in the study. Finally, we do not expect there to be any additional costs to the patients if they participate in this study. Items related to the routine medical care that patients would receive even if they did not participate in this study will be billed to their insurance provider. Finally, there will be no compensation for participation in this study.

6.8 Treatment with Conivaptan

Note: An Investigational New Drug (IND) application for this label use of conivaptan has be submitted to the FDA. After extensive discussions, it was felt this use at this dose did not require an IND (FDA IND submission/exemption # 119424).

Patients will receive 20mg IV of the study drug every 12 hours equaling 40mg/day over 2 days (4 doses total), in addition to the standardized ICH management targets using the PI's version of standardized ICH management targets which are adapted from the 2015 AHA/ASA *Guidelines for the Management of Spontaneous Intracerebral Hemorrhage* and the *2007 Brain Trauma Foundation Head Injury Guideline*. This will ensure that all the patients will be managed similarly, to decrease the potential for variability commonly seen in "standardized" treatments. Usual standard of care can include sedation and analgesia as needed, elevation of the head of the bed, mannitol and/or saline as needed to reduce ICP, and temperature control with antipyretics such as acetaminophen.

The conivaptan bolus (20mg), which is premixed with 100ml of 5% dextrose in water, is infused (peripherally) over 30 minutes, most commonly through an already placed central line. The conivaptan will be ordered through the hospital's clinical pharmacy. Daily doses greater than the 40mg/day dose being used in this study (i.e., 80mg/day) have been shown to be safe in several studies (Zeltser et al., 2007; Verbalis et al., 2008; Annane et al., 2009; Ghali et al., 2009).

Seven (7) patients will be receiving conivaptan in addition to standardized management.

Electrolytes (obtained from a comprehensive metabolic panel, magnesium, & phosphorus test) will be drawn 6 hours after every conivaptan dose (4 total doses over 2 days). However, these labs may be done sooner (e.g., 2 hours after a conivaptan dose) based on the patient's progress/need and/or the attending physician's direction. The comprehensive metabolic panel will be utilized for these 4 analyses due to its incorporation of several additional parameters (over the basic metabolic panel) needed for the study. The study will cover the costs of this. If the patient's serum Na^+ becomes $\geq$ 160

mmol/L, or increases >12 mmol/L in a 24 hour period, further administration of the study drug will cease. If the patient has not completed the sequence of doses, they will be eligible for the remaining doses if their serum sodium falls below the threshold of 150 mmol/L, or after 24 hours in the case of increases of >12 mmol/L. Need for further use of hypertonic saline or mannitol is left to discretion of the treating physician

All patients will have CT scans at baseline and ~24, 72, and 168 hours (7 days) from enrollment to check for bleeding, lasting edema, or rebound edema. An 8 hour variance is permitted. It is preferable that the CT scans be done at 3mm increments as this is helpful for volume analysis, but 5mm is acceptable. Further imaging is left to the discretion of the treating/primary service physician.

Electrolytes (standard-of-care, basic metabolic panel) for all subjects/patients will be measured every 12 hours for the first 72 hours of the study, and then daily after 72 hours. This is considered a regular schedule based on clinical need. However, during the ~48 hour period when the subjects are receiving conivaptan, a comprehensive metabolic panel, Mg, and PO_4 will be drawn and analyzed 6 hours after each conivaptan dose. These labs may be done sooner based on the patient's progress/need and/or the attending physician's direction.

Neurological exams (e.g., EEGs), vital signs, and urine output measurements will be conducted as per Neuro-ICU protocol.

The need for ancillary monitoring tools (i.e. EVDs, bolts, microdialysis, EEG, near-infrared spectroscopy) will be at the discretion of the treating physicians.

No statin will be initiated within the 1st week following treatment with conivaptan. And, all statin medications will be held from enrollment to day 7 following conivaptan in patients selected for the study. Statins can promote hemorrhage. Those patients who are in-eligible or refuse the study will resume/assume statin use at the treating physician's discretion.

Neuro-ICU personnel/nurses will assist the PI and Co-I with patient care following both standard-of-care and study parameters as part of their normal duties, to maintain the flow of excellent patient care. Therefore, they are not listed on the study budget as study personnel.

