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TITLE: Novel Treatment for Patients with Traumatic Brain Injury (TBI)

PRINCIPAL INVESTIGATOR: Kenneth G. Proctor, PhD

CONTRACTING ORGANIZATION:
Naval Medical Logistics Command
Attention: Code 05
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Fort Detrick, MD 21702 REPORT

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Naval Medical Research Center
503 Robert Grant Avenue
Silver Spring, MD 20910

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14. ABSTRACT
Systemic hypotension independently increases morbidity and mortality after traumatic brain injury. The goal of all treatments is avoid hypotension and maintain cerebral perfusion. If this cannot be achieved with fluids, pressors are required. Unfortunately, refractoriness and other adverse events are common with standard of care catecholamine pressors and there are no FDA-approved alternatives if refractoriness develops or severe adverse events occur during treatment of a brain injured patient. This project was designed to provide an alternative and thereby extend the existing capability of physicians to treat patients with life threatening brain injury.

15. SUBJECT TERMS

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List of Personnel Receiving Pay:

1. Proctor, Kenneth
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INTRODUCTION:

This three-year project was designed to develop a new drug for the treatment of brain injured patients with refractory intracranial hypertension. The method was to purse a 505(b)(2) regulatory path to seek a new indication for an existing drug (AVP).

In the first year, the plan was to compile all clinical and pre-clinical data (including adverse events) in a format amenable to the FDA, schedule a pre-IND meeting with the FDA, then place the data in an acceptable format for the FDA to support an IND submission. The government was the sponsor. Funding for years 2 & 3 was contingent on the decision of the FDA. In years 2 & 3, we planned to conduct phase 1 or 2 trials under "good clinical practice" guidelines, if necessary, to support any additional requirements for the new label. There was no way to know a priori whether the FDA will require this since the relative safety and efficacy of the candidate drug (AVP) is well known.

BODY OF REPORT

Appendix 1 is the 34 pg document submitted to the FDA containing a summary of all the data.
Appendix 2 is the 3 pg FDA response to our submission

KEY RESEARCH ACCOMPLISHMENTS:

1) AVP is a safe alternative to catecholamines in TBI patients who require pressor therapy.
2) Despite data from experimental models, AVP does not exacerbate cerebral edema in patients
3) Decompressive craniectomy for urgent evacuation of intracranial hemorrhage improves intracranial and cerebral perfusion pressures and overrides benefits of vasopressors in TBI patients

REPORTABLE OUTCOMES:

1. AVP (arginine vasopressin, pitressin) is a safe and effective alternative to standard of care CAT (catecholamines) for the management of CPP (cerebral perfusion pressure) after TBI (traumatic brain injury) and support the continued investigation and use of AVP when vasopressors are required for CPP management in TBI patients. This conclusion is based on data from 95 patients. To maintain CPP >60 mm Hg after during recovery from TBI, 60 patients required no vasopressors, 23 patients required catecholamines (CAT, 70% levophed, 22% dopamine, 9% phenylephrine) and 12 patients received vasopressin (AVP). Those in the "no vasopressor" group were the least severely injured and had the best outcomes. Those in the two vasopressor groups had similar demographics, but Injury Severity Score (ISS) and fluid requirements on admission to the intensive care unit Day 1 were worse in the AVP versus the CAT groups (all $p < 0.05$) before treatment. These differences indicate more severe injury with accompanying hemodynamic instability. Adverse events were not increased with AVP versus CA. Trends favored AVP versus CAT, but no apparent differences were statistically significant at this interim point. There was no difference in mortality rates between CAT and AVP.

Ref: Van Haren RM et al: Vasopressin for cerebral perfusion pressure management in patients with severe traumatic brain injury: preliminary results of a randomized controlled trial. ***J Trauma Acute Care Surg*** 2013 Dec;75(6):1024-30.

2. There is strong evidence that endogenous AVP exacerbates secondary injury in rodent TBI models. This is the first radiographic and clinical evidence to suggest that exogenous AVP does not promote cerebral edema after human TBI and in fact decreases the use of osmotherapy relative to CAT. This conclusion is based on data from 205 patients who received invasive ICP (intracranial pressure) monitors. To maintain CPP > 60 mmHg, 205 patients required no vasopressors, 41 received a single CAT, 12 received AVP, and 28 required both CAT and AVP. Those who required no pressors were less injured, required less osmolar therapy and less total fluid, had lower plasma sodium, lower ICP, less cerebral edema, and lower mortality (all $p<0.05$). With AVP vs CAT, cerebral edema, daily sodium levels (mean, minimum and maximum), and mortality were similar, but the daily requirement of mannitol and hypertonic saline were reduced by 45% and 35%, respectively (both $p<0.05$).

Ref: Meizoso JP et al: Does arginine vasopressin exacerbate cerebral edema after traumatic brain injury? Presented at 29th Eastern Assoc for Surgery of Trauma Annual Scientific Assembly at the JW Marriott San Antonio in San Antonio, TX Jan 2016

3. Severe TBI patients often require neurosurgical intervention to evacuate intracranial hematoma and reduce ICP. Many of these patients also require vasopressors to maintain target CPP, so it is difficult to determine the relative benefits of medical or surgical therapy. These affirm the benefit of early DC (decompressive craniectomy) in severe TBI patients. In 227 patients requiring invasive ICP monitoring, age was 41±17 years, 82% male, 155 28±11, GCS 6±4, AIS head 4±1, LOS 32(15) days, with 27% mortality. Fifty patients with decompressive craniectomies following intracranial hematoma evacuation were matched to fifty patients with no craniectomy with similar demographics, hemodynamics, 155, GCS, AIS head, transfusion requirements, and need for vasopressor therapy between the groups. In comparing DC vs non-DC groups, hours of abnormal ICP (>20mmHg) were 1(10) vs 7.5(16) ($p=0.017$), hours of abnormal CPP (<60mmHg) were 0(6) vs 4(9) ($p=0.008$), daily minimum CPP (mmHg) was 67(13) vs 62(17) ($p=0.010$), daily maximum ICP (mmHg) was 18(9) vs 22(11) ($p<0.001$), LOS 33(47) vs 25(34) (p=NS), and mortality of 24% vs 30% (p=NS). Daily minimum CPP and maximum ICP values were significantly improved with deco!'Ylpressive craniectomy (both $p<0.001$).

Allen CJ, et al Craniectomy following urgent evacuation of intracranial hemorrhage improves intracranial and cerebral perfusion pressures in severe traumatic brain injured patients. Presented at 74th Annual Meeting of the American Association for the Surgery of Trauma & Clinical Congress of Acute Care Surgery Las Vegas, NV Sept 2015

CONCLUSION

On Oct 30, 2015, a pre-IND meeting with the FDA was requested and granted for developing a new indication for AVP in TBI patients. Our FDA consultant, recommended that three questions should be submitted to the FDA for consideration prior to the meeting. By Jan 2016, the FDA issued a written statement that some/all of the questions were premature because "There is no independent pathway for an individual to effect changes (e.g., add a new indication) to labeling of a product that he/she does not own. However, an individual may contact the product owner or manufacturer to investigate their interest in a proposal to expand the product's approved indications." The FDA pointed out that while a clinical trial might be approved, the end result would not lead to a change in labeling without the partnership of a current manufacturer of the generic AVP. We could not find a manufacturer that would be willing to form a partnership.

REFERENCES:

1) Van Haren RM, Thorson CM, Ogilvie MP, Valle EJ, Guarch GA, Jouria JA, Busko AM, Harris LT, Bullock MR, Jagid JR, Livingstone AS, Proctor KG: Vasopressin for cerebral perfusion pressure management in patients with severe traumatic brain injury: preliminary results of a randomized controlled trial. ***J Trauma Acute Care Surg*** 2013 Dec;75(6):1024-30.
2) Meizoso JP, Subhawong TK, Allen CJ, Chehala L, Ray JJ, Jagid JR, Bullock MR, Namias N Schulman CI, Proctor KG: Does arginine vasopressin exacerbate cerebral edema after traumatic brain injury? Presented at 29th Eastern Assoc for Surgery of Trauma Annual Scientific Assembly at the JW Marriott San Antonio in San Antonio, TX Jan 2016
3) Allen CJ, Meizoso JP, Ray JJ, Hanna MM, Manning RJ, Schulman CI, Namias N, Bullock MR, Jagid JR, Proctor KG. Craniectomy following urgent evacuation of intracranial hemorrhage improves intracranial and cerebral perfusion pressures in severe traumatic brain injured patients. Presented at 74th Annual Meeting of the American Association for the Surgery of Trauma & Clinical Congress of Acute Care Surgery Las Vegas, NV Sept 2015

Appendix 1

Submission to the FDA

UHealth | UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

October 30, 2015

Dr. Jacqueline Ware
Jacqueline.Ware@fda.hhs.gov

Pre-IND Consultation Program
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Phone # 301-796-1160

Re: Type B - PRE-IND CONSULTATION

Dear Dr. Ware:

According to the Guidance for Industry, "Formal Meetings between the FDA and Sponsors or Applicants", I am writing to request a Pre-IND Type B meeting with the Agency.

As an Investigator at the University of Miami, I seek guidance from the Agency for an expanded indication for Arginine Vasopressin – a FDA approved drug that has a long established safety profile since the 1950s.

Relevant information in a summary format is provided on the following pages of this Meeting Request letter. A pre-IND Briefing Document is also enclosed with this request.

Please do not hesitate to contact me for any additional information that you may need or to discuss the meeting dates. I can be reached by telephone or email as listed below.

Sincerely,

Kenneth Proctor, Ph.D.
Professor of Surgery
Leonard M. Miller School of Medicine, University of Miami
Miami, FL 33136
Telephone: (305) 355-4960
Email: KProctor@med.miami.edu

Pre-IND Request – Information Summary

1.	Proposed Study Name:	**Use of Arginine Vasopressin (AVP) for patients with traumatic brain injury**
2.	Product name:	Vasopressin Injection, USP
3.	Proposed Indication(s):	Arginine Vasopressin is a safe alternative to catecholamines for patients with traumatic brain injury (TBI).
4.	The type of meeting being requested:	Pre-IND **Type B**
5.	A brief statement of the purpose of the meeting.	The purpose of the meeting is to review the existing preclinical and clinical data to date, consider the established (>50 year) safety profile of AVP and seek guidance on the sufficiency of current data to support the expanded indication in the management of TBI. Please see **Pre-IND Briefing Document** for a synopsis of the preclinical and clinical data.
6.	A list of the specific objectives/outcomes expected from the meeting.	a) Concurrence from the Agency that the >50 year safety profile of AVP, the preclinical and clinical data specifically in TBI are sufficient to support an expanded indication in the treatment of TBI? b) Concurrence from the Agency that the >50 year safety profile of AVP, the preclinical and clinical data specifically in TBI are sufficient to support an expanded indication in the treatment of TBI for military personnel only? c) Guidance from the Agency on appropriate pathways and data sets required to secure an expanded indication for AVP; specifically in the management of intracranial pressure in acute/sub-acute TBI.
7.	The preliminary proposed agenda.	a) Introductions b) Review of the Agency's Comments to Dr. Proctor's Questions c) Closing Summary

Pre-IND Request – Information Summary

8.	Summary	Traumatic brain injury [TBI] affects 1.7 million Americans each year [1]. After TBI, cerebral ischemia is the most important secondary event that determines outcome [2]; a single episode of hypotension doubles mortality rate [3]. TBI disrupts cerebral autoregulation so that blood flow is directly proportional to cerebral perfusion pressure [CPP]. To minimize episodes of ischemia, standard treatment guidelines are aimed at maintaining a minimum CPP. The medical management of CPP involves reducing intracranial pressure [ICP] and/or maintaining or increasing mean arterial pressure [MAP]. There is no Level 1 evidence for the ideal target CPP, but a CPP between 50 and 70 mm Hg is desired [4] and is considered standard of care in the management of TBI induced cerebral ischemia. In a hypotensive trauma patient, fluid resuscitation generally increases MAP, which tends to increase CPP. After TBI, excessive fluid promotes filtration across a damaged blood brain barrier, which tends to increase ICP and decrease CPP. There is no precise definition of "excessive fluid", and many neurotraumatologists restrict intravenous fluid. Osmotic agents are often administered to promote transient resorption of fluid from damaged interstitium, but these substances also cause a brisk diuresis, which can deplete vascular volume and/or increase the risk of acute renal failure (especially if fluid is restricted). Catecholamines are the next line of defense to increase MAP and CPP [5-9], however refractoriness [10] and side effects such as arrhythmias and peripheral ischemic complications are common[11]. The clinical need is that there is no safe, effective FDA-approved alternative to the current standard of medical care (fluid resuscitation, osmotherapy, catecholamines) if refractoriness develops or if severe adverse events occur. The only other salvage options are craniectomy or drug-induced coma. Arginine vasopressin [AVP] is the endogenous fluid and electrolyte hormone. It is rapidly depleted in many different shock states, and exogenous supplements reverse many sequelae of shock. It is structurally dissimilar to catecholamines and acts at different tissue sites by means of a different class of receptors to evoke its anti-diuretic, vasopressor, and anti-inflammatory actions. We have data from animals and humans suggesting that AVP may be a safe alternative to the current standard of medical care in TBI patients, but it is not FDA approved for this purpose.

