Intravenous Exenatide Infusion in Critically Ill Patients with Acute Brain Injury

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SPECIFIC AIMS

Hyperglycemia is associated with worsened clinical outcome following neurologic injury.[1-10] Early landmark clinical trials have demonstrated that maintaining normoglycemia by intensive insulin therapy (IIT), as compared with tolerating hyperglycemia as an adaptive response, significantly decreased mortality in critically ill surgical patients and those in the coronary care unit.[11-13] However, more recent trials have failed to confirm this benefit, and in some studies IIT was associated with significantly higher rates of all-cause mortality.[14-24] There is evidence to suggest that insulin-induced hypoglycemia is an independent risk factor for mortality in critically ill patients.[25-28] IIT following neurologic injury has been shown to increase the risk for hypoglycemic episodes with no subsequent reduction in mortality and has been associated with a significant decrease in cerebral extracellular glucose levels and an increased incidence of other markers of cerebral cellular distress including, elevated glutamate, lactate/pyruvate ratio, and glycerol.[29-32] Emerging evidence and data from the pooled post-hoc analysis of the two prospective, randomized, interventional Leuven trials also suggest that glycemic variability has a strong, independent effect on mortality in critically ill populations.[33-41] Nevertheless, the benefit of IIT in the Leuven trials was determined to be associated with decreases in mean glucose levels and glycemic variability, and avoidance of severe hypoglycemia. We have preliminarily found and reported that glycemic variability in neurocritical care patients is associated with higher in-hospital mortality.[42] Thus it is plausible that optimum benefit on mortality in critically ill patients would result from decreasing mean glucose levels while at the same time minimizing both glycemic variability and the occurrence of severe hypoglycemia.

A potential role for incretin-based therapy in the management of critically ill patients with hyperglycemia exists. Glucagon-like peptide-1 (GLP-1) is the most well characterized naturally occurring incretin hormone. On ingestion of meals, GLP-1 is secreted from L-cells of the small intestine and subsequently enhances glucose-dependent insulin secretion, suppresses postprandial glucagon secretion from pancreatic alpha-cells, slows gastric emptying, and signals satiety.[43-46] Because the former effects are glucose dependent, the use of GLP-1 does not appear to be associated with hypoglycemic risk. The major limitation of endogenous GLP-1 is its relatively short half-life due to degradation by the enzyme dipeptidyl peptidase IV (DPP-IV).[47] Exenatide, a DPP-IV resistant GLP-1 receptor agonist, has recently been added to the therapeutic armamentarium targeting hyperglycemia. The effect of GLP-1-based therapy on hyperglycemia following neurologic injury has recently been evaluated in patients with acute ischemic stroke.[48] Daly and colleagues administered exenatide subcutaneously in eleven patients over a median duration of six-days. They reported no symptomatic hypoglycemia or serious adverse effects and a low rate of hyperglycemia (4.9%; defined as > 155 mg/dL); however, glycemic variability was not assessed in this study. Additionally, the incidence of nausea and vomiting with subcutaneous administration was high with 55% and 45% of patients experiencing these adverse effects, respectively. Despite these promising results with subcutaneous administration, other studies have evaluated exenatide's therapeutic use as a continuous infusion in critically ill populations and have reported low incidence of gastrointestinal side effects.[49-52] Therefore, *there is a need* to evaluate the feasibility of exenatide infusion in critically ill patients with acute brain injury and investigate its impact on glycemic variability.

Our *long-term goal* is to reduce mortality associated with hyperglycemia in critically ill patients. The *objective* of this proof of concept study is to explore the effects of exenatide infusion for hyperglycemia following acute neurologic injury. We are well prepared to undertake the proposed research. Our extensive experience in recruiting individuals is demonstrated by the excellent response rates to our previous acute neurologic injury studies.[6,42] Additionally, we have assembled a research team with extensive experience in exenatide-based, neurologic injury and medical intervention studies, and experienced neurointensivist collaborator.

We plan to accomplish the grant objectives by pursuing the following specific aims:

1. ***To demonstrate the feasibility of exenatide infusion in critically ill patients with acute brain injury utilizing continuous glucose monitoring.***

   Background and Rationale:

   Hyperglycemia, hypoglycemia, and glycemic variability are all associated with poor outcomes in critically ill patients. Elevated glucose during the acute period of hospitalization has been linked to mortality in patients with traumatic brain injury and intracerebral hemorrhage.[6,49] Hypoglycemia is associated with increased mortality in critically ill patients achieving goal glucose levels of 80 – 120 mg/dL and has been associated with cerebral distress.[25,27,32,50] Glycemic variability has also been found to be an independent risk factor for mortality in critically ill patients.[33,51-54] In a study comparing the impact of glycemic variability in patients with and without diabetes, high glycemic variability was associated with increased mortality in patients without diabetes.[36] Recent studies have also begun to demonstrate the impact of glycemic variability on clinical outcomes in patients with acute brain injury. Matsushima and colleagues demonstrated that glucose variability was significantly associated with poorer long-term functional outcomes in patients with traumatic brain injury.[55] Kurtz and colleagues reported that glucose variability was associated with cerebral metabolic distress and increased mortality at hospital discharge in patients with severe brain injury.[56] Blayau and colleagues found that glycemic variability is an independent predictor of mortality in ICU patients with traumatic brain injury.[57] Investigators in our group reported that large glucose variability during the acute phase of spontaneous intracerebral hemorrhage is associated with higher in-hospital mortality.[58] ***Therefore, it might be reasonable to hypothesize that optimal benefit might occur in patients with acute brain injury from control of overall glycemic levels (mean glucose levels) in conjunction with minimizing glycemic variability, while strictly avoiding the occurrence of hypoglycemia.***