Table 1. Project Schema

Assessment	Baseline	Enrollment[b] (within 48 hrs of onset)	6 hours from dose	12 hours from enrollment	6 hours from dose	24 hours from enrollment	6 hours from dose	36 hours from enrollment	6 hours from dose	72 hours from enrollment	Days 3-6	Day 7	Discharge	Follow-up
Inclusion/ exclusion criteria	X[a]													
Consent Process	X[a]													
Patient demographics	X[a]													
Medical history	X[a]													
Clinical Assessment														
GCS	X[c]					X[c]				X[c]		X[c]	X[c]	X[i]
APACHE II	X[c]													
mRS	X[c]												X[c]	X[i]
ICH	X[c]													
RIFLE	X[c]												X[c]	X[i]
Imaging														
CT scan (non-contrast)	X[d]					X[d]				X[d]		X[d]		X[i]
Study Drug														
Conivaptan (20mg)		X[f]		X[f]		X[f]		X[f]						
Laboratory Tests														
Comprehensive metabolic Panel	X		X[e]		X[e]		X[e]		X[e]					
Magnesium	X		X[e]		X[e]		X[e]		X[e]					
Phosphorus	X		X[e]		X[e]		X[e]		X[e]					
EMR Data Collection[h]														
Vital signs	X		X	X	X	X	X	X	X	X	X	X		
ICP monitoring	X		X	X	X	X	X	X	X	X	X	X		
Mannitol monitoring	X		X	X	X	X	X	X	X	X	X	X		
Sodium monitoring	X		X	X	X	X	X	X	X	X	X	X		
Medication log	X					X					X	X		
Cardiac monitoring	X		X	X	X	X	X	X	X	X	X	X		
Intake/Output	X					X				X	X	X		
Adverse event log	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]

[a]Occurs prior to enrollment. Other standard-of-care activities that will have occurred (between hospital arrival to 6 hrs post-arrival): 1) CT +/- CTA/CTV, 2) identify and correct coagulopathy, 3) identify and correct blood pressure (BP), 4) identifiy and correct ICP, and 5) admission to Neuro-ICU.

[b]Enrollment needs to occur within 48 hrs from initial symptoms.

[c]Clinical assessments can be study only or standard-of-care activites with a time window of +/- 6 hours.

[d]Admission and 24-hr stability CT scans are standard-of-care. Additional CT scans, other than the study related 72-hr and 7-day (168 hours) scans, may be done as clinically indicated by treating physician. All scans have a time window of +/- 8 hours.

[e]Dependent on conivaptan dose. Each needs to be drawn and analyzed 6 hours after each conivaptan dose. However, these labs may be done sooner (e.g., 2 hours after a conivaptan dose) based on the patient's progress/need and/or the attending physician's direction. Otherwise, standard-of-care labs (e.g., BMP) are drawn and analyzed every 12 hrs during the first 72 hrs after admission, followed by daily draws and analyses.

[f]Dependent on when the 1st of the 4 doses was started.

[h]Standard-of-care information collected as part of normal clinical practice will be recorded from the electronic medical record. Information may be recorded on a daily basis or after the protocol is complete.

[i]Follow-up visits will be conducted as part of normal clinical practice and information recorded, if available, from the electronic medical record. Three month post-discharge follow-up visits are standard-of-care.

Note: Training and informational sessions covering all aspects of the study (e.g., patient enrollment, treatment, ordering of lab tests, data collecting, etc.) will be held prior to the start of the study.

6.9 Primary Assessments (Safety and Tolerability)

Conivaptan was approved by the FDA in 2005 for the treatment of euvolemic and hypervolemic hyponatremia in a hospitalized setting using doses of 20-40mg/day. In the 11 years it has been on the market, numerous studies using it at doses ranging from 20-80mg/day have been done furthering the data on its effect on hyponatremia (National Monograph, 2006; Ghali et al., 2009; Zeltser et al., 2007; Verbalis et al., 2008; Annane et al., 2009; Human et al., 2012; Marik & Rivera, 2013), as well as studies showing its lowering of ICP in patients with TBI (Dhar & Murphy-Human, 2011; Galton et al., 2011). These benefits should relate to a decrease in CE.