Pre-IND Request – Information Summary

9.	A list of all individuals (including titles) who will attend the proposed meeting from the Sponsor's or applicant's organization and consultants	(a) Kenneth G. Proctor, Ph.D., Principal Investigator, Professor of Surgery, University of Miami. (b) Capt. Sheri Parker, Ph.D. Program Manager, Advanced Medical Development, Naval Medical Research Center. (c) Michael B. Given, Ph.D., Office of Naval Research (d) Jonathan P. Meizoso, M.D., University of Miami (e) Charles A. Karcutskie, M.D., University of Miami
10.	A list of Agency staff requested by the sponsor or applicant to participate in the proposed meeting	Request is for appropriate Agency/CDER reviewers to assess clinical pharmacology of Arginine Vasopressin.
11.	The approximate date on which briefing document will be sent to the review division	**October 30, 2015 [The briefing document is enclosed with this request letter]**
12.	Suggested dates and times for the meeting	The week of **November 30 – December 4, 2015 or at a time during December 7 – December 18, 2015** that is convenient for the agency. Preference is for an afternoon time.

Pre-IND Briefing Document

Use of arginine vasopressin for patients with traumatic brain injury

Investigator

Kenneth G. Proctor, Ph.D.
Professor of Surgery
University of Miami Miller School of Medicine

Funding Sponsor

Naval Medical Logistics Command
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Date of Submission: October 30, 2015

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List of Abbreviations

ANF = atrial natriuretic factor
AKI = acute kidney injury
ANG = angiotensin
ARDS = acute respiratory distress syndrome
AVP = arginine vasopressin
BD = base deficit
COI = cyclooxygenase inhibitor
CNS = central nervous system
CPP = cerebral perfusion pressure
CSF = cerebral spinal fluid output
GCS = Glasgow coma scale
GOSE = Glasgow outcome score extended
Hct = hematocrit
head JP = Jackson-Pratt drainage
HR = heart rate
ICP = Intracranial pressure
ICU = intensive care unit,
IQR = interquartile range
ISS = injury severity score,
IVF = intravenous fluid
LOS = length of stay in hospital
MAP = mean arterial pressure
NE = norepinephrine
PE = phenylephrine
PRBC = packed red blood cells
SAP = systolic arterial pressure
SvO2 = mixed venous O2 saturation
TBI = Traumatic brain injury
TNF = tumor necrosis factor
UOP = urine output
WBC = white blood cells, leukocytes

1.0 INTRODUCTION

1.1 The clinical need

Traumatic brain injury [TBI] affects 1.7 million Americans each year [1]. After TBI, cerebral ischemia is the most important secondary event that determines outcome [2]; a single episode of hypotension doubles mortality rate [3]. TBI disrupts cerebral autoregulation so that blood flow is directly proportional to cerebral perfusion pressure [CPP]. To minimize episodes of ischemia, standard treatment guidelines are aimed at maintaining a minimum CPP.

The medical management of CPP involves reducing intracranial pressure [ICP] and/or maintaining or increasing mean arterial pressure [MAP]. There is no Level 1 evidence for the ideal target CPP, but a CPP between 50 and 70 mm Hg is desired [4] and is considered standard of care in the management of TBI induced cerebral ischemia.

In a hypotensive trauma patient, fluid resuscitation generally increases MAP, which tends to increase CPP. After TBI, excessive fluid promotes filtration across a damaged blood brain barrier, which tends to increase ICP and decrease CPP. There is no precise definition of "excessive fluid", and many neurotraumatologists restrict intravenous fluid. Osmotic agents are often administered to promote transient resorption of fluid from damaged interstitium, but these substances also cause a brisk diuresis, which can deplete vascular volume and/or increase the risk of acute renal failure (especially if fluid is restricted). Catecholamines are the next line of defense to increase MAP and CPP [5-9], however refractoriness [10] and side effects such as arrhythmias and peripheral ischemic complications are common[11].

The clinical need is that there is no safe, effective FDA-approved alternative to the current standard of medical care (fluid resuscitation, osmotherapy, catecholamines) if refractoriness develops or if severe adverse events occur. The only other salvage options are craniectomy or drug-induced coma.

Arginine vasopressin [AVP] is the endogenous fluid and electrolyte hormone. It is rapidly depleted in many different shock states, and exogenous supplements reverse many sequelae of shock. It is structurally dissimilar to catecholamines and acts at different tissue sites by means of a different class of receptors to evoke its anti diuretic, vasopressor, and anti-inflammatory actions. We have data from animals and humans suggesting that AVP may be a safe alternative to the current standard of medical care in TBI patients, but it is not FDA approved for this purpose.

1.2 Current standard of care to manage clinical need

In a normal individual with intact autoregulation, cerebral blood flow is independent of CPP over a range of about 50-150 mm Hg. However, after TBI, autoregulation is lost and the brain is vulnerable to ischemia. The goal of all management strategies is to avoid secondary insults caused by hypoxia and hypotension. Ideally, hemostasis and fluid resuscitation will stabilize MAP. If not, osmotherapy can promote fluid resorption from

damaged interstitium to acutely reduce ICP. If intracranial hypertension persists in volume replete patients, MAP is increased with catecholamines, to theoretically increase CPP, which should improve cerebral blood flow. Unfortunately, these therapies are all commonly associated with adverse effects that offset the benefits.

Per current labeling [indications and usage statements], catecholamines are prescribed as an adjunct in the treatment of profound hypotension. This use is described in the contraindication statements. For example, the product insert for LEVOPHED (NE, norepinephrine bitartate) states *"LEVOPHED should not be given to patients who are hypotensive from blood volume deficits except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed."* Although a gradual refractoriness can develop [10], the main side effects with all catecholamines, include arrhythmias and peripheral ischemia [11]. As described in the package insert, *"if LEVOPHED is continuously administered to maintain blood pressure in the absence of blood volume replacement, the following may occur: severe peripheral and visceral vasoconstriction, decreased renal perfusion and urine output, poor systemic blood flow despite "normal" blood pressure, tissue hypoxia, and lactate acidosis"*. In addition, increasing intravascular pressure can promote fluid extravasation by Starling's Law, especially across a damaged blood brain barrier, which offsets any reduced edema associated with the osmotic agent. Thus, supplemental catecholamines can exacerbate a potentially life-threatening condition in neurotrauma patients. Nevertheless, if catecholamines and osmotic agents lose potency, there are no FDA-approved alternatives [4].

Normal CPP is about 80 mm Hg. There is no level 1 evidence to indicate the optimal target CPP using pressors after TBI [4]. Maintaining CPP>70 mm Hg with catecholamines acutely improves cerebral blood flow after TBI [4], but there is a detrimental effect on outcome because of extracranial complications [2-7]. Thus, current management guidelines [4] recommend a target CPP of 60 instead of 70 mmHg. Regardless, few pressors except catecholamines, in combination with osmotic diuretics, have been evaluated in clinically relevant animal models or in these highly vulnerable patients. Since most evidence demonstrates physiological benefits to the brain from maintaining CPP >70 mmHg in both animals and man, it is important to find safer means of achieving such augmentation, in ways that reduce the adverse events or extracranial complications.

Immediately after most injuries, there is often a surge in circulating corticoids and catecholamines; this has evolved to confer a survival advantage. The parasympathetic system normally responds to this sympathetic hyperactivity with compensatory inhibition to restore homeostasis and begin the process of recovery. However, the autonomic system is often malignantly dysregulated, which can lead to dysreflexia, hyperreflexia, or "sympathetic storms" [12]. It is a potentially life-threatening condition characterized by paroxysmal hypertension, profound hyperthermia, pupillary dilatation, tachycardia, cardiac arrhythmias, hyperhydrosis, hyperglycemia, dystonia, and profound

hypermetabolism. These sympathetic storms are episodic, spontaneous, especially after TBI or spinal cord injury [13-15].

The first storms can occur any time after injury [13, 14]. The onset, symptoms, duration, and intensity vary with injury severity. Susceptable victims generally manifest minimal alertness, minimal awareness, and no reflex motor responses; storming takes a seemingly peaceful individual into a sudden state of chaos [12].

The delay in clinical presentation is probably related to multiple drugs used in early management, such as paralytic agents, sedatives, and narcotics. ICP often spikes during, or immediately after, the episode, but there is no consensus whether elevated ICP is a cause or an effect of the storm [16].

In any case, sympathetic hyperactivity greatly increases the risk of secondary brain injury [14, 15]. Extreme or prolonged hyperthermia and increased basal metabolic rate with hyperglycemia can cause further neuronal dysfunction, hypoxia, and cell death [14, 15]. Insulin may be required to regulate blood glucose. Energy needs can be increased by 100%-200%, which can lead to protein wasting [14, 15]. Hyperhydrosis increases the risk of dehydration, which decreases the ability to mobilize secretions, which increases the risk for pneumonia. Electrolyte imbalances [12] provoke ECG changes, which can lead to heart damage [14].

Treatment is symptomatic with a goal to attenuate sympathetic outflow. Sedatives, opiate receptor agonists, beta-blockers, and central nervous system (CNS) depressants have been used. Logically, the condition is especially complicated if catecholamine pressors are required to stabilize CPP. Unfortunately, these medications can dampen responsiveness in an already minimally responsive individual, making assessment of neurological changes difficult. [12] Thus, the appropriate drug regime is frequently determined by trial and error [12].