   A potential role for incretin-based therapy in the management of critically ill patients with hyperglycemia exists. The effect of GLP-1-based therapy via *continuous infusion* on hyperglycemia following acute brain injury has not been previously evaluated, however, few studies have evaluated its therapeutic use in other critically ill populations. Following major surgery, GLP-1 infusion (1.2 pmol/kg/min) administered to eight patients with type 2 diabetes resulted in normalization of hyperglycemia (126 mg/dL) within 150 minutes of initiation.[59] Following coronary artery bypass graft surgery, GLP-1 infusion had been demonstrated to normalize blood glucose compared to both placebo and IIT with doses of 1.5 and 3.6 pmol/kg/min, respectively.[59,60] Other published data support that GLP-1 infusion attenuates glycemic response in severely ill patients hyperglycemic during total parenteral nutrition, enteral or intragastric feeding.[61,62] Intravenous GLP-1 infusion has been well-tolerated in all critically ill populations evaluated with minimal adverse events reported. Hypoglycemic events were not recorded in the majority of studies.[58,59,61,62] One episode of asymptomatic hypoglycemia (43 mg/dL) occurred with GLP-1 treatment, but resolved following temporary cessation of the infusion.

   The main <u>*expected outcome*</u> of this work is to demonstrate the feasibility of exenatide infusion in the management of hyperglycemia following acute brain injury. We are proposing to evaluate this aim by utilizing continuous glucose monitoring (CGM). CGM has the potential to provide real-time measurement of systemic glucose concentrations. This allows for more intensive monitoring of glycemic variability as well as hyper- and hypoglycemic events. Schuster and colleagues reported CGM is reasonable and accurate in surgical ICU patients, many of whom had recent abdominal surgery and required use of pressors and large-volume resuscitation.[63] Holzinger and colleagues found that CGM reduced hypoglycemic events in critically ill patients[64] and also reported that the accuracy and reliability of CGM in critically ill patients was

not impacted by circulatory shock requiring norepinephrine therapy.[65] CGM will provide a direct representation of the overall glycemic status in order to evaluate the potential of exenatide as a treatment of hyperglycemia following acute brain injury.

2. ***To evaluate the pharmacokinetic parameters of exenatide in critically ill patients with acute brain injury.***
Background and Rationale:
Critically ill patients and patients with acute brain injury have been shown to experience a hyperdynamic state resulting in an elevation of creatinine clearance, termed augmented renal clearance (ARC).[66-68] Patients with ARC have the potential to eliminate exenatide more quickly than we currently anticipate, as renal clearance is the predominant route of elimination of this drug. This will directly impact the ability to achieve therapeutic drug concentrations with the current recommended dosing regimen.

A recent study by Udy and colleagues evaluated the incidence of ARC in generally critically ill patients throughout their ICU stay.[66] They found that 65.1% of patients manifested ARC on at least one occasion during the first seven days in the ICU. More specifically, a limited amount of information exists evaluating ARC in patients with acute brain injury. In patients with traumatic brain injury, Udy and colleagues demonstrated an incidence of ARC in 85% of patients with the mean maximum creatinine clearance being 179 mL/min/1.73 m^2.[67] In addition, an abstract recently presented at the 2013 Neurocritical Care Annual Meeting utilized vancomycin serum concentrations and determined that patients with aneurysmal subarachnoid hemorrhage also appear to have an increase in renal clearance, with an estimated creatinine clearance of > 140 mL/min.[68]

Our research team has experience in this area as we have also utilized vancomycin serum concentrations to describe drug pharmacokinetics in patients with acute brain injury who underwent thermoregulation.[69] In patients who underwent controlled normothermia and received vancomycin, we found that the median measured trough concentration and median calculated half-life were significantly lower than predicted values, suggesting that the elevated renal elimination of vancomycin due to ARC outweighs a potential reduction in drug elimination caused by controlled normothermia. This resulted in subtherapeutic vancomycin serum concentrations, which may lead to serious complications.[69]

Therefore, determining the incidence of ARC in this patient population and its impact on exenatide pharmacokinetic parameters is a critical area for further study *as ARC may result in subtherapeutic concentrations of exenatide*. We are proposing to evaluate this aim by measuring serum concentrations of exenatide and directly measuring urinary creatinine clearances concurrently. This will provide a direct representation of the overall renal function along with the incidence of ARC and allow for comparison of the patient's renal function with exenatide serum concentrations.

3. ***To determine the impact of exenatide infusion on cerebral extracellular glucose levels and other markers of cellular distress utilizing cerebral microdialysis in eligible critically ill patients with acute brain injury.***
Background and Rationale:
Recently both experimental and clinical studies have shown that even mild hypoglycemia may result in cerebral metabolic distress.[70-72] Overall these studies show that the brain can be acidotic even with "normal" serum glucose concentrations and this cerebral glycopenia is related to poor functional outcome.[72] There is convincing evidence to suggest that measures to avoid both hyperglycemia and hypoglycemia in neurocritical care patients are essential.

Studies conducted that have evaluated IIT in neurocritical care patients have not shown differences in mortality or functional outcome when tight glucose control is used.[29-32,73-75] Some of these studies have shown lower infection rates in neurocritical care patients but increased risk of hypoglycemic episodes (serum glucose < 50-80 mg/dL).[29-31] This increased risk of hypoglycemia is of significant concern as evidenced by an observational study of 172 patients following subarachnoid hemorrhage who were treated with an IIT protocol targeting blood glucose between 80 and 110 mg/dL and the adverse effect this complication had on functional outcome.[76] In this study a blood glucose nadir of < 80 mg/dL was independently associated with higher rates of cerebral infarction, symptomatic cerebral vasospasm, and poor functional outcome.