In all these studies, conivaptan was well tolerated and safe, with no drug-related serious adverse events observed. For example, in the Ghali et al (2009) study, no deaths were study related, and the side effects of headache, hypotension, nausea, and constipation occurred most frequently. Based on these observations, we expect only minimal, if any, side effects in our study, since we are using a dose (40mg/day) which is lower than the 80mg/day used in several of the above mentioned studies. And, we feel there are no special concerns in the patient population included in our study (non-traumatic ICH) since conivaptan has already been safely used in TBI ICH patients.

An evaluation of the safety assessment parameters of each of the seven (7) subjects will be done by the PI and Co-I during the patient's care. Should events occur regarding the administration of conivaptan that raise safety concerns, the PI has the authority to withdraw the subject and/or halt the study pending further investigation.

Specific safety assessment parameters will include the following-

- **Neurologic tolerability:**
  1. Seizure frequency (15-20% of patients with ICH have seizures associated; EEGs will be used and measured; all treatments will be the same, using anti-seizure drugs).
  2. Total Na+ mEq received.
  3. ICP variability. In all patients for whom ICP is monitored, the hourly mean and median ICP will be compared. Further, patients will be graphed and the area-under-the-ICP-curve and above 10, 15, and 20 mmHg will be calculated and averaged to provide a more continuous comparison.
  4. ICP response to osmotic therapy. In patients receiving mannitol or 23.4% NaCl boluses, the average ICP reduction in the hour following administration will be compared.
  5. Development of central pontine demyelination, expansion of initial ICH, new ICH or stroke.

- **Cardiac tolerability:**
  1. Troponin values.
  2. Development of new arrhythmia during ICU stay.

- **Pulmonary tolerability:**
  1. Development of pulmonary edema as determined by chest X-ray.
  2. Average PO2, FiO2, A-a gradient.

- **Renal tolerability:**
  1. Change in renal function/urine output. RIFLE criteria will be used to assess for development of renal dysfunction (Appendix 1).
  2. Need for renal replacement therapy (RRT).

- **Infectious tolerability:**
  1. Compare rates of BSI, VAP/HAP, UTI, and sepsis.

- In-hospital mortality stratified by APACHE II, GCS, and ICH Score.

6.10 Secondary Assessments (Effectiveness)

- Reduction in CE as measured on CT. Goal is a 5-10% reduction in CE over time. Reduction will be measured both as absolute reduction, and as relative reduction, comparing the ratio of ICH to edema volume. The absolute edema reduction is more clinically relevant, while the ratio of ICH to edema volume has more research relevance, to aid in designing the next related studies.
- Outcome. mRS (Appendix 2) at discharge from ICU and from hospital stratified by APACHE II (Appendix 3), GCS (Appendix 4), and ICH Score (Appendix 5)
- Cost
  1. Length of stay in the neuro ICU.
  2. Need for EVD/bolt or surgical procedures (craniectomy, clot evacuation,VPS) for reduction/management of CE.
  3. Need for central venous lines, arterial lines, PICC lines, tracheostomy/PEGs.
  4. Duration on ventilator.
  5. Duration of EVD/bolt.

7. Safety Variables

7.1 Risks and Benefits

7.1.1 Potential risks

Potential risks associated with conivaptan may include hypotension, excessive rise in serum sodium, development of central pontine myelinolysis, increase in seizure frequency, expansion of initial ICH, development of new ICH and/or stroke, development of new cardiac arrhythmia, development of pulmonary edema, change in renal function, and development of an infection.

Potential risks involving blood draws may include temporary discomfort from the needle stick, pain or bruising, lightheadedness, and infection at the site.

Potential risks of CT scans are exposure to radiation from X-rays, dizziness, cold sensation at injection site, worsening of poor kidney function, allergic reaction to injection dye, soreness or swelling at the injection site.

Potential risks will be minimized by blood pressure monitoring, monitoring of total Na^+ mEq received, EEG monitoring and measurement (15-20% of patients with ICH have seizures, anti-seizure medications will be used), ICH/ICP monitoring, monitoring of troponin levels, chest x-ray and monitoring of pulmonary parameters (such as PO2, FiO2, A-a gradient), assessment of renal function by the RIFLE criteria, monitoring for infections.

Training sessions for all clinical study personnel will occur prior to the start of the study to discuss the potential risks that could occur, and the monitoring for and treatments that are in place.