1.3 Proposed Use of AVP for management of MAP and CPP in TBI

Results of preclinical testing in several animal models suggest that AVP in combination with low volume fluid resuscitation, was safe and more effective for traumatic shock resuscitation than either structurally dissimilar vasopressors alone or fluid resuscitation alone. Preliminary data in TBI patients suggested that AVP was no less effective than catecholamine pressors. On this basis, we propose a new/expanded label indication that *AVP is a safe alternative to catecholamines in patients with TBI.*

1.4 Sponsor-Investigator and translational team

The Sponsor-Investigator, Dr. Kenneth G. Proctor and colleagues have more than three decades of government sponsored research experience in TBI and use of AVP in animal and clinical settings. They have published more than 150 scientific studies in peer reviewed journals - approximately one third of these studies have been in patients, one third in rodents, and one third in swine. Since 1982, the PI has received >$10.9M in grants and contracts for this work, including:

a) Naval Medical Research Center Advanced Medical Development Program N62645-15-C-4009; Novel treatment for patients with traumatic brain injury;
b) Sub-contract #N5019-34 from Office of Naval Research for Autonomous Critical Care System.
c) Sub-contract #W81K04-11-C-0016 from Department of Defense for mass casualty training exercise for U.S. Army Forward Surgical Teams.
d) Grant from U.S. Army Medical Research & Materiel Command [USAMRMC] W81XWH-11-2-0098 "Evaluation of SOCOM Wireless Monitor in Trauma Patients,"
e) Grant from Office of Naval Research N0001406160670 "Novel Resuscitation Strategies"
f) Contract from Naval Medical Research Center N0018907CZ085 for "Novel Salvage Therapy for Severe Polytrauma"
g) Sub-contract #W81K04-06-C-0021 from Department of Defense for mass casualty training exercise for U.S. Army Forward Surgical Teams
h) Grant from Office of Naval Research N0001406160670 "Novel Resuscitation Strategies"
i) Grant from Office of Naval Research: "Fluid Resuscitation of Traumatic Shock"
j) Grant from Office of Naval Research: "Acute LD50 Models of Traumatic Shock"
k) Grant from Office of Naval Research: "AICAR in CRS for the resuscitation of Traumatic Shock"
l) Grant-in-Aid from the Am. Heart Assoc.: "Regulation of the Peripheral Circulation"
m) Grant-in-aid from the Am. Heart Assoc.: [Tennessee Affiliate]; "Control of the Peripheral Circulation,"
n) Grant #HL-30663 from the NHLBI; "Regulation of Peripheral Circulation,"
o) Grant-in-Aid from the Am. Heart Assoc.: [Tennessee Affiliate]; "Adenosine, Prostaglandins, and Intestinal Absorptive Hyperemia,"
p) Grant-in-Aid #83-1033 from the Am. Heart Assoc.: "Regulation of Intestinal Absorptive Hyperemia,"
q) Grants-in-Aid #83-1077 and #86-1071 from the Am. Heart Assoc.: "Metabolic Control of Striated Muscle Contraction-Induced Hyperemia,"
r) National Research Service Award #HL-06234 from the NHLBI; "Local Microvascular Control During Maturation,"

2.0 PRODUCT BACKGROUND

2.1 AVP

This compound is somewhat unique as an FDA-approved substance. Unlike other drugs, it is an endogenous hormone found in most mammals. It was among the first fully sequenced peptides. Its mechanisms of action are well known and fundamental to fluid and electrolyte homeostasis. The antidiuretic action of AVP is ascribed to reabsorption of water by the renal tubules and is mediated by V2 vasopressinergic receptors. AVP can also cause V1 receptor-mediated contraction of smooth muscle of the gastrointestinal tract and all parts of the vascular tree, and V3 mediated release of

adrenocorticotropin hormone. Long before most of the current FDA regulations were enacted, AVP was approved for human use in the 1950s. It is indicated for the prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows and in diabetes insipidus. In the subsequent 60 years, AVP was commonly used (off label) in virtually every hospital every day for its vasoconstrictor properties as an alternative to catecholamines in a wide range of critically ill patients. With new laws, revised labeling was required for AVP along with many other already approved, and commonly used, drugs. More relevant to the DoD/Navy is that to issue a clinical practice guideline the military requires that the drug be FDA approved for that use.

On April 17 2014, a generic drug manufacturer [http://www.parpharm.com] received a new indication for AVP injection; "to increase blood pressure in adults for post-cardiotomy shock or septic shock". The new revised warning and precautions are that AVP can worsen cardiac function. The new revised common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia [coronary, mesenteric, skin, digital]. Multiple drug interactions were also cited when administered to patients in vasodilatory shock.
[www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/204485Orig1s000ltr.pdf]

2.2 Prescription Drug Status

PITRESSIN™ (Vasopressin Injection, USP) Synthetic is a sterile, aqueous solution of synthetic vasopressin (8-Arginine vasopressin) of the posterior pituitary gland. It is substantially free from the oxytocic principle and is standardized to contain 20 pressor units/mL. The solution contains 0.5% Chlorobutanol (chloroform derivative) as a preservative. The acidity of the solution is adjusted with acetic acid.

PITRESSIN™ is indicated for prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus.

VASOCONSTRICT™ (vasopressin injection) is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (1)

The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

Pressor effects of catecholamines and Vasostrict are expected to be additive. Indomethacin may prolong effects of Vasostrict. Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. Co-administration of drugs causing diabetes insipidus may decrease the pressor response.

2.3 Clinical Pharmacology and Safety

2.3. 1 Mechanism of Action (extracted from www.drugs.com)

Exogenous AVP elicits all the pharmacologic responses usually produced by endogenous AVP (antidiuretic hormone); the primary physiologic role of AVP is to maintain serum osmolality within a normal range.

AVP concentrates urine by increasing water reabsorption in the renal tubules by V2 receptors that are coupled to adenyl cyclase and the generation of cyclic AMP. AVP also increases reabsorption of urea by the collecting ducts. At the tubular level, AVP stimulates adenyl cyclase activity, leading to increases in cyclic adenosine monophosphate (AMP). Cyclic AMP increases water permeability at the luminal surface of the distal convoluted tubule and collecting duct, resulting in increased urine osmolality and decreased urinary flow rate.

At low doses, AVP increases coronary blood flow and the availability of oxygen to the myocardium (www.drugs.com) In doses greater than those required for antidiuretic effects, AVP directly stimulates contraction of smooth muscle V1 receptors. The vasoconstrictive action of AVP is mediated by vascular V1 receptors coupled to phospholipase C, resulting in release of calcium from sarcoplasmic reticulum in smooth muscle cells, leading to vasoconstriction. Blood flow to the splanchnic, coronary, GI, pancreatic, skin, and muscular systems is most effected at these doses.

When administered into the celiac or superior mesenteric arteries, AVP constricts gastroduodenal, left gastric, superior mesenteric, and splenic arteries; however, hepatic arteries are not constricted and, instead, hepatic blood flow often increases (www.drugs.com). In the intestinal tract, AVP increases peristaltic activity, particularly of the large bowel; also causes an increase in GI sphincter pressure and a decrease in gastric secretion but has no effect on gastric acid concentration. Contraction of smooth muscle of the gallbladder and of the urinary bladder also occurs.

In summary, the vasoconstrictive effects of AVP are mediated by vascular V1 receptors that are directly coupled to phopholipase C, resulting in release of calcium. AVP stimulates antidiuresis via stimulation of V2 receptors, which are coupled to adenyl cyclase, which inserts aquaporin channels in the basolateral membrane of cells lining the collecting duct. AVP stimulates V3 receptors in the pituitary gland and stimulates the release of adrenocorticoptropic hormone via phosphatidylinositol/calcium signaling mechanism.

2.3.2 Pharmacodynamics

At nanomolar concentrations, exogenous AVP elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, AVP at these pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V1-receptors and release of prolactin and ACTH via V3

receptors. At thousand fold lower picomolar concentrations typical for the antidiuretic hormone, AVP inhibits water diuresis via renal V2 receptors.

In patients with vasodilatory shock, AVP in therapeutic (nanomolar) doses increases systemic vascular resistance and MAP and reduces the dose requirements for NE and other catecholamines. AVP tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous AVP. Onset of the pressor effect of AVP is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of AVP in patients.

2.3.3 Pharmacokinetics

At infusion rates used in vasodilatory shock patients (0.01-0.1 units/minute) the clearance of AVP is 9 to 25 mL/min/kg. The apparent $t^{1/2}$ of AVP at these levels is 10 minutes. AVP is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of AVP is primarily by liver and kidney. Serine protease, carboxypeptidase and disulfide oxido-reductase cleave AVP at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites retain no important pharmacological activity.

Indomethacin more than doubles the time to offset for AVP's effect on peripheral vascular resistance and cardiac output in healthy subjects. The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of AVP by 20% in healthy subjects. Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when coadministered with exogenous AVP in healthy subjects Other specific drug interactions extracted from www.drugs.com.

Table 2.3.3: Interaction with AVP	
Alcohol	May block the antidiuretic activity in varying degrees
Antidepressants, tricyclic	May potentiate the antidiuretic response
Carbamazepine	May potentiate the antidiuretic response
Chlorpropamide	May potentiate the antidiuretic response
Clofibrate	May potentiate the antidiuretic response
Demeclocycline	May block the antidiuretic activity
Epinephrine	May block the antidiuretic activity
Fludrocortisone	May potentiate the antidiuretic response
Heparin	May block the antidiuretic activity
Lithium	May block the antidiuretic activity
NE	May block the antidiuretic activity
Ganglionic blocking agents	May produce a marked increase in sensitivity to the pressor effects
Phenformin	May potentiate the antidiuretic response
Urea	May potentiate the antidiuretic response

Halothane, morphine, fentanyl, alfentanyl and sufentanyl have no obvious effect.

3.0 PROPOSED USE OF AVP FOR TBI

3.1 Preclinical testing relevant to proposed TBI indication

In six different animal studies over a twenty-year period, we investigated basic mechanisms, side effects, as well as practical applications, of AVP in the microcirculation in normal and shock states [17-22]. Table 3.1 below contains brief outlines of the studies.

Table 3.1: Summary of Preclinical Testing

Ref	Question	Test System	Results / Findings
17	Does AVP modulate WBC-mediated inflammation relative to an equieffective dose of phenylephrine (PE)?	In anesthetized, mechanically ventilated rats (n=75); cremaster skeletal muscle microcirculation was observed with intravital fluorescent video microscopy. TNF-evoked rolling WBC, sticking WBC, and macromolecule permeability were measured. Series 1: either AVP (0.2 U/mL) or its vehicle was suffused for 10 min washed out for 30 min, then TNF (5 ng/mL) was suffused for 30 min. Series 2: identical to series 1, except AVP (0.2 U/mL) or an equleffective pressor dose of PE (0.04 mg/mL) was administered i.v. (4.5 mL/h) for 15 min before, during, and 45 min after TNF. Series 3, series 2, except venous hemorrhage to MAP=20 preceded i.v. AVP or PE. Series 4, series 3, except AVP antagonist (vaprisol, 1 mg/kg i.v.) or its vehicle was administered after hemorrhage. Series 5, inflammation evaluated either with a different suffusate, different antigen, or hemorrhage only (no antigen).	This is the first demonstration that, by a receptor-mediated mechanism in skeletal muscle, TNF-evoked WBC infiltration, activation and permeability changes that were attenuated by AVP, but not by PE. The magnitude of this novel anti-inflammatory effect depends on volume status, the type of resuscitation fluid, and is possibly specific to the antigenic stimulus. This suggests that, in addition to its role in fluid and electrolyte homeostasis, AVP may be a physiologic modulator of inflammation.
18	Does AVP maintain braln and muscle tissue O2 during CPP management after TBI relative to an equieffective dose of PE?	Anesthetized and mechanically ventilated swine (n=35) received blasts to the closed head and bilateral chests. To mimic prehospital care for the first 30-45 min postinjury, IV saline only was administered. To mimic hospital resuscitation for 45-120 min, SAP was maintained >100 mm Hg with unlimited saline plus 250 mg/kg mannitol for ICP>20 mm Hg. To mimic critical care for 120-500 min, saline was titrated to filling pressure >12 mm Hg plus glucose was infused to maintain normoglycemia, plus CPP was titrated to >70 mm Hg with either PE or AVP (randomized and blinded)	With either PE (0.5-5 μg/kg/min) or AVP (0.4-4 U/hr), hemodynamics were stablized after resuscitation from TBI+polytrauma. However, with PE vs AVP titrated to the same CPP, ICP was >10 mm Hg higher and brain PO2 was 6 mm Hg lower, whereas shoulder and hindlimb muscle O2 saturations were >10% higher (all $p < 0.05$). Thus, AVP was as effective as PE for maintaining CPP, but ICP and brain O2 were improved because blood flow was diverted to the brain from skeletal muscle.
19	Does AVP improve outcome after TBI and severe hemorrhagic	Anesthetized, mechanically ventilated swine (n=33) received TBI + hemorrhage. Series 1 (n = 19), blood was withdrawn until the EEG was isolelectric for 12 min. For the first 30 min, survivors (n=16) received a saline bolus only. From 30-90 min, either AVP or placebo	In series 1, with AVP (0.1 U/kg/hr) vs. placebo, fluid and transfusion requirements were reduced, ICP was improved, and intracranial compliance was improved (all $p < .01$). In series 2, with AVP (0.2 U/kg)