Cerebral microdialysis is a well-established laboratory tool that is increasingly used as a bedside monitor of brain tissue biochemistry in the neurocritical care unit. Metabolic crisis, measured in the interstitial space by cerebral microdialysis, is defined as a high lactate pyruvate ratio (LPR >40) in combination with a low extracellular cerebral glucose level (<0.7 mmol/l).[77-79] Serum glucose levels directly affect the availability of extracellular brain glucose and therefore brain metabolism. Under optimal conditions, energy supply to the brain is adjusted to meet the individual demand, which is higher after severe brain injury.[80-81] A reduction in energy supply can be caused by reduced cerebral blood flow, which decreases oxygen and glucose supply, resulting in a shift to anaerobic metabolism with increased brain lactate.[82] Alternatively, low glucose availability can lead to a decrease in brain pyruvate without an increase in lactate.[32,72] This metabolic crisis has been linked to poor outcome in comatose patients.[83,84]

Recently, tight glycemic control with IIT has been associated with metabolic crisis in patients with acute brain injury.[32,49,71] In these studies, tight glucose control (goal 80-120 mg/dL) was associated with a significant increase in the incidence of dialysate glucose levels <0.7 mmol/L, LPR >30, and increased in glutamate. Marcoux et al. reported that the percentage of time LPR was above 30 was significantly correlated with the extent of frontal lobe atrophy 6 months following injury even in patients with a normal frontal lobe on initial CT scan.[50] It is becoming apparent that IIT is not only associated with hypoglycemic episodes but also with direct extracellular evidence of cellular distress and brain metabolic crisis.

Therefore, in neurocritical care patients, interventions that maintain cerebral extracellular glucose levels without causing an increase in markers of cellular distress are anticipated to be particularly effective in the management of acute hyperglycemia. We propose to determine the impact of exenatide infusion on cerebral extracellular glucose levels in eligible critically ill patients with acute brain injury.

APPROACH

Study Design: Single-center, prospective, non-randomized, open-label feasibility demonstration trial of exenatide infusion following acute brain injury.

Randomized Design (if applicable): NA

Study Population: Critically ill patients with acute brain injury.

Major Inclusion Criteria for Initiation of Study Drug:
1. Adults ≥18 years
2. Acute brain injury resulting in admission to the NSICU for an anticipated length of stay >48 hours
3. Two blood glucose concentrations > 150 mg/dL and ≤ 300 mg/dL
4. Informed consent obtained via patient's designated proxy

Major Exclusion Criteria for Initiation of Study Drug:
1. Pregnant (verified by urine or serum pregnancy test within 24 hours of initiation of infusion) or lactating females
2. Type 1 diabetes mellitus
3. History of pancreatitis or risk factors for acute pancreatitis (i.e ethanol abuse, gall stones)
4. Renal insufficiency defined as CrCL < 45 mL/min
5. Known history of gastroparesis
6. History of surgery on stomach, esophageous or duodeneum
7. Diabetic Ketoacidosis or Hyperosmolar Hyperglycemic Nonketotic Syndrome
8. Concurrent steroid use or planned post-operative steroid use
9. History of organ transplantation
10. Brain death or suspected imminent brain death within the next 72 hours
11. Refractory intracranial hypertension defined as ICP > 25 mmHg for greater than 15 minutes and refractory to medical intervention
12. Currently enrolled in another investigational drug or device protocol
13. Insulin infusion within 3 hours of study drug administration or confirmed long acting insulin or sulfonylurea use prior to admission within 24 hours of study drug administration
14. Known allergy to exenatide

Methodology:

1. Subjects: Adult patients (≥18 years) with two consecutive blood glucose readings of >150 mg/dL and ≤300 mg/dL will be eligible for inclusion in this study. The study population will be limited to those with acute brain injury resulting in admission to the NSICU for an anticipated length of stay >48 hours and who will not have planned steroid use post-operatively. Patients with imminent brain death or refractory intracranial hypertension will not be enrolled. Pregnant (verified by urine or serum pregnancy test within 24 hours of initiation of exenatide infusion) or lacting females, and those with a history of type 1 diabetes mellitus, pancreatitis or risk factors for acute pancreatitis (i.e. ethanol abuse, gall stones), renal insufficiency (CrCL < 45 mL/min), gastroparesis, surgery on stomach, esophageous, or duodeneum or those with organ transplantation will be excluded. Additionally, those presenting with diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome will be excluded. Individuals receiving steroids or planned post-operative administration, insulin infusion within 3 hours of study drug administration, long acting insulin or sulfonylureas within 24 hours of study drug administration, another investigational drug or device, or those with known allergy to any of the study protocol drugs will be excluded. Recruitment will continue until 24 subjects receive study drug and complete the study protocol.