7.1.2 Potential benefits for the study subjects/society

Because the current medications used have their own side-effects, participation may result in better reduction of the patient's CE, and prevent/lessen the brain damage caused by CE/ICH, with less side effects from other typically used medications.

The patients enrolled would help demonstrate if conivaptan is safe, well-tolerated, and effective in patients with CE. This knowledge will help further the understanding of this therapy, and its role in treating CE, as well as assisting with the designing of future clinical studies.

7.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study procedures. Since this is a study involving an FDA drug, conivaptan, used for approved purposes, exempt from IND regulations, we do not anticipate adverse events to be a common occurrence in this research study.

In case of such occurrence, for all AEs, the investigator will obtain adequate information to determine the following:
• The appropriate descriptive term
• Severity

• Onset/resolution dates and outcome.
• Causality: the relationship of each AE will be defined as “unrelated” or “related” to study procedures:
Unrelated: There is little or no possibility that the study procedures caused the AE;
Related: There exists at least a reasonable possibility that the study procedures caused or contributed to the AE; an inability to identify an alternate etiology for an AE should not, by itself, justify a “related” attribution.
• Whether it meets the criteria for classification as a SAE.

7.3 Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:
• Death
• Requires initial or prolonged inpatient hospitalization
• Is life-threatening (that is, immediate risk of dying).
• Is a persistent or significant disability/incapacity.
• Other significant medical hazard.

7.4 Adverse Events Reporting

The investigator will document all directly observed AEs and all AEs spontaneously reported by the study subject. SAEs will also be reported to regulatory authorities in accordance with all applicable regulations, as appropriate.

8. Data Management

8.1 Data Reviewed

- Demographics: Age, race, gender, and risk factors (hypertension, diabetes, illicit drug use, coronary artery disease, stroke, alcohol use).
- Clinical Grading Scores:
    - Outcome: mRS (Appendix 2) at baseline and discharge (if available). This can be performed by study team or as part of normal clinical practice.
    - ICH score at baseline (Appendix 5).
    - GCS score at baseline, 24 hrs from enrollment, 72 hrs from enrollment 7 day and discharge (if available) (Appendix 4).
    - APACHE II at baseline (Appendix 3).
- Duration of Neruo-ICU and hospital stay.
- Need for any of the following:
    - EVD/Bolt.
    - Hemi-craniectomy.
    - Central venous line/PICC/Arterial line.
    - RRT.
- Concomitant osmotherapy:
    - Hypertonic saline. The total mEq delivered and form of delivery (i.e. NS vs. 3% NaCl solution vs 23.4% NaCl solution.)
    - Mannitol. Number of doses and total grams received.
- Concomitant medications
- Imaging evaluation: CT scans will be dichotomized and ICH volume and CE volume will be compared over time. The individual summed and averaged volumes, net ICH volume and edema volumes will be compared. A board certified/eligible radiologist will calculate serially

the hemorrhage volume on CT during the study period. ICH volume will be serially assessed both by the (AxBxC)/2 method and by volumetric calculations using volumetric software. Serial assessments of edema will occur by measurements of the length and width of regional edema in the CT slice demonstrating the greatest amount of edema. Volumetric calculations using volumetric software will also be employed to evaluate for CE volume. Further, the same measurements one slice above and below will be performed to allow for a volumetric comparison. Completed CT scan measurements and calculations will be e-mailed to the research coordinator for data entry. In addition to the planned imaging and chemistry panels, any other imaging or basic laboratory work, deemed medically necessary for patient care outside the study, will be evaluated in the final analysis.

Clinical data collected from time of ICU admission to day 7:

- Vital signs (BP, HR, Temp)
- Daily weights and admission height
- ICP/CPP values- when available/when a monitor is being used
- CVP values- when available
- Volumes for intake and output.
- Na+ values
- Cl- values
- Cr values
- BUN values
- PO2 values- when available
- PCO2 values-when available
- A-a gradient- when available
- Urinalysis results-when available
- All culture results

Data sources will include medical records, lab results, device reports, and vital signs. Information from Excellian will need to be obtained within a couple days of the patient leaving the Neuro-ICU.

We have the support of the Neuro-ICU nurses/personnel through the Neuro-ICU unit manager Chirs Allen, RN. The research coordinator will stop by each subject's room 1-2x/day during the patients study duration to confirm safety assessments are being monitored, and to collect data and information.