Table 3.1: Summary of Preclinical Testing			
Ref	**Question**	**Test System**	**Results / Findings**
	shock?	(randomized and blinded) plus blood plus saline was titrated to MAP≥60 mm Hg. After 90 min, 1 g/kg mannitol was given and additional saline was given to a target CPP ≥60 mm Hg. Series 2 (n = 14), the identical protocol was followed except the shock period was 20 min and survivors (n = 10) received a bolus of either AVP or placebo plus saline during first 30 min of resuscitation.	vs. placebo, CPP was more rapidly corrected and all survived 300 min vs 2/5 (all $p < .05$). Thus, AVP rapidly corrected CPP, improved cerebrovascular compliance, and prevented circulatory collapse during fluid resuscitation of hemorrhagic shock after TBI.
20	Does AVP improve outcome after severe chest trauma plus shock?	Series 1: anesthetized, mechanically-ventilated pigs (n = 20) received a blast to the chest, followed by a "controlled" arterial hemorrhage to MAP <30 mm Hg. At 20 min, a saline bolus was followed by either AVP (0.1 U/kg) or saline (randomized and blinded). From 30-300 min, either AVP (0.4U/kg/hr) or saline was infused as needed to MAP>70 mm Hg. Series 2: Swine (n = 15) received the chest injury followed by partial left hepatectomy to produce "uncontrolled" hemorrhage. Resuscitation was the same as series 1	In Series 1, there were 3/20 deaths before randomization, 0/8 deaths after resuscitation with AVP vs 4/9 deaths with saline ($p = 0.029$). In survivors, with AVP vs saline, fluid requirements and peak airway pressures were lower while P/F was higher (all $p < 0.05$). In Series 2, there were 5/15 deaths before randomization. With AVP vs saline resuscitation, survival time and blood loss were both improved, but the differences did not reach statistical significance. Thus, after severe chest trauma with controlled hemorrhage, early AVP decreased mortality, reduced fluid requirements and improved pulmonary function. With uncontrolled hemorrhage, early AVP did not increase bleeding risk.
21	What is the optimal fluid resuscitation strategy after TBI and severe hemorrhagic shock?	Anesthetized, ventilated swine (n = 39) received TBI followed by hemorrhage to MAP < 30mmHg, then received one of five fluid combinations (randomized and blinded) to maintain MAP > 60mmHg for 30 to 60min, then CPP > 60mmHg for 60 to 300min: either unlimited saline only (n = 9), saline plus AVP (0.1 U/kg bolus followed by 0.4 U/ml infusion, n = 9), saline plus PE (0.05mg/kg bolus followed by 1 mg/ml infusion, n = 9), AVP only (n = 5), or PE only (n = 5). Transfusions were administered if hematocrit fell < 13, and mannitol was administered if ICP increased > 20 mmHg.	Upon resuscitation, MAP and CPP goals were achieved with all five solutions. With saline only, more blood and mannitol were required, ICP and peak inspiratory pressure were higher, and cerebrovascular reactivity was decreased (all $p < 0.05$). With saline plus either AVP or PE, cardiac output, heart rate, lactate, and SvO2 were similar to saline only, but total fluid requirements and urine output were both reduced ($p < 0.05$). With either AVP or PE only, ICP remained low, but SvO2, cardiac output, and urine output were decreased (all $p < 0.05$). Thus, to correct vasodilatory shock after TBI, either PE or AVP plus low volume saline was superior to either unlimited saline alone or pressor alone.

Table 3.1: Summary of Preclinical Testing			
Ref	**Question**	**Test System**	**Results / Findings**
22	Is atrial natriuretic factor (ANF) an equieffective antagonist for the constrictor actions of AVP, NE or angiotensin (ANG)?	The microcirculation of the jejunum (n=32) or the spinotrapezius muscle (n=18) of anesthetized rats was prepared for direct observation of blood flow using intravital video microscopy. ANF was either added to suffusate solutions (30 nM) or infused iv (0.1 nanomol/min/100 g). Either ANG, NE or AVP was added to the suffusates in the presence or absence of a cyclooxygenase inhibitor (COI) to reduce vasoactive prostaglandins. Series 1 (intestine): ANG (500 nM) caused 40 ± 2% vasoconstriction but only 23 ± 6% during ANF. ANG (162 nM)+COI caused 19 ± 4% vasoconstriction but only 8 ± 5% with COI +ANF. In contrast, NE (2-5 μM) caused vasoconstriction that was not altered by ANF, alone or in combination with COI. Series 2 (muscle): ANG (1-2 nM) plus COI caused 40-60% vasoconstriction but only 20-30% during ANF. In contrast, vasoconstriction evoked by AVP (0.5-1.0 nM) or by NE (40-230 nM) was not altered by ANF.	1) supraphysiologic concentrations of ANF produced no direct vasodilation in the intestine or muscle; 2) in skeletal muscle, AVP is 2x more potent as a vasoconstrictor than ANG and 40-200x more potent than NE; 3) ANF modulates the vasoconstriction caused by ANG by mechanism that did not involve prostaglandins; and 4) ANF is not a physiologic regulator of the vasoconstriction caused by NE or AVP.

3.2 Analysis of Preclinical Studies

In general, Table 3.1 demonstrates that the combination of AVP plus low volume fluid resuscitation is safe and more effective than other fluid combinations (at least in controlled laboratory conditions). In particular, in one clinically relevant model that combined TBI and polytrauma, we observed that both cerebral oxygenation and ICP were improved with AVP, relative to phenylephrine (PE), at doses titrated to the same CPP [18]. We also demonstrated that, unlike PE, AVP can attenuate TNF-evoked leukocyte infiltration, activation or permeability changes in the microcirculation by a mechanism that is probably receptor mediated and does not entirely depend on sheer stress in venules or Starling forces in capillaries (17). The magnitude of this anti-inflammatory effect is influenced by several conditions, including volume status, type of resuscitation fluid, and nature of the antigenic stimulus (17).

3.3 Clinical testing relevant to proposed TBI indication

Soon after the completion of preclinical studies, we began transitioning from bench to bedside. The current dogma is that pressors are absolutely contraindicated in hypotensive trauma patients. To challenge that idea, we retrospectively reviewed 225 patients, and showed that vasopressors, combined with low volume resuscitation, were an effective salvage therapy during emergency surgery for life-threatening bleeding [23]. These and other results were presented at an international conference on novel actions and future applications of AVP [24].

In 2008, we designed a prospective, open-label, randomized, non-inferiority clinical trial to compare AVP to catecholamines in patients who required CPP therapy. The study was funded by the Office of Naval Research, registered at Clinicaltrials.gov [identifier NCT00795366] and was approved by local institutional review boards with informed consent. Preliminary results are published [25] and two others on related topics have followed [26, 27].

From 2008-2013, >300 TBI patients admitted to the ICU were screened. Minors, pregnant women, incarcerated individuals were excluded. After insertion of ICP monitor, informed consent was obtained from the patient's healthcare proxy. Patients were then randomized to either standard of care catecholamines or AVP, but only received vasopressors for CPP management if medically indicated.

The target values were CPP > 60 and ICP < 20 mm Hg. If CPP>60 mm Hg, then no vasopressors were required. If CPP < 60, ICP < 20, and SBP <90 mm Hg, respectively, then resuscitation was performed with fluid and blood products. If the patient was fully resuscitated [base deficit (BD) >-3 mEq/L, hematocrit (Hct) >30, urine output (UOP)>0.5 ml/kg/hr], but with CPP < 60 and/or ICP < 20 mm Hg, then vasopressors were initiated to raise CPP > 60. The amount and type of pressor to maintain CPP was at the discretion of the clinical team. Because patient safety was a primary concern of this study, this was an open-label trial; if the attending physician at any time deemed that any pressor was ineffective, he was allowed to switch.

According to survivingsepsis.org/guidelines, AVP (1.8 U/hr) can be added to NE with intent of either raising MAP or decreasing NE dosage. Low dose AVP is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension. AVP doses higher than 1.8-2.4 U/hr should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).

In our study, the starting AVP dose was 1.2 U/hr and was incrementally increased to a maximum of 4 U/hr. If CPP could not be maintained >60 mm Hg with the maximum dose, then AVP was decreased to 2.4 U/hr and catecholamines were added or AVP was abandoned altogether [25]. The dose range for catecholamine vasopressors is presented in Table 3.3A below.

Table 3.3A	**Starting Dose**	**Titration parameter**	**Maximum dose**
NE	5 mcg/min	2.5 mcg/min every 5 min	100 mcg/mln
PE	50 mcg/min	25 mcg/mln every 15 min	350 mcg/min
Dopamine	5 mcg/kg/min	2.5 mcg/kg/min every 5 min	20 mcg/kg/min

Patients with isolated TBI were first stabilized in the trauma resuscitation area, then admitted to neurosurgery and transferred to the neurosurgery ICU, which is staffed by neuro-intensivists. These patients were co-managed by neurosurgeons and neuro-intensivists. Patients with TBI + polytrauma were also stabilized in the resuscitation area, but were admitted to trauma surgery and transferred to the trauma ICU, which is staffed by trauma surgeons who are board-certified in critical care medicine. These

patients are co-managed by neurosurgeons, trauma surgeons, and trauma ICU team. In both circumstances, residents and attending physicians were involved in daily care. Neurosurgeons make decisions on when/what kind of osmolar and/or vasopressor therapies are used [25].

Table 3.3B shows demographics and intent-to-treat information. The study was a parallel group design with subject-level randomization occurring with a 1:1 block of 8 allocation ratio [25].

Table 3.3B intention to treat:	CATECHOLAMINE (n=54)	AVP (n=42)	p=
Age, yrs	38±18	40±16	0.619
Male gender, %	81%	81%	0.947
Blunt mechanism, %	96%	93%	0.651
Cranlotomy, %	28%	31%	0.734
Polytrauma, %	72%	88%	0.066
ISS	26±11	27±12	0.803
Time to pressor start, hrs	56 (150)	16 (59)	0.158
Admission Values			
HR, bpm	95±26	98±26	0.645
SBP, mm Hg	137±35	150±36	0.097
GCS≤8	**87%**	**71%**	**0.031**
Intubated at arrival, %	98%	90%	0.159
First Day of ICU			
HR, bpm	74±16	76±19	0.688
SBP, mm Hg	102 (20)	101 (21)	0.734
MAP, mm Hg	74±12	74±15	0.985
ICP Min, mm Hg	6 (9)	8 (7)	0.102
ICP Max, mm Hg	**19 (9)**	**23 (13)**	**0.049**
ICP >20, hrs	0 (2)	1 (4)	0.093
CPP min, mm Hg	64 (14)	58 (16)	0.089
CPP max, mm Hg	93±15	95±14	0.530
CPP <60, hrs	0 (1)	0 (2)	0.222

The next Table, Table 3.3C shows the corresponding data "as treated".

Table 3.3C as treated:	None (n=60)	CATECHOLAMINE (n=23)	AVP (n=12)	p=
Age, yrs	38±16	38±18	45±18	0.408
Male gender, %	82%	74%	92%	0.436
Blunt mechanism, %	97%	96%	92%	0.733
Craniotomy, %	32%	22%	25%	0.643
Polytrauma, %	75%	83%	92%	0.408
ISS	24±10	29±13	33±12	**0.014**
Time to pressor start, hrs	-----	56 (113)	14 (36)	0.113
Admission Values				
HR, bpm	94±22	101±31	98±27	0.455
SBP, mm Hg	146±38	127±26	150±33	0.073
GCS≤8	77%	96%	67%	0.064
Intubated at arrival, %	96%	96%	83%	0.188
First day of ICU				
HR, bpm	75±18	75±18	71±18	0.756

Table 3.3C as treated:	None (n=60)	CATECHOLAMINE (n=23)	AVP (n=12)	p=
SBP, mm Hg	107 (22)	97 (10)	97 (40)	**0.007**
MAP, mm Hg	77±13	72±10	65±17	**0.008**
ICP Min, mm Hg	8 (8)	6 (9)	9 (12)	0.258
ICP Max, mm Hg	19 (9)	22 (18)	27 (25)	0.124
ICP >20, hrs	0 (1)	2 (3)	4 (8)	**0.023**
CPP min, mm Hg	64 (14)	60 (13)	53 (22)	**0.005**
CPP max, mm Hg	95±14	89±13	95±18	0.156
CPP <60, hrs	0 (1)	1 (5)	1 (2)	**0.030**

The next Table, Table 3.3D shows the first day of ICU "as treated".