2. Glycemic Control Protocol: All study related protocols will be conducted in the Neuroscience Intensive Care Unit (NSICU). All patients admitted to the NSICU and that meet the eligibility criteria will be approached for consent to the study. Study drug will only be administered to those subjects providing consent via legally authorized representative and meeting glycemic thresholds. The study nurse will initiate the exenatide infusion

for the second consecutive blood glucose value >150 mg/dL but ≤300 mg/dL and continue per protocol for a maximum duration of 48 hours. Exenatide will be administered by intravenous infusion (50 ng/min for 30 minutes, then start exenatide infusion 25 ng/min) for the second consecutive blood glucose value >150 mg/dL but ≤300 mg/dL and continue per protocol for a maximum duration of 48 hours (dose, route, titration schedule, and duration). Exenatide will be prepared by the Investigational Drug Service. The exenatide infusion initiation and maintenance protocols are outlined in Tables 1&2 of the attached study protocol.The exenatide infusion blood glucose goal will be 110-180 mg/dL. During the exenatide infusion, glucose measurements will be obtained hourly. The exenatide infusion will be temporarily discontinued for blood glucose <110 mg/dL. The exenatide infusion will be restarted once the blood glucose level is at least 110 mg/dL. Episodes of hypoglycemia will be treated according to the following guidelines: 1) glucose <70 mg/dL will be provided 25 mL of dextrose 50% (1/2 amp) 2) blood glucose will be re-checked in 5 minutes; if mental status changes caused by hypoglycemia are not reversed or blood glucose remains <70 mg/dL, the above dextrose administration will be repeated, 3) serum glucose will be checked hourly after dextrose administration and the episode has resolved. Exenatide infusion will be restarted beginning with the second hourly glucose check that is ≥110 mg/dL. Insulin sensitive sliding scale using formulary rapid acting insulin will be used for blood glucose 181-300 mg/dL starting at the 2nd hourly glucose check (≥2 hours since exenatide initiation). The physician will be notified for any blood glucose >300 mg/dL for initiation of a rescue insulin infusion protocol. All glucose values will be documented in the ICU Electronic Documentation System.

Table 1: Exenatide Infusion Initiation Protocol

Glucose (mg/dL)	Action
151-300	Give exenatide 50 ng/min for 30 minutes, then start exenatide infusion 25 ng/min Give prokinetic agent per NSICU protocol (reglan, erythomycin, etc) Check glucose hourly Monitor blood pressure continuously during exenatide infusion. If SBP <100 mmHg, contact physician. Decision to discontinue exenatide infusion will be made at the discretion of the treating physician.

Table 2: Exenatide Infusion Maintenance Protocol

Glucose (mg/dL)	Action
<70	Discontinue exenatide infusion. Give 25 mL of dextrose 50% (1/2 amp) IVP – Recheck glucose in 5 minutes and notify physician. Check glucose hourly after hypoglycemia is resolved. When 2 in a row hourly glucose checks are greater than 109 restart exenatide infusion at 25 ng/min Notify physician when glucose greater than 80 mg/dL Monitor blood pressure continuously during infusion (if SBP<100 mmHg, contact physician)
80-109	Temporarily discontinue exenatide infusion Check glucose hourly When glucose greater than 109 restart exenatide infusion at 25 ng/min Note: If 3 in a row hourly checks are less than 110 restart protocol from beginning. Change glucose check to q4h and exenatide protocol for second glucose greater than 180 mg/dL Monitor blood pressure continuously during infusion (if SBP<100 mmHg, contact physician)

110-180	Continue exenatide infusion per protocol Check glucose hourly Monitor blood pressure continuously during infusion (if SBP<100 mmHg, contact physician)
181-216	1st hourly glucose check (=1 hour since exenatide initiation): continue exenatide infusion protocol ≥2nd hourly glucose check (≥2 hours since exenatide initiation): Give 2 units of formulary available rapid acting insulin subcutaneously and continue exenatide infusion protocol Check glucose hourly Monitor blood pressure continuously during infusion (if SBP <100 mmHg, contact physician)
217-252	1st hourly glucose check (=1 hour since exenatide initiation): continue exenatide infusion protocol ≥2nd hourly glucose check (≥2 hours since exenatide initiation): Give 4 units of formulary available rapid acting insulin subcutaneously and continue exenatide infusion protocol Check glucose hourly Monitor blood pressure continuously during infusion (if SBP <100 mmHg, contact physician)
253-300	1st hourly glucose check (=1 hour since exenatide initiation): continue exenatide infusion protocol ≥2nd hourly glucose check (≥2 hours since exenatide initiation): Give 6 units of formulary available rapid acting insulin subcutaneously and continue exenatide infusion protocol Check glucose hourly Monitor blood pressure continuously during infusion (if SBP <100 mmHg, contact physician)
>300	Recheck blood glucose within 5 minutes If confirmed, contact physician to discontinue exenatide and initiate rescue insulin infusion protocol (NSICU insulin infusion protocol)

3. Glycemic Variability Protocol: The Guardian REAL-Time Continuous Glucose Monitoring System (CGMS, Medtronic MiniMed, Northridge, CA) will be used to assess glycemic variability. The CGMS device carries an FDA-approved indication to supplement but not replace routine standard monitoring in patients. As such, the nursing staff will be blinded to the CGMS readings. All therapeutic decisions will be based upon standard of care glucose monitoring as outlined in the glycemic control protocol.

The CGMS is composed of a subcutaneous sensor that uses the glucose oxidase reaction for generation of an electrical current. A wireless transmitter connects to the sensor, and the signal is analyzed and converted to a measurement of the subcutaneous glucose level by a pager-sized device. Glucose levels are measured and recorded every 5 minutes. The subcutaneous glucose sensor will be deployed using the insertion kit available by the manufacturer. The sensors will be preferentially placed in the anterior abdomen. In the event the anterior abdomen is not available, the sensor will be placed in the upper thigh. Routine blood glucose measurements will be obtained hourly while the patient is receiving exenatide for purposes of calibration of the CGMS. After the initial calibration, the CGMS will be calibrated every 12 hours at a minimum. Sensors will be monitored daily by an investigator and 1 day after removal. The CGMS will be performed for 72 hours (48 hours during study drug infusion and an additional 24 hours during follow-up after study drug is discontinued).