8.2 Data Entry & Database Completion

All completed data collection forms will be sent to the data entry person for entry into the study database.

All paper forms will be stored in a locked cabinet, with only the study personnel knowing the location of the key.

All database & study computers will be password-protected, with only the study team members knowing the password.

Following completion of the database, random data validation by manual re-entry will occur to ensure the accuracy of previous data and information entry.

All patient identifiers will be deleted. Electronic data will be stored in a protected server accessible only to team members. Paper forms will be stored in a locked file in the PI's JNNI office. Upon completion of the study, all paper forms will be destroyed.

The completed & validated de-identified database will then be delivered to the biostatistician for statistical analyses to be performed.

8.3 Data Sharing

1) The results obtained from this study will be prepared within a manuscript for submission to a peer-reviewed journal.

2) The results will also be used as preliminary data for future studies, including a rigorous, controlled study of the efficacy and safety of conivaptan compared to traditional treatments/a phase II dosing study.

9. Statistical Analysis

Descriptive statistics will be used to summarize the baseline characteristics and the outcomes, such as adverse events and the hospital length of stay. In addition, Mixed model with unequally spaced repeated measures will be performed to evaluate the change of the variables with unequally spaced repeated measures, such as edema content, ICH score, GCS score, and APACHE II score, where unequally spaced repeated edema content measurements for 7 patients will be plotted; while Mixed model with equally spaced repeated measures will be performed to analyze the change of the variables with equally spaced repeated measures, such Mg and PO_4.

10. Study Oversight

The PI and the research team will be responsible for all safety assessments. Safety will be assessed for all patients enrolled in an ongoing fashion based on the incidence of AEs, SAEs, and treatment discontinuations due to AE. If any significant safety issues arise, a decision to modify or terminate the trial will be made. If requested, the study will be made available for monitoring, auditing, IRB review, and regulatory inspection by providing direct access to study related source data to oversight bodies like FDA.

11. IRB Review/Ethics/Informed Consent

ICH GCP guidelines require that all investigational studies be conducted under the auspices of an IRB/EC. This committee will approve all aspects of the study, including the protocol and informed consent to be used and any modifications made to the protocol or informed consent. The investigator will retain a copy of the communication from the IRB/EC to the investigator indicating approval/favorable opinion of the protocol and consent form. All changes to the protocol or consent form will be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human patients. The investigator will also be responsible for obtaining periodic IRB/EC re-approval throughout the duration of the study. Copies of the investigator's periodic report to the IRB/EC and copies of the IRB/EC's continuance of approval will be retained in the site study files.

A sample informed consent form will also be provided to the IRB/EC. Prior to the beginning of the study, the investigator will obtain the IRB/ECs written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to patients. The written approval of the IRB/EC together with the approved subject information/Informed Consent Forms will be filed in the study files. The Informed Consent Form will contain all elements required ICH Good Clinical Practices (GCP) Guidelines in addition to other elements required by federal, state, local or institutional policy. The investigator will be responsible for obtaining an Informed Consent signed by each subject or his/her legally authorized representative, prior to his/her participation in the study, in accordance with ICH GCP guidelines. Informed Consent will be obtained from a subject or his/her legally authorized representative after a full explanation of the purpose of the study, the risks and discomforts involved, potential benefits, etc., have been provided by the investigator or designee, both verbally and in writing. The investigator is responsible to see that informed consent is obtained from each subject or legal representative and to obtain the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures. Participation in the study and date of informed consent given by the subject will be documented appropriately in the subject's files.

The original or copy of the signed copy of the Informed Consent will be maintained in the institution's records. The subject or his/her legally authorized representative will also be given a copy of the signed consent form.

12. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will not be retained in the database after completion of data collection and not used during any data analysis. Only the subject number will be recorded in the study database, and if the subject name appears on any other document (eg. radiology report), it will be obliterated before a copy of the source document is retained. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, EC/IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential.

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14. Appendices

-Appendix 1 – RIFLE criteria
-Appendix 2 – modified Rankin Score
-Appendix 3 – Apache II score system
-Appendix 4 – Glasgow coma scale
-Appendix 5 – ICH score criteria
-Appendix 6 – Conivaptan monograph