Table 3.3D as treated	None (n=60)	CATECHOLAMINE (n=23)	AVP (n=12)	p=
Mannitol, gm	0 (43)	0 (220)	313 (496)	**0.004**
Mannitol, %	33%	43%	75%	**0.027**
PRBC, mL	0 (0)	0 (0)	500 (1249)	**0.006**
PRBC, %	18%	13%	58%	**0.005**
IVF, mL	2125 (1795)	3388 (3749)	4472 (1504)	0.007
UOP, mL	2405 (1545)	3675 (2833)	2696 (3981)	**0.059**
CSF, mL	0 (0)	0 (16)	14 (68)	0.079
Head JP, mL	0 (68)	0 (60)	0 (0)	0.362

Power analysis estimated a sample size of 110-190 patients in the standard of care and test groups. Primary endpoints were adverse events, specifically ICP > 20 mm Hg, tachycardia/arrhythmias, acute kidney injury (2x increase from baseline creatinine), acute respiratory distress syndrome [acute onset, PaO2:FiO2 ratio < 200, bilateral pulmonary infiltrates, and pulmonary artery occlusion pressure ≤ 18 mm Hg or no evidence of left heart failure], and peripheral ischemia/gangrene. Secondary endpoints were duration of CPP management, duration of vasopressors, and length of stay (LOS). Data were collected for five days after placement of the ICP monitoring device [or death] [25].

Each death and adverse event was reviewed by the IRB and by an independent data safety monitoring board as either:

- Definitely Related - Certainty that event is related to the study procedures;
- Probably Related - High likelihood that event is related to the study procedures;
- Possibly Related - Study procedures could be the cause, but other causes cannot be ruled out,
- Unlikely to be Related - Not likely related to study procedures, and other causes are more likely,
- Unrelated - Evidence exists that event is related to something other than the study procedures.

Data were analyzed using PASW Statistics Ver. 18.0 [IBM Corporation, Armonk, NY]. Data were reported as mean ± standard deviation or median [interquartile range], as appropriate and analyzed with both intention to treat [ITT] and as treated analysis methods. ITT analysis included student T-test for parametric data, Mann-Whitney U test

for nonparametric data. Per protocol analysis will involve ANOVA with post-hoc Bonferroni correction for parametric data and Kruskal-Wallis test for nonparametric data. Categorical data are compared with Pearson Chi-square; if cell counts were <5 Fisher's Exact Test is used. Paired data are compared with paired samples t-test or Wilcoxon signed rank test. Because some patients did not receive vasopressors, as treated analysis resulted in 4 groups: single catecholamine (standard of care), AVP, combination of multiple catecholamines ± AVP, and no vasopressors. Significance is assessed at $p<0.05$.

At the interim safety analysis, shown in Table 3.3E (intention to treat), and Table 3.3F (as treated), preliminary results from 96 consented patients suggest that AVP is a safe alternative to catecholamines for the management of CPP after TBI and support the continued use of AVP when vasopressors are required for CPP management in TBI patients [25]. Enrollment ended in 2013. At that time, it was determined, based on enrollment history, that the study could not be completed in a reasonable amount of time. The decision was made to end the study and present the data as preliminary evidence to support an indication change to the FDA.

Table 3.3E intention to treat	CATECHOLAMINE (n=54)	AVP (n=42)	p=
Pressor duration, hrs	55 (141)	52 (157)	0.908
ICP monitoring, hrs	190 (248)	196 (196)	0.695
Sinus tach, hrs/day	7.3±5.9	7.7±6.1	0.745
CPP min, mm Hg	65 (9)	65 (10)	0.642
Time CPP<60, hrs	1 (1)	1 (1)	0.365
ICP Max, mm Hg	20 (10)	22 (6)	0.091
Time ICP>20, hrs	0.9 (2.6)	1.7 (1.8)	0.095
ICU days	22 (17)	20 (23)	0.747
LOS, days	38 (33)	40 (80)	0.230
Mortality, %	12%	15%	0.641

Table 3.3F As treated	None (n=60)	CATECHOLAMINE (n=23)	AVP (n=12)	p=
Pressor duration, hrs	-----	58 (115)	52 (155)	0.451
ICP monitoring, hrs	184 (226)	279 (234)	166 (127)	0.062
Sinus tach, hrs/day	5.8 (9.3)	7.4 (8.1)	5.3 (9.0)	0.321
AKI: overall, %	5%	17%	23%	0.056
AKI: study period %	2%	13%	23%	0.009
AKI: during pressor, %	----	13%	23%	0.391
ARDS: overall, %	62%	57%	69%	0.832
ARDS: study period, %	52%	52%	46%	0.992
ARDS: during pressor, %	----	48%	39%	0.728
Peripheral necrosis	0%	0%	0%	1.0
CPP min, mm Hg	67 (8)	62 (9)	65 (9)	**0.037**
Time CPP<60, hrs	0.4 (1.0)	0.7 (1.9)	0.9 (1.7)	0.052

ICP Max, mm Hg	19 (9)	21 (6)	25 (6)	**0.030**
Time ICP>20, hrs	0.9 (2.3)	1.4 (2.7)	2.0 (5.5)	0.090
Refractory to pressors, %	----	22%	8%	0.640
ICU days	20 (17)	25 (28)	19 (15)	0.242
LOS, days	37 (31)	52 (70)	25 (50)	0.281

There were 3/60 deaths in the no pressor group, 4/23 in the catecholamine group, and 5/14 in the AVP group, which translates to mortality rates of 5%, 18% and 42% respectively. Each of the deaths was reviewed by the data safety monitoring board and was related to the injury severity, rather than to the study compound. Due to the small sample sizes, there was no difference between the two pressor groups, but the mortality rate in the no pressor group was significantly less (p=0.002) than the mortality rate in the two pressor groups combined (24%, 9/37).

In the entire study population, the median midline shift on initial head CT was 0 mm but some patients had intracranial hemorrhages that shifted the midline as much as 60 mm obliterating the ventricles. Our trauma center is especially aggressive with early treatment for intracranial hematoma with decompressive craniectomy. This surgical procedure is controversial depending on the timing after injury. In most centers, decompressive craniectomy is a last ditch salvage maneuver for refractory intracranial hypertension after failure of medical therapy. It is also a standard of care for early evacuation of large intracranial hemorrhages. There is broad consensus that craniectomy reduces ICP. The value is controversial because evidence suggests that neither mortality nor Glasgow Outcome Score Extended (GOSE) is improved, and risks of infection and lifetime disability are higher.

In the last 5 years at our center, 41% (116/286) received decompressive craniectomy at a median[IQR] of 6[8] hrs after admission and 92% of those patients received the ICP monitor at the time of craniectomy. Afterward, only 25% (29/116) of the patients who received this surgery required pressors to maintain CPP>60 even though the midline shift was 7±5 mm. For comparison, there was 30% (50/168) pressor use in the group with no surgery and a median[IQR] midline shift of 0[2].

Decompressive craniectomy confounded interpretation of the AVP-TBI study [25] because it was performed in 25% of the patients in AVP group (3/12), and about 1.5x more often in all the other groups (42% of those in the no pressor (87/205), 37% (14/38) catecholamine, or 39% (12/31) in the multiple pressor groups). This is an issue because removing the bone flap and evacuating the hematoma could have a bigger effect on ICP and CPP than any pressor agent. It was not clear if this was a cause or an effect, but this could definitely confound interpretation of the results.

To investigate this issue further, we retrospectively reviewed 227 (consented and non-consented) patients with IRB approval [26]. Our results were consistent with previous studies that urgent evacuation of intracranial hemorrhage with decompressive craniectomy reduced ICP and makes it easier to achieve CPP targets in severe TBI

patients. However, decompressive craniectomy had no effect on mortality or functional recovery, as indicated by GOSE, in patients matched with propensity scores [26]. Thus, in context, the data are consistent with the idea that AVP reduced the need for craniectomy.

Another major concern is a theoretical, and potentially serious, adverse effect related to the biological properties of AVP [27]. By a V1a mediated mechanism, in rodent models, AVP can promote disruption of the blood-brain barrier, increase inflammatory mediator production, exacerbate edema, and augment the loss of neural tissue [28-31]. Also, the antidiuretic action of AVP is attributed to water resorption by the renal tubules and is mediated by V2 receptors, and this may lead to hyponatremia. In humans, hyponatremia after TBI is associated with significant morbidity and mortality [32] and an AVP antagonist reverses these changes [33, 34]. To address this issue, we retrospectively reviewed 286 consecutive patients [27] who had ICP monitors. Cerebral edema was assessed by computed tomography using the gray white ratio, where a low ratio indicates the presence of cerebral edema [27].

The data showed that 205 patients required no vasopressors to maintain CPP> 60 mmHg, 41 received a single catecholamine, 12 received AVP, and 28 required both catecholamines and AVP. Those who required no pressors were generally less injured, required less osmolar therapy, less total fluid, had lower plasma sodium, lower ICP, less cerebral edema, and lower mortality [all $p<0.05$]. Cerebral edema, daily sodium levels, and mortality were similar in those who required AVP or catecholamine pressors, but the daily requirement of mannitol and hypertonic saline were reduced by 45% and 35%, respectively by AVP [both $p<0.05$]. Of course absence of proof is not proof of absence, but this is the first radiographic and clinical evidence to suggest that exogenous AVP does not promote cerebral edema. In fact, the data showed decreased use of osmotherapy relative to catecholamine in severe TBI patients [27].

4.0 APPROACHES FOR PROPOSED LABELING

Based on the well-understood pharmacological attributes, the established (>50 year) safety profile of AVP, and the preclinical and clinical trial data presented in section 3.1 - 3.3 above, the purpose of this pre-IND is to seek guidance from the agency in the following areas:

1) Sufficiency of current data to support expanded indication in the treatment of TBI.
2) Sufficiency of current data to support expanded indication in the treatment of TBI for a very narrow population, i.e. use of AVP in TBI for military use only.
3) The appropriate pathways and data sets required to secure an expanded indication for AVP specifically in the management of ICP in acute/sub-acute TBI, given that the sponsor is neither a manufacturer, nor a holder of an existing ANDA for AVP.

5.0 LIST OF QUESTIONS FOR THE AGENCY

5.1 Does the agency concur that the >50 year safety profile of AVP, the preclinical and clinical data specifically in TBI are sufficient to support an expanded indication in the treatment of TBI?

Sponsor Position:

While we recognize that the data is limited to establish efficacy, the completed preclinical and clinical studies provide sufficient safety data concerning the use of AVP in TBI. To this end, although the only clinical study is a single center investigation, it was conducted in a prospective, controlled manner with limited potential for bias. Additionally, the dose ranges used were within the current use profile with no adverse events that could be attributed to the use of AVP or the dosage of AVP. Further, the alternative to not using AVP is the current standard of care – continued use of catecholamines, which are not beneficial and may be contraindicated in some cases. Therefore, we believe there is sufficient evidence to suggest AVP is safe for use in TBI patients refractory to catecholamines.

5.2 Does the agency concur with the sponsor that the >50 year safety profile of AVP, the preclinical and clinical data specifically in TBI are sufficient to support an expanded indication in the treatment of TBI for military personnel?

Sponsor Position:

The investigational or off-label use of AVP creates an added layer of complexity in an austere medical practice associated with military personnel. However, with reduced payer/reimbursement concerns, the use of AVP, even as salvage therapy may be of value in this population where severe TBI has a greater prevalence.

5.3 Given that the sponsor is neither a manufacturer, nor a holder of an existing ANDA for AVP, what appropriate pathways and data sets are required to secure an expanded indication for AVP? specifically in the management of ICP in acute/sub-acute TBI?