4. Pharmacokinetic Protocol:

All patients admitted to the NSICU that meet the eligibility criteria will be approached for consent of blood samples obtained for pharmacokinetic analysis. Blood samples will be collected at 0, 12, 24, 36, and 48 hours after the start of the infusion. Approximately 30 mL of blood will be collected over 48 hours for pharmacokinetic sampling. The exenatide concentrations will be processed by Tandem Labs. An 8-hour urine collection for measuring creatinine clearance will be performed as the primary method of measuring renal

function. Eight-hour urine collections will be obtained on a daily basis for 72 hours (48 hours during study drug infusion and an additional 24 hours during follow-up after study drug is discontinued).

5. Bedside Cerebral Microdialysis Protocol: Patients admitted to the NSICU that meet the eligibility criteria and who also receive invasive intracranial multimodal monitoring as part of their standard of care will be invited to participate in the bedside cerebral microdialysis protocol. The bedside cerebral microdialysis protocol is in addition to the glycemic control, glycemic variability, and pharmacokinetic protocols. These patients will have the option of declining cerebral microdialysis but still remaining part of the other components of the study.

The addition of the FDA approved Cerebral Microdialysis probe (please see attached appendix) will be placed through the pre-existing invasive multimodal monitoring used as standard of care in these patients. No additional invasive procedures will be initiatied in these study participants. The microdialysis probes (CMA70, 10-mm membrane length, CMA Microdialysis, Stockholm, Sweden) will be placed in a standard fashion via a triple lumen skull bolt used as standard of care. The catheter location will be assessed in patients who have a follow-up CT scan. Catheters will be perfused by a battery driven microdialysis pump (CMA106, CMA Microdialysis) with artificial cerebrospinal fluid perfusion fluid (CMA Microdialysis, Stockholm, Sweden: NaCl 147 mmol/L, KCL 2.7 mmol/l, $CaCl_2$ 1.2 mmol/l, $MgCl_2$ 0.85 mmol/l) at a flow rate of 0.3 ml/min, which yields a recovery rate between 65-72%.[92] The dialysate will be collected in microvials designed for low evaporation and minute volumes. The samples will be analyzed immediately with the bedside mobile photometric, enzyme-kinetic analyzer (CMA600 Microdialysis analyzer; CMA Microdialysis, Stockholm, Sweden) every hour using a method previously described.[93] The initial 60 minute sample will not be used to allow for stabilization of the probe. The biochemical analysis includes parameters of energy metabolism (glucose, pyruvate, lactate, lactate:pyruvate ratio), glutamate (marker of cerebral ischemia), and glycerol (marker of cell membrane degradation). Microdialysis will be performed for 72 hours (48 hours during study drug infusion and an additional 24 hours during follow-up after study drug is discontinued) and daily medians of the microdialystate concentrations will be calculated for each patient. The microdialysis samples collected will be stored at -80 °C in a freezer for a period of three years. The samples will be stored in the event that the samples need to be re-run during the study period. The freezer is connected to an alarm system and these stored samples will not be shared.

6. General Management Protocol: All patients will be managed using standard NSICU protocols. ICP will be kept < 25 mmHg using a stepwise management strategy (management strategies will be recorded). Patients fluid will be maintained with crystalloids without glucose and enteral nutrition will be started as soon as possible. No patients will receive intravenous or oral steroids for their brain injury. Seizure prophylaxis will be provided per protocol for 7 days and sedation/analgesia will be provided as needed and titrated to standard monitoring scales or ICP. A prokinetic agent will be initiated for study subjects per NSICU protocol. Blood pressure will be monitored continuously throughout the study period for all subjects. All medications received during study drug infusion will be recorded.

7. Safety Data:

1 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any

unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

1.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies.)

NOTE:

The following hospitalizations are not considered SAEs in clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

1.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to the study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

1.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

1.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

1.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF Page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

1.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Not applicable.

Not applicable.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

1.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

1.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

2 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

8. Measurements: Blood glucose from the arterial line will be measured at baseline (prior to exenatide), hourly during the 48 hour exenatide infusion per protocol (table 2) and continue for an additional 24 hours following exenatide discontinuation. The continuous glucose monitor will measure the interstitial glucose level every 5 minutes beginning at baseline (prior to exenatide) until 24 hours following exenatide discontinuation. Blood samples for pharmacokinetic analysis will be collected in serum separator tubes at 0, 12, 24, 36 and 48 hours after the start of the infusion. Eight-hour urine collections will be obtained on a daily basis for 72 hours (48 hours during study drug infusion and an additional 24 hours during follow-up after study drug is discontinued). Microdialystate concentrations will be collected at baseline (prior to exenatide), and hourly during the 48-hour exenatide infusion for parameters of energy metabolism (glucose, pyruvate, lactate, lactate:pyruvate ratio), glutamate (marker of cerebral ischemia), and glycerol (marker of cell membrane degradation) and for an additional 24 hours following study drug discontinuation. Blood pressure will be measured continuously throughout the study period. Intracranial pressure (ICP) will be measured continuously during the exenatide infusion. Intracranial pressure values will be recorded at baseline (prior to exenatide) and daily mean ICP and cerebral perfusion pressure values will be reported. Baseline demographic information (e.g. gender, age, ethnicity) and disease severity information [e.g. Glasgow coma score, SOFA score (Sequential Organ Failure Assessment), Hunt Hess classification, Fisher grade, primary diagnosis, past medical history (including measurement of hemoglobin A1c), neurologic exam/computed tomography scan abnormalities] will be collected. The ICU day of study drug administration will be recorded and the total hospital and ICU lengths of stay will be recorded.