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Assoc for Surgery of Trauma Annual Scientific Assembly at San Antonio, Texas Jan 12-16, 2016

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Appendix 2

Response from FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 128596

**MEETING REQUEST-
WRITTEN RESPONSES**

University of Miami
Miller School of Medicine
Attention: Kenneth Proctor, PhD
Professor of Surgery
1600 NW 10th Ave #1140
Miami, FL 33136

Dear Dr. Proctor:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Arginine Vasopressin.

We also refer to your submission dated October 30, 2015, containing a pre-IND/Type C meeting request.

Further reference is made to our Meeting Granted letter dated December 2, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 30, 2015 background package.

If you have any questions, email Vandna, Regulatory Project Manager at Vandna.Kishore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Pre-IND

Application Number: 128596
Product Name: Arginine Vasopressin (AVP)
Indication: Traumatic Brain Injury (TBI)
Sponsor/Applicant Name: Kenneth Proctor, MD

1.0 BACKGROUND

Proposed Study Name:	Use of Arginine Vasopressin (AVP) for patients with traumatic brain injury
Product name:	Vasopressin Injection, USP
Proposed Indication(s):	Traumatic brain injury (TBI).
The type of meeting being requested:	Pre-IND Type B
A brief statement of the purpose of the meeting:	The purpose of the meeting is to review the existing preclinical and clinical data to date, consider the established (>50 year) safety profile of AVP and seek guidance on the sufficiency of current data to support the expanded indication in the management of TBI.

2.0 QUESTIONS AND RESPONSES

Question 1: Does the agency concur that the >50 year safety profile of AVP, the preclinical and clinical data specifically in TBI are sufficient to support an expanded indication in the treatment of TBI?

FDA Response to Question 1:

This question is premature. Please see response to Question 3.

Question 2: Does the agency concur with the sponsor that the >50 year safety profile of AVP, the preclinical and clinical data specifically in TBI are sufficient to support an expanded indication in the treatment of TBI for military personnel?

FDA Response to Question 2:

This question is premature. Please see response to Question 3.

Question 3: Given that the sponsor is neither a manufacturer, nor a holder of an existing ANDA for AVP, what appropriate pathways and data sets are required to secure an expanded indication for AVP specifically in the management of ICP in acute/sub-acute TBI?

FDA Response to Question 3:

There is no independent pathway for an individual to effect changes (e.g., add a new indication) to labeling of a product that he/she does not own. However, an individual may contact the product owner or manufacturer to investigate their interest in a proposal to expand the product's approved indications.

We recommend that you seek input from CDER's small business and industry assistance program (SBIA) or obtain regulatory counsel to seek guidance.

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/s/

ERIC P BASTINGS
01/22/2016

Appendix 3

Reference 1

Vasopressin for cerebral perfusion pressure management in patients with severe traumatic brain injury: preliminary results of a randomized controlled trial.

WTA-2013-044(R1)

VASOPRESSIN FOR CEREBRAL PERFUSION PRESSURE MANAGEMENT IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY: PRELIMINARY RESULTS OF A RANDOMIZED CONTROLLED TRIAL

Robert M. Van Haren MD, Chad M. Thorson MD MSPH, Michael P. Ogilvie MD MBA, Evan J. Valle MD, Gerardo A. Guarch MD, Jassin A. Jouria MD, Alexander M. Busko BS, Leo T. Harris PA, M. Ross Bullock[1] MD PhD, Jonathan R. Jagid[1] MD, Alan S. Livingstone MD FACS, and Kenneth G. Proctor PhD

Dewitt-Daughtry Family Department of Surgery and Department of Neurosurgery[1], University of Miami Miller School of Medicine, Ryder Trauma Center

Presented at 43rd Annual Western Trauma Association Meeting, March 3-8, 2013. Aspen, CO.

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We have no conflicts of interest to declare.

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SHORT TITLE: Vasopressin for Traumatic Brain Injury

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LEVEL of evidence: Level II, therapeutic

KEYWORDS: traumatic brain injury, cerebral perfusion pressure, vasopressors, catecholamines

ABSTRACT

Background: After traumatic brain injury (TBI), catecholamines (CA) may be needed to maintain adequate cerebral perfusion pressure (CPP), but there are no recommended alternative vasopressor therapies. This is an interim report of the first study to test the hypothesis that arginine vasopressin (AVP) is a safe and effective alternative to CAs for the management of CPP in patients with severe TBI.

Methods: Since 2008, all TBI patients requiring intracranial pressure (ICP) monitoring at this level 1 trauma center have been consented and randomized to receive either CA or AVP if vasopressors were required to maintain CPP > 60 mm Hg.

Results: To date, 96 patients have been randomized and analyzed with similar demographics, vital signs, and lab values. As treated, 60 required no vasopressors and were the least severely injured group with the best outcomes. 23 patients received CA (70% levophed, 22% dopamine, 9% phenylephrine), 12 patients received AVP. The two vasopressor groups had similar demographics, but ISS and fluid requirements on ICU Day 1 were worse in AVP vs. CA (all $p<0.05$) prior to treatment. These differences indicate more severe injury with accompanying hemodynamic instability. Nevertheless, adverse events were not increased with AVP vs. CA. Trends favored AVP vs. CA, but no apparent differences were statistically significant at this interim point. There was no difference in mortality rates between CA and AVP.

Conclusions: These preliminary results suggest that AVP is a safe and effective alternative to CA for the management of CPP after TBI and support the continued investigation and use of AVP when vasopressors are required for CPP management in TBI patients.

BACKGROUND

Each year 1.7 million Americans suffer traumatic brain injury (TBI)[1]. After TBI, cerebral ischemia is the most important secondary event that determines outcomes[2]; a single episode of hypotension doubles mortality rate[3]. TBI disrupts cerebral autoregulation and blood flow is thought to be directly proportional to cerebral perfusion pressure (CPP). To minimize episodes of ischemia, standard treatment guidelines are aimed at maintaining a minimum CPP.

The management of CPP generally includes reducing intracranial pressure (ICP) and maintaining mean arterial pressure (MAP). There is no Level 1 evidence for the ideal target CPP, however a CPP value between 50 and 70 mm Hg is recommended[4]. Fluid resuscitation can be used to increase MAP and CPP, but when this fails vasopressors are needed. Catecholamines (CA) are the current standard of care [5-9], however refractoriness[10] and side effects such as arrhythmias and peripheral ischemic complications can develop[11]. Unfortunately, there are limited alternatives.

Arginine vasopressin (AVP) is the anti-diuretic hormone and is produced in the posterior pituitary. Pitressin (Vasopressin Injection, USP) is a sterile, aqueous solution of synthetic vasopressin (8-Arginine vasopressin). The antidiuretic action of AVP is ascribed to increasing reabsorption of water by the renal tubules and is mediated by V2 vasopressinergic receptors. AVP can also cause V1 receptor mediated contraction of smooth muscle of the gastrointestinal tract and of all parts of the vascular bed, especially the small arterioles and venules, with less effect on the smooth musculature of the large veins. Pitressin is FDA approved for the prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus. However, AVP is most often used off-label

for its vasoconstrictor properties[12] as an alternative to CA for the treatment of septic shock and during cardiopulmonary resuscitation[13-17]. In five previous studies, we demonstrated that vasopressors, specifically AVP, in combination with low volume fluid resuscitation were safe and more effective for traumatic shock resuscitation than either vasopressors alone or fluid resuscitation alone[18-22]. Furthermore, in one clinically relevant model that combined blunt polytrauma to the head and chest, we showed that AVP was as safe and effective as phenylephrine for maintaining CPP, but improved both ICP and cerebral tissue oxygenation[22]. This present study was designed to translate those findings from benchtop to bedside. This is an interim report of the first study to test the hypothesis that AVP is a safe and effective alternative to CA for the management of CPP in patients with severe TBI.

METHODS

This study is a single institution, prospective, open-label, randomized, controlled non-inferiority clinical trial conducted at the Ryder Trauma Center (University of Miami / Jackson Memorial Hospital). The study was registered at Clinicaltrials.gov (identifier NCT00795366) and was approved by local institutional review boards with informed consent.

Since September 2008, patients with TBI admitted to the ICU with an ICP monitoring device (i.e. ventriculostomy) were screened. Minors, pregnant women, incarcerated individuals were excluded. After insertion of ICP monitor, informed consent was obtained from the patient's healthcare proxy. Patients were then randomized to either CAs (standard of care) or AVP (experimental group) for CPP management, but only receive vasopressors if medically indicated.

The study was a parallel group design with subject-level randomization occurring with a 1:1 block of 8 allocation ratio.

At our institution, patients with isolated TBI are first stabilized in the trauma resuscitation area, then admitted to neurosurgery and transferred to the NICU (neurosurgery intensive care unit), which is staffed by neuro-intensivists. These patients are co-managed by neurosurgeons and neuro-intensivists. Patients with TBI + polytrauma are also stabilized in the resuscitation area, but are admitted to trauma surgery and transferred to the TICU (trauma intensive care unit). The TICU is staffed by trauma surgeons who are board-certified (or board-eligible) in critical care medicine. These patients are co-managed by neurosurgeons, trauma surgeons, and trauma ICU team. In both circumstances, residents and attending physicians are involved in daily care. Neurosurgeons make decisions on when/what kind of hyperosmolar and/or vasopressor therapies are used.

Treatment protocols were established with target values of CPP > 60 and ICP < 20 mm Hg. If CPP>60 mm Hg, then no vasopressors were required. If CPP < 60, ICP < 20, and SBP <90 mm Hg, respectively, then resuscitation was performed with fluid and blood products. If the patient was fully resuscitated (base deficit >-3 mEq/L, hematocrit >30, urine output >0.5 ml/kg/hr), but with CPP < 60 and/or ICP < 20 mm Hg, then vasopressors were initiated to raise CPP > 60 and SBP > 90 mm Hg. The amount and type of CA to maintain CPP is at the discretion of the clinical team. Because patient safety was a primary concern of this study, this was an open-label trial; if the neurosurgeon at any time deemed that any pressor was ineffective, he was allowed to switch. The starting AVP dose was 1.2 U/hr and was incrementally increased to a maximum of

4 U/hr. If CPP could not be maintained >60 mm Hg with the maximum dose, then AVP was decreased to 2.4 U/hr and CA were added or AVP was abandoned altogether.

This study was designed as a noninferiority clinical trial; power analysis estimated a sample size of 110-190 patients Primary endpoints were adverse events, specifically intracranial hypertension (ICP > 20 mm Hg), tachycardia/arrhythmias, acute kidney injury (2x increase from baseline creatinine), acute respiratory distress syndrome (acute onset, PaO_2:FiO_2 ratio < 200, bilateral pulmonary infiltrates, and pulmonary artery occlusion pressure ≤ 18 mm Hg or no evidence of left heart failure), and peripheral ischemia/gangrene. Secondary endpoints were duration of CPP management, duration of vasopressors, and length of stay (LOS). Additional data were collected daily on vital signs: Glascow coma scale (GCS), systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, heart rate (HR), temperature, CPP, and ICP; fluids intake/outtake; and medications administered (specifically vasopressors, sedatives, and pain medications). Patients who were switched from CA to AVP or AVP to CA were defined as "refractory" to that agent. Demographic data and admission laboratory data were also collected. Data were collected daily from admission until the removal of intracranial monitoring device (or death).

Each death was reviewed by the IRB and by an independent data safety monitoring board as either:

Definitely Related - Certainty that event is related to the study procedures;

Probably Related - High likelihood that event is related to the study procedures;

Possibly Related - Study procedures could be the cause of the event, but other causes cannot be ruled out,

Unlikely to be Related - Not likely that event is related to study procedures, and other more likely causes are present,

Unrelated - Evidence exists that event is related to something other than the study procedures.

Data were analyzed using PASW Statistics Ver. 18.0 (IBM Corporation, Armonk, NY). Data are reported as mean±standard deviation or median (interquartile range), as appropriate. Data were analyzed with both intention to treat (ITT) and as treated analysis methods. ITT analysis included student T-test for parametric data, Mann-Whitney U test for nonparametric data, and Per protocol analysis involved ANOVA with post-hoc Bonferroni correction for parametric data and Kruskal-Wallis test for nonparametric data. Categorical data were compared with Pearson Chi-square; if cell counts were <5 Fisher's Exact Test was used. Paired data was compared with paired samples t-test or Wilcoxon signed rank test. Because some patients did not receive vasopressors, as treated analysis resulted in 3 groups: CA, AVP, and no vasopressors. Significance was assessed at $p<0.05$.

RESULTS

A total of 301 patients with TBI and an ICP monitoring device were screened during the study period. The overall patient population and enrollment is shown in the CONSORT diagram (Figure 1).

There were 54 patients randomized to CA and 42 patients randomized to receive AVP. These groups were similar in terms of age, gender, mechanism of injury, admission vital signs, and vital signs on first day of ICU (Table 1). Patients who were randomized to AVP were less likely to have GCS≤8 on admission (71 % vs. 87%, p=0.031), but had higher ICP maximum on first day of ICU (23 vs. 19 mm Hg, p=0.049).

As treated, 23 patients received CA, 12 patients received AVP, but the majority of patients (n=60, 63%) did not receive either vasopressor. The most common CA administered was levophed (70%), followed by dopamine (22%) and phenylephrine (9%). These CA, AVP, and no vasopressor groups were similar in terms of age, gender, and mechanism of injury (Table 2). However, the AVP group had a higher ISS (AVP: 33±12 vs. CA: 29±13 vs. None: 24±10, p=0.014). On admission, and prior to treatment, vital signs were similar; there was a tendency for fewer in the AVP group to have GCS≤8 on admission (AVP: 67% vs. CA: 96% vs. None: 77%), but this apparent difference was not statistically significant (p=0.064). On the first day of ICU, also prior to treatment patients who eventually required vasopressors (CA or AVP) had significantly lower SBP (AVP: 97[40] vs. CA: 97[10] vs. None: 107[22] mm Hg, p=0.007) and minimum CPP (AVP: 53[22] vs. CA: 60[13] vs. None: 64[14] mm Hg, p=0.005). Patients who received AVP had significantly lower MAP (AVP: 65±17 vs. CA: 72±10 vs. None: 77±13 mm Hg, p=0.008) and increased time ICP>20 (AVP: 0[1] vs. CA: 2[3] vs. None: 4[8] mm Hg, p=0.023). Patients who received CA had increased time CPP<60 mm Hg (AVP: 1 [2] vs. CA: 1[5] vs. None: 0[1] hrs, p=0.030).

There were also significant differences in requirements for hyperosmolar therapy and fluid between the groups on the first ICU day prior to vasopressor treatment (Table 3). Patients in the AVP group required increased mannitol (AVP: 313[496] vs. CA: 0[220] vs. None: 0[43] gm, $p=0.004$), packed red blood cells (PRBCs) (AVP: 500[1249] vs. CA: O[O] vs. None: 0[0] mL, $p=0.006$), and intravenous fluid (IVF) (AVP: 4472[1504] vs. CA: 3388[3749] vs. None: 2125[1795] mL, $p=0.007$).

Altogether Tables 1-3 show that both vasopressor groups were more unstable than the no vasopressor group, and that prior to initiating treatment, the AVP group was at least as hemodynamically unstable, if not more so, than the CA group.

Intention to treat analysis did not reveal any significant differences in primary or secondary outcomes (Table 4). However, as treated analysis displayed numerous significant differences (Table 5). When comparing patients who received CA to those that received no vasopressors, duration of ICP monitoring was increased (279[234] vs. 184[226] mm Hg), minimum CPP was decreased (62[9] vs. 87[8] mm Hg), and duration CPP<60 was increased (0.7[1.9] vs. 0.4[1.0], hrs) (all $p<0.05$). When comparing patients who received AVP to those that received no vasopressors, maximum ICP was increased (25[6] vs. 19[9] mm Hg) and mortality was increased ($n=5$, 42% vs. $n=3$, 5%) (all $p<0.05$). There were no significant differences in primary outcomes such as duration of sinus tachycardia (AVP: 5.3[9.0] vs. CA: 7.4[8.1] vs. None: 5.8[9.3] hrs, $p=0.321$). There were no significant differences in any outcome between CA and AVP groups.

All deaths were determined to be "unrelated to the study procedures" by the independent data safety monitoring board. The cause of death in patients who received no vasopressors was withdrawal of care (n=1) and multi-organ system failure (MOSF) (n=2). The cause of death in patients who received CA was brain death (n=2), herniation (n=1), and MOSF (n=1). The cause of death in patients who received AVP was brain death (n=2), withdrawal of care (n=1), herniation (n=1), and MOSF (n=1).

DISCUSSION

This is an interim report of the first clinical trial to compare the effectiveness of CA to AVP for the management of CPP after TBI. The data so far suggest that AVP is a safe and effective alternative to CA for the management of CPP after TBI.

Patients randomized to receive AVP had higher ISS compared to those who received no vasopressors, and decreased values of SBP, MAP, and CPP on first day of ICU (Table 2). Also, more fluid was required to achieve these values (Table 3). This hemodynamic instability is consistent with more severe injury prior to starting treatment. Patients who received AVP had increased mortality rate vs. no vasopressors (42% vs. 5%, $p<0.05$), but there was no significant difference between the two pressor groups. With small sample sizes at this interim time point, it is impossible to absolutely determine cause and effect, but each death was reviewed by the independent data safety monitoring board and by the IRB and was judged as "unrelated to the study procedures". Other outcomes such as duration of sinus tachycardia, duration of ICP monitoring, LOS, and ICU days were not significantly different.

Similarly, patients who received CA had evidence of more severe injury compared to those who received no vasopressors. The CA group had lower SBP, minimum CPP, and duration CPP<60 mm Hg on the first day of ICU. Patients who received CA had increased duration of ICP monitoring, increased duration CPP<60 mm Hg, and lower minimum CPP (although clinically within normal range) compared to those who received no vasopressors. There were no differences in mortality rates between CA and those who received no vasopressors (18% vs. 5%).

Altogether, these results indicate that those who received vasopressors (CA or AVP) were more severely injured and had worse outcomes than those who did not require vasopressors. These findings are not surprising, and confirm the findings of many previous studies.

Patients who received AVP had similar demographics compared to those that received CAs. However, on the first day of ICU, prior to the initiation of vasopressor therapy, the group that eventually received AVP required significantly more mannitol, packed red blood cells, and IVF (Table 3). All primary and secondary outcomes (including mortality) were not significantly different between groups. Patients who received CA were more likely to be refractory to vasopressor therapy compared to those who received AVP (22% vs. 8%), although this trend did not reach statistical significance. Minimum CPP was decreased in the AVP group on ICU day 1, but was similar to CA and no vasopressors groups on ICU days 2-7. Altogether, these results suggest noninferiority of AVP vs. CA.

AVP is FDA approved for the treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus, but many off-label

actions of AVP have been reported. AVP is effective for patients in septic shock[23, 2416, 25], refractory cardiac arrest[17], numerous animal hemorrhagic shock models show that AVP is effective in combination with fluid resuscitation[18-22, 26]. Lienhart and Wenzel et al are currently performing the VITRIS trial comparing AVP to saline placebo for treatment of prehospital hemorrhagic shock[27, 28]. Recently, Cohn et al performed a randomized prehospital trial comparing a combination of fluid resuscitation and low dose AVP to fluid resuscitation alone in hypotensive trauma patients (SBP <90 mm Hg). Patients who received AVP in combination with fluid resuscitation required significantly less total fluids and total blood products, and had no difference in mortality or adverse event rates[29]. Similarly, our study reports a novel off-label indication for AVP.

There is no consensus regarding the optimal vasopressor for CPP management in TBI patients and almost no information on the use of AVP in this context. There is little doubt that decreased CPP is associated with worse outcomes in patients with TBI[30-32], and that manipulating CPP with fluid resuscitation and vasopressors can be harmful. Systemic side effects such as ARDS and episodes of intracranial hypertension can develop with vasopressor use[2, 33]. Our institutional policy is to maintain CPP>60 mm Hg with fluid and blood products until the patient is fully resuscitated, and use vasopressors if the patients remains refractory to treatment. Our institution also utilizes ICP monitoring devices in patients with severe TBI as recommended by the Brain Trauma Foundation[34]. However, Chesnut et al recently reported that targeting ICP<20 mm Hg was not superior to care based on imaging and clinical examination[35]. Clearly, there are many areas of TBI management where controversy remains. This study furthers the state of the art by

suggesting that AVP is a safe and effective alternative to CA for the management of CPP after TBI.

The major limitation is that this is an interim analysis with a relatively small sample size. Furthermore, most of consented patients did not even receive vasopressors. Because so many patients did not receive vasopressors an "as treated" analysis was needed, however this method is not the gold standard of analysis for clinical trials. Patients were not randomized to receive a specific CA, which creates further variability. Patients also received vasopressors that they were not randomized to receive, which weakens the design of our study. The multi-discipline team that manages isolated and polytrauma TBI patients create the potential for crossover between treatment groups. With so many disciplines (trauma surgeons, trauma-intensivists, neurosurgeons, and neuro-intensivists) and individuals (residents and attending physicians), there was inevitable crossover between study groups, but that is the clinical reality in a busy level 1 trauma center. We did not find any differences in outcomes between those receiving AVP vs. CA, however there are numerous reasons for not finding a difference (type II error). It is logical to assume that AVP would be most effective in those with a deficiency, as demonstrated previously (15, 16 reference format), but endogenous AVP is not routinely measured at our institution, and was not measured in this study. Another limitation is that there was no predefined time point for an interim analysis. We chose to perform the interim analysis at this time because the lower limit of estimated sample size (n= 110) was being approached and there was major concern about the number of deaths in the AVP group (n=5). Fortunately, the independent DSMB determined that all deaths were unrelated to the study drugs, which provided the green light to critically evaluate and interpret the results. The decision to present the results

at the 43rd Annual Western Trauma Association Meeting was to determine (1) whether the trauma community at large agreed with our interpretation and (2) whether there was interest in a multi-center trial. One thing is clear after 4 years of enrolling patients, even a busy level I trauma center cannot enroll enough TBI patients with ICP monitors to adequately compare AVP vs. CA.

The bottom line is that this is a preliminary report, and it is difficult to make unequivocal conclusions because the sample size is small. For this reason, enrollment continues. Of course, we plan to examine whether any trends reach statistical significance with the larger sample size, but the definitive answer will probably depend on a multi-center trial.

In conclusion, the interim data analysis suggests that AVP is a safe and effective alternative to CA for the management of CPP after TBI and support the continued investigation and use of AVP when vasopressors are required for CPP management in TBI patients.

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AUTHOR CONTRIBUTIONS

RMVH is directly responsible for all aspects of this study. He participated in the collection, analysis and interpretation of data; drafting and revision of the manuscript, figures and tables.

CMT participated in the collection of data, revision of the manuscript, figures and tables.

EJV participated in the collection of data, revision of the manuscript, figures and tables.

MPO participated in the conception and experimental design, collection, analysis and interpretation of data, revision of the manuscript, figures, and tables.

GAG participated in the collection of data, revision of the manuscript, figures and tables.

JAJ participated in the collection of data, revision of the manuscript, figures and tables.

AMB participated in the collection of data, revision of the manuscript, figures and tables.

LTH participated in the collection of data, revision of the manuscript, figures and tables.

MRB was medically responsible for the patients in this study; treatments were administered at his discretion. In addition, he participated in the conception and experimental design; revision of the manuscript, figures and tables.

JRJ was medically responsible for the patients in this study; treatments were administered at his discretion. In addition, he participated in the conception and experimental design; revision of the manuscript, figures and tables.

ASL participated in the conception and experimental design, analysis and interpretation of data, revision of the manuscript, figures, and tables.