9. Data Management: Each participant will be assigned a unique identification number. No personal identification will be used. All study files will be stored in locked cabinets in the Principal Investigator's office in the Pharmacy Administration Department. Data will be entered into the study database using double entry (entry and verification) and will be checked for missing or ineligible responses.

10. Outcomes

10.1 The following feasibility endpoints are based upon prior literature (Nice-Sugar and Exenatide Study in the Cardiac ICU):

Proportion of patients experiencing severe hypoglycemia (<40 mg/dL), Proportion of patients achieving plasma glucose goal (110-180 mg/dL), Proportion of patients experiencing nausea requiring discontinuation of exenatide therapy

10.2 The following descriptive endpoints are included for describing experience with exenatide use in the NSICU population:

Average blood glucose value during exenatide infusion (48 hours), percent time in glucose range (48 hours), mean time to reach plasma glucose goal (110-180 mg/dL), variability outcome (SD)-MADGE, mean insulin use required (units/kg body weight), proportion of subjects requiring rescue insulin infusion protocol, number of hypoglycemic episodes (<80 mg/dL)/total number of glucose measurements (48 hours), number of subjects with >1 hypoglycemic episode (<80 mg/dL)/total number of subjects (48 hours), correlation of exenatide concentrations with creatinine clearance during infusion, elimination rate constant and area under the concentration-time curve utilizing concentrations after discontinuation of infusion, side effects and adverse events (AEs and SAEs), average daily ICP and CPP during study drug infusion, number of hypotensive episodes (SBP<100 mmHg) (48 hours), number of subjects with >1 hypotensive episode/total number of subjects (48 hours). Other adverse effects will be collected specifically assessing any alterations in gastric motility.

In patients receiving invasive intracranial multimodal monitoring as part of their standard of care, the following endpoints associated with exenatide use will be described:
Percent time outside of range for energy metabolism (glucose <0.7 mmol/L and lactate:pyruvate ratio > 40), glutamate (marker of cerebral ischemia), and glycerol (marker of cell membrane degradation) parameters (48 hours).

Based upon prior literature, the prespecified criteria for determing feasibility include the following: 1) no more than 6 patients (25%) experiencing severe hypoglycemia (<40 mg/dL); 2) at least 18 patients (75%) achieving the plasma glucose goal (110-180 mg/dL); 3) no more than 6 patients (25%) experiencing nausea leading to exenatide discontinuation. These criteria will be utilized to determine whether a future efficacy trial will be pursued.

11. Sample size and justification: A sample size was determined using prior exenatide in critically ill patients studies and patient screening information at our site. Based upon this data, we determined to enroll 24 patients who complete 48 hours of exenatide infusion and continuous glucose monitoring. In eligible patients, cerebral microdialysis monitoring will also be performed. It is estimated based on proposed eligibility criteria that 24% (n = 200) patients admitted to the NSICU will be eligible for enrollment annually. With an approximate rate of enrollment at 15 – 20%, we are confident we could enroll 30 – 40 subjects annually.

12. Data analysis plan: Prior to analysis, data will be examined for errors, outliers, and asymmetry. When appropriate, transformations will be used to reduce asymmetry. An intent-to-treat analysis (defined as all individuals consented in the study) will be utilized. Descriptive statistics will be performed. Data will be expressed as means ± standard error (SE) or success rates and corresponding 95%CI for continuous and

dichotomous outcomes, respectively. Analyses will be completed using the statistical software package SAS, version 9.2 (SAS institute, Cary, North Carolina).

13. Ethical consideration: The consent procedures will be reviewed and approved by the Institutional Review Board. All subjects will provide written informed consent via proxy. The informed consent process will allow the proxy to gain an in-depth knowledge of the study purposes and procedures and allow them to make informed decisions about willingness to proceed. Participation is voluntary. The proxy will be encouraged to ask questions and will be assessed for adequate understanding.

Exenatide required: yes

Placebo required: no

Clinical study duration of treatment: Subjects will be exposed to exenatide treatment for 48 hours.

Clinical study dosing schedule and frequency: exenatide 50 ng/min for 30 minutes, start exenatide infusion 25 ng/min x 48 hours

Clinical study number of sites: one

Clinical study expected number of subjects screened: It is estimated based on proposed eligibility criteria that 24% (n = 200) patients admitted to the NSICU will be eligible for enrollment annually with an approximate rate of enrollment at 15-20%.

Clinical study expected number of subjects enrolled: 24

Clinical study expected number of subjects to complete study: 24

Planned Study Start Date: January 1, 2015

Planned Study End Date: June 30, 2016

Literature Cited

1. Godoy DA, Pinero GR, Svampa S, Papa F, Di Napoli M. Hyperglycemia and short-term outcome in patients with spontaneous intracerebral hemorrhage. *Neurocrit Care.* 2008;9(2):217-229.
2. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. *J Trauma.* Jan 2005;58(1):47-50.
3. Kimura K, Iguchi Y, Inoue T, et al. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage. *J Neurol Sci.* Apr 15 2007;255(1-2):90-94.
4. Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg.* Oct 1991;75(4):545-551.
5. Lanzino G, Kassell NF, Germanson T, Truskowski L, Alves W. Plasma glucose levels and outcome after aneurysmal subarachnoid hemorrhage. *J Neurosurg.* Dec 1993;79(6):885-891.
6. Liu-DeRyke X, Collingridge DS, Orme J, Roller D, Zurasky J, Rhoney DH. Clinical impact of early hyperglycemia during acute phase of traumatic brain injury. *Neurocritical care.* 2009;11(2):151-157.