KGP had overall responsibility for the study; including conception and experimental design; analysis and interpretation of data; drafting and revision of the manuscript, figures and tables; statistical expertise and evaluation; obtaining funding for this project; supervision.

Table 1. Demographics and first day of ICU, intention to treat analysis

	CA (n=54)	AVP (n=42)	p=
Age, yrs	38±18	40±16	0.619
Male gender, %	81%	81%	0.947
Blunt mechanism, %	96%	93%	0.651
Craniotomy, %	28%	31%	0.734
Polytrauma, %	72%	88%	0.066
ISS	26±11	27±12	0.803
Time to pressor start, hrs	56 (150)	16 (59)	0.158
	Admission Values		
HR, bpm	95±26	98±26	0.645
SBP, mm Hg	137±35	150±36	0.097
GCS≤8	**87%**	**71%**	**0.031**
Intubated at arrival, %	98%	90%	0.159
	First Day of ICU		
HR, bpm	74±16	76±19	0.688
SBP, mm Hg	102 (20)	101 (21)	0.734
MAP, mm Hg	74±12	74±15	0.985
ICP Min, mm Hg	6 (9)	8 (7)	0.102
ICP Max, mm Hg	**19 (9)**	**23 (13)**	**0.049**
ICP >20, hrs	0 (2)	1 (4)	0.093
CPP min, mm Hg	64 (14)	58 (16)	0.089
CPP max, mm Hg	93±15	95±14	0.530
CPP <60, hrs	0 (1)	0 (2)	0.222

ISS – injury severity score, HR – heart rate, SBP – systolic blood pressure, GCS – Glascow coma scale, MAP – mean arterial pressure, ICP – intracranial pressure, CPP – cerebral perfusion pressure

Table 2. Demographics and First day of ICU, as treated analysis

	None (n=60)	CA (n=23)	AVP (n=12)	p=
Age, yrs	38±16	38±18	45±18	0.408
Male gender, %	82%	74%	92%	0.436
Blunt mechanism, %	97%	96%	92%	0.733
Craniotomy, %	32%	22%	25%	0.643
Polytrauma, %	75%	83%	92%	0.408
ISS	24±10*	29±13	33±12*	**0.014**
Time to pressor start, hrs	-----	56 (113)	14 (36)	0.113
Admission Values				
HR, bpm	94±22	101±31	98±27	0.455
SBP, mm Hg	146±38	127±26	150±33	0.073
GCS≤8	77%†	96%*†	67%*	0.064
Intubated at arrival, %	96%	96%	83%	0.188
First day of ICU				
HR, bpm	75±18	75±18	71±18	0.756
SBP, mm Hg	107 (22)*†	97 (10)*	97 (40)†	**0.007**
MAP, mm Hg	77±13*	72±10	65±17*	**0.008**
ICP Min, mm Hg	8 (8)	6 (9)	9 (12)	0.258
ICP Max, mm Hg	19 (9)	22 (18)	27 (25)	0.124
ICP >20, hrs	0 (1)†	2 (3)	4 (8)†	**0.023**
CPP min, mm Hg	64 (14)*†	60 (13)*	53 (22)†	**0.005**
CPP max, mm Hg	95±14	89±13	95±18	0.156
CPP <60, hrs	0 (1)*	1 (5)*	1 (2)	**0.030**

* and †indicate significant differences. ISS – injury severity score, HR – heart rate, SBP – systolic blood pressure, GCS – Glascow coma scale, MAP – mean arterial pressure, ICP – intracranial pressure, CPP – cerebral perfusion pressure

Table 3. First day of ICU hyperosmolar therapy and fluid requirements, as treated analysis

	None (n=60)	CA (n=23)	AVP (n=12)	p=
Mannitol, gm	0 (43)*	0 (220)	313 (496)*	**0.004**
Mannitol, %	33%*	43%	75%*	**0.027**
PRBC, mL	0 (0)†	0 (0)*	500 (1249)*†	**0.006**
PRBC, %	18%†	13%*	58%*†	**0.005**
IVF, mL	2125 (1795)†	3388 (3749)	4472 (1504)†	0.007
UOP, mL	2405 (1545)*	3675 (2833)*	2696 (3981)	**0.059**
CSF, mL	0 (0)*	0 (16)	14 (68)*	0.079
Head JP, mL	0 (68)	0 (60)	0 (0)	0.362

* and †indicate significant differences. PRBC – packed red blood cells, IVF – intravenous fluid, UOP – urine output, CSF – cerebral spinal fluid output, head JP – Jackson-Pratt drainage

Table 4. Outcomes, intention to treat analysis.

	CA (n=54)	AVP (n=42)	p=
Pressor duration, hrs	55 (141)	52 (157)	0.908
ICP monitoring, hrs	190 (248)	196 (196)	0.695
Sinus tach, hrs/day	7.3±5.9	7.7±6.1	0.745
CPP min, mm Hg	65 (9)	65 (10)	0.642
Time CPP<60, hrs	1 (1)	1 (1)	0.365
ICP Max, mm Hg	20 (10)	22 (6)	0.091
Time ICP>20, hrs	0.9 (2.6)	1.7 (1.8)	0.095
ICU days	22 (17)	20 (23)	0.747
LOS, days	38 (33)	40 (80)	0.230
Mortality, %	12%	15%	0.641

ICP – intracranial pressure, sinus tach – sinus tachycardia, CPP – cerebral perfusion pressure, ICU – intensive care unit, LOS – length of stay

Table 5. Outcomes, as treated analysis.

	None (n=60)	CA (n=23)	AVP (n=12)	p=
Pressor duration, hrs	-----	58 (115)	52 (155)	0.451
ICP monitoring, hrs	184 (226)*	279 (234)*	166 (127)	0.062
Sinus tach, hrs/day	5.8 (9.3)	7.4 (8.1)	5.3 (9.0)	0.321
AKI: overall, %	5%	17%	23%	0.056
AKI: study period %	2%*	13%	23%*	0.009
AKI: during pressor, %	----	13%	23%	0.391
ARDS: overall, %	62%	57%	69%	0.832
ARDS: study period, %	52%	52%	46%	0.992
ARDS: during pressor, %	----	48%	39%	0.728
Peripheral necrosis	0%	0%	0%	1.0
CPP min, mm Hg	67 (8)*	62 (9)*	65 (9)	**0.037**
Time CPP<60, hrs	0.4 (1.0)*	0.7 (1.9)*	0.9 (1.7)	0.052
ICP Max, mm Hg	19 (9)†	21 (6)	25 (6)†	**0.030**
Time ICP>20, hrs	0.9 (2.3)	1.4 (2.7)	2.0 (5.5)	0.090
Refractory to pressors, %	-----	22%	8%	0.640
ICU days	20 (17)	25 (28)	19 (15)	0.242
LOS, days	37 (31)	52 (70)	25 (50)	0.281
Mortality, %	5% (n=3)*	18% (n=4)	42% (n=5)*	**0.002**

* and †indicate significant differences. ICP – intracranial pressure, sinus tach – sinus tachycardia, AKI – acute kidney injury, ARDS – acute respiratory distress syndrome, CPP – cerebral perfusion pressure, ICU – intensive care unit, LOS – length of stay

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Appendix 4

Reference 2

Does arginine vasopressin exacerbate cerebral edema after traumatic brain injury?

Presented at 29th Eastern Assoc for Surgery of Trauma Annual Scientific Assembly at the JW Marriott San Antonio in San Antonio, TX Jan 2016

DOES ARGININE VASOPRESSIN EXACERBATE CEREBRAL EDEMA AFTER TRAUMATIC BRAIN INJURY?

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Objectives: Arginine vasopressin (AVP) is commonly used as an alternative pressor to catecholamines (CAT); unlike CAT, AVP has powerful antidiuretic actions. AVP contributes to cerebral edema after experimental traumatic brain injury (THI), but there are no data in humans. We tested the hypothesis that AVP promoted cerebral edema and/or increased osmotherapy use, relative to CAT in TBI patients.

Methods: We reviewed data on 286 consecutive patients with intracranial pressure (ICP) monitors admitted to a large American College of Surgeons verified level J trauma center from 09/2008-01/2015. Clinical parameters and fluid requirements were retrospectively reviewed. Cerebral edema was assessed by computed tomography using the gray white ratio (GWR) calculation method, where a low GWR indicates the presence of cerebral edema. Significance was assessed at $p \leq 0.05$.

Results: To maintain cerebral perfusion pressure > 60 mmHg, 205 patients required no vasopressors, 41 received a single CAT, 12 received AVP, and 28 required both CAT and AVP. Those who required no pressors were generally less injured, required less osmolar therapy and less total fluid, had lower plasma sodium, lower ICP, less cerebral edema, and lower mortality (all $p < 0.05$). Cerebral edema, daily sodium levels (mean, minimum and maximum), and mortality were similar with AVP vs. CAT, but the daily requirement of mannitol and hypertonic saline were reduced by 45% and 35%, respectively (both $p < 0.05$).

Conclusions: This is the first radiographic and clinical evidence to suggest that exogenous AVP does not promote cerebral edema and in fact decreases the use of osmotherapy relative to CAT in TBI patients.

Appendix 5

Reference 3

Craniectomy following urgent evacuation of intracranial hemorrhage improves intracranial and cerebral perfusion pressures in severe traumatic brain injured patients.

Presented at 74th Annual Meeting of the American Association for the Surgery of Trauma & Clinical Congress of Acute Care Surgery Las Vegas, NV Sept 2015

CRANIECTOMY FOLLOWING URGENT EVACUATION OF INTRACRANIAL HEMORRHAGE IMPROVES INTRACRANIAL AND CEREBRAL PERFUSION PRESSURES IN SEVERE TRAUMATIC BRAIN INJURED PATIENTS

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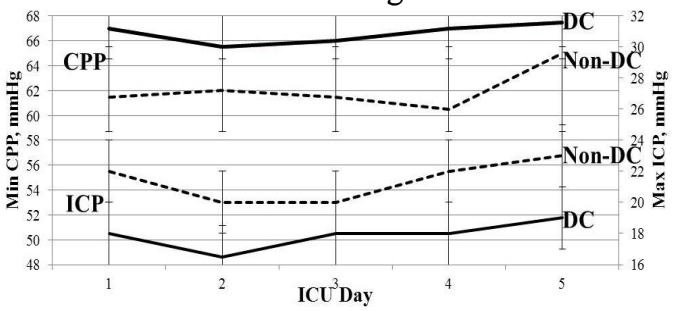
Introduction: The benefits of decompressive craniectomy (DC) are controversial. We hypothesize that DC following urgent evacuation of intracranial hemorrhage (ICH) improves intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in severe TBI patients.

Methods: 227 patients requiring invasive ICP monitoring at a single level 1 trauma center were prospectively observed. Patients who underwent DC following ICH evacuation within 24h were identified. DC and non-DC patients were propensity score matched 1:1 based on injury characteristics, and groups were compared using Mann Whitney U test or Fisher's exact test with significance at $p \leq 0.05$. Data are presented as M±SD or median (IQR).

Results: The cohort was age 41±17 years, 82% male, ISS 28±11, GCS 6±4, AIS head 4±1, LOS 32(15) days, and 27% mortality. 50 DC following ICH evacuation were matched to 50 non-DC patients achieving similar demographics, hemodynamics, ISS, GCS, AIS head, transfusion requirements, and need for vasopressor therapy between the groups. In comparing DC vs non-DC groups, hours of abnormal ICP (>20mmHg) were 1(10) vs 7.5(16) (p=0.017), hours of abnormal CPP (<60mmHg) were 0(6) vs 4(9) (p=0.008), daily minimum CPP (mmHg) was 67(13) vs 62(17) (p=0.010), daily maximum ICP (mmHg) was 18(9) vs 22(11) (p<0.001), LOS 33(47) vs 25(34) (p=NS), and mortality of 24% vs 30% (p=NS). Daily minimum CPP and maximum ICP values are in the figure.



Conclusion: DC following urgent evacuation of ICH decreases abnormal ICP and CPP time and improves overall ICP and CPP thresholds. These findings give evidence of benefit of early DC in severe TBI patients.