7. Passero S, Ciacci G, Ulivelli M. The influence of diabetes and hyperglycemia on clinical course after intracerebral hemorrhage. *Neurology.* Nov 25 2003;61(10):1351-1356.
8. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery.* Feb 2000;46(2):335-342; discussion 342-333.
9. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ.* May 3 1997;314(7090):1303-1306.
10. Williams LS, Rotich J, Qi R, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology.* Jul 9 2002;59(1):67-71.
11. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol.* Jul 1995;26(1):57-65.
12. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* Nov 8 2001;345(19):1359-1367.
13. Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation.* May 25 1999;99(20):2626-2632.
14. Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA.* Jan 27 2010;303(4):341-348.
15. Arabi YM, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med.* Dec 2008;36(12):3190-3197.
16. Azevedo JR, Lima ER, Cossetti RJ, Azevedo RP. Intensive insulin therapy versus conventional glycemic control in patients with acute neurological injury: a prospective controlled trial. *Arq Neuropsiquiatr.* Sep 2007;65(3B):733-738.
17. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med.* Jan 10 2008;358(2):125-139.
18. Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care.* Apr 2006;29(4):765-770.
19. De La Rosa Gdel C, Donado JH, Restrepo AH, et al. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care.* 2008;12(5):R120.
20. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* Mar 26 2009;360(13):1283-1297.
21. Johnston KC, Hall CE, Kissela BM, Bleck TP, Conaway MR. Glucose Regulation in Acute Stroke Patients (GRASP) trial: a randomized pilot trial. *Stroke.* Dec 2009;40(12):3804-3809.
22. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med.* Oct 2009;35(10):1738-1748.
23. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* Feb 2 2006;354(5):449-461.
24. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA.* Aug 27 2008;300(8):933-944.

25. Egi M, Bellomo R, Stachowski E, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clinic proceedings. Mayo Clinic.* Mar 2010;85(3):217-224.
26. Hermanides J, Bosman RJ, Vriesendorp TM, et al. Hypoglycemia is associated with intensive care unit mortality. *Crit Care Med.* Jun 2010;38(6):1430-1434.
27. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med.* Oct 2007;35(10):2262-2267.
28. Kosiborod M, Inzucchi SE, Goyal A, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA.* Apr 15 2009;301(15):1556-1564.
29. Bilotta F, Caramia R, Cernak I, et al. Intensive insulin therapy after severe traumatic brain injury: a randomized clinical trial. *Neurocrit Care.* 2008;9(2):159-166.
30. Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. *Anesthesiology.* Mar 2009;110(3):611-619.
31. Bilotta F, Spinelli A, Giovannini F, Doronzio A, Delfini R, Rosa G. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. *J Neurosurg Anesthesiol.* Jul 2007;19(3):156-160.
32. Vespa P, Boonyaputthikul R, McArthur DL, et al. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. *Crit Care Med.* Mar 2006;34(3):850-856.
33. Dossett LA, Cao H, Mowery NT, Dortch MJ, Morris JM, Jr., May AK. Blood glucose variability is associated with mortality in the surgical intensive care unit. *Am Surg.* Aug 2008;74(8):679-685; discussion 685.
34. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology.* Aug 2006;105(2):244-252.
35. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. *Crit Care Med.* Mar 2010;38(3):838-842.
36. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med.* Nov 2008;36(11):3008-3013.
37. Krinsley JS. Glycemic variability in critical illness and the end of Chapter 1. *Crit Care Med.* Apr 2010;38(4):1206-1208.
38. Lundelin K, Vigil L, Bua S, Gomez-Mestre I, Honrubia T, Varela M. Differences in complexity of glycemic profile in survivors and nonsurvivors in an intensive care unit: a pilot study. *Crit Care Med.* Mar 2010;38(3):849-854.
39. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Crit Care Med.* Apr 2010;38(4):1021-1029.
40. Pidcoke HF, Wanek SM, Rohleder LS, Holcomb JB, Wolf SE, Wade CE. Glucose variability is associated with high mortality after severe burn. *J Trauma.* Nov 2009;67(5):990-995.
41. Waeschle RM, Moerer O, Hilgers R, Herrmann P, Neumann P, Quintel M. The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. *Crit Care.* 2008;12(5):R129.
42. Freyburger G MG, Labrouche S, Sztark F. Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: Two observational studies in patients undergoing total hip or total knee replacement. *Thrombosis research.* 2011;127:457-465.
43. Drucker DJ. Glucagon-like peptides. *Diabetes.* Feb 1998;47(2):159-169.

44. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest.* Feb 1 1998;101(3):515-520.
45. Larsson H, Holst JJ, Ahren B. Glucagon-like peptide-1 reduces hepatic glucose production indirectly through insulin and glucagon in humans. *Acta Physiol Scand.* Aug 1997;160(4):413-422.
46. Nauck MA, Wollschlager D, Werner J, et al. Effects of subcutaneous glucagon-like peptide 1 (GLP-1 [7-36 amide]) in patients with NIDDM. *Diabetologia.* Dec 1996;39(12):1546-1553.
47. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. *Diabetes.* Sep 1995;44(9):1126-1131.
48. Daly SC, Chemmanam T, Loh P, et al. Exenatide in acute ischemic stroke. *Stroke.* 2013;8:E44.
49. Crow JR, Hall-Zimmerman LG, Parker D, Rhoney DH. Glucose Control and Clinical Outcome in Patients with Intracerebral Hemorrhage. Crit Care Med 2008; 36 (Suppl):A129.
50. Marcoux J, McArthur DA, Miller C, et al. Persistent metabolic crisis as measured by elevated cerebral microdialysis lactate-pyruvate ratio predicts chronic frontal lobe brain atrophy after traumatic brain injury. *Crit Care Med.* Oct 2008;36(10):2871-2877.
51. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. *Crit Care Med.* Mar 2010;38(3):838-842.
52. Meynaar IA, Eslami S, Abu-Hanna A, van der Voort P, de Lange DW, de Keizer N. Blood glucose amplitude variability as predictor for mortality in surgical and medical intensive care unit patients: a multicenter cohort study. *J Crit Care* 2012;27:119-24.
53. Cueni-Villoz N, Devigili A, Delodder F, et al. Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest. *Crit Care Med.* Oct 2011;39(10):2225-2231.
54. Ali NA, O'Brien JM, Jr., Dungan K, et al. Glucose variability and mortality in patients with sepsis. *Critical care medicine.* Aug 2008;36(8):2316-2321.
55. Matsushima K, Peng M, Velasco C, Schaefer E, Diaz-Arrastia R, Frankel H. Glucose variability negatively impacts long-term functional outcome in patients with traumatic brain injury. *J Critical care.* Apr 2012;27(2):125-131.
56. Kurtz P, Schmidt JM, Claassen J, Helbok R, Hanafi K, Fernandez L, Presciutti M, Ostapkovich ND, Stuart RM, Connolly ES, Lee K, Badjatia N, Mayer SA. Serum glucose variability and brain-serum glucose ratio predict metabolic distress and mortality after severe brain injury. *Crit Care* 2009, 13(Suppl 3):P50.56. C. B. Impact on outcome of the high variability of glycemia in patients with traumatic brain injury. *American Society of Anesthesiologists Annual Meeting.* 2010:A1567.
57. Liu-DeRyke X, Collingridge D, Crow J, Rhoney DH. Significance of glucose variability following acute intracrebral hemorrhage. Proceeding from 2009 Neurocritical Care Society Annual Meeting.
58. Meier JJ, Weyhe D, Michaely M, et al. Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. *Crit Care Med.* Mar 2004;32(3):848-851.
59. Mussig K, Oncu A, Lindauer P, et al. Effects of intravenous glucagon-like peptide-1 on glucose control and hemodynamics after coronary artery bypass surgery in patients with type 2 diabetes. *Am J Cardiol* 2008;102:646-7.
60. Sokos GG, Bolukoglu H, German J, et al. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. *Am J Cardiol.* 2007;100(5):824-829.61.
61. Deane AM, Chapman MJ, Fraser RJ, Burgstad CM, Besanko LK, Horowitz M. The effect of exogenous glucagon-like peptide-1 on the glycaemic response to small intestinal nutrient in the critically ill: a randomised double-blind placebo-controlled cross over study. *Crit Care.* 2009;13(3):R67.

62. Deane AM, Chapman MJ, Fraser RJ, et al. Effects of exogenous glucagon-like peptide-1 on gastric emptying and glucose absorption in the critically ill: relationship to glycemia. *Crit Care Med.* May 2010;38(5):1261-1269.
63. Schuster KM, Barre K, Inzucchi SE, Udelsman R, Davis KA. Continuous glucose monitoring in the surgical intensive care unit: concordance with capillary glucose. *J Trauma Acute Care Surg* 2014;76:798-803.
64. Holzinger U, Warszawska J, Kitzberger R, et al. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. *Diabetes Care.* Mar 2010;33(3):467-472.
65. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PG, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. *Intensive Care Med.* Aug 2009;35(8):1383-1389.
66. Udy AA, Baptista JP, Lim NL, et al. Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Crit Care Med 2014;42:520-7.
67. Udy AA, Boots R, Senthuran S, et al. Augmented creatinine clearance in traumatic brain injury. Anesth Analg 2010;111:1505-10.
68. Cook AG, M; Parli, S; Arora S. Pharmacokinetics of aminoglycosides and vancomycin in patients with subarachnoid hemorrhage. Neurocritical Care Society Annual Meeting. Philadelphia, PA 2013.
69. Morbitzer KA, Jordan JD, Durr EA, Rhoney DH. Vancomycin pharmacokinetic parameters in patients with acute brain injury undergoing controlled normothermia. Submitted to Neurocritical Care Society Annual Meeting 2014.
70. Choi IY, Seaquist ER, Gruetter R. Effect of hypoglycemia on brain glycogen metabolism in vivo. *J Neurosci Res.* Apr 1 2003;72(1):25-32.
71. Helbok R, Schmidt JM, Kurtz P, et al. Systemic glucose and brain energy metabolism after subarachnoid hemorrhage. *Neurocrit Care.* Jun 2010;12(3):317-323.
72. Vespa PM, McArthur D, O'Phelan K, et al. Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study. *J Cereb Blood Flow Metab.* Jul 2003;23(7):865-877.
73. Gray CS, Hildreth AJ, Sandercock PA, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol.* May 2007;6(5):397-406.
74. McCormick M, Hadley D, McLean JR, Macfarlane JA, Condon B, Muir KW. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol.* May 2010;67(5):570-578.
75. Bruno A, Kent TA, Coull BM, et al. Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. *Stroke.* Feb 2008;39(2):384-389.
76. Naidech AM, Levasseur K, Liebling S, et al. Moderate Hypoglycemia is associated with vasospasm, cerebral infarction, and 3-month disability after subarachnoid hemorrhage. *Neurocrit Care.* Apr 2010;12(2):181-187.
77. Vespa P, Bergsneider M, Hattori N, et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab.* Jun 2005;25(6):763-774.
78. Hillered L, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. *J Neurotrauma.* Jan 2005;22(1):3-41.
79. Bellander BM, Cantais E, Enblad P, et al. Consensus meeting on microdialysis in neurointensive care. *Intensive Care Med.* Dec 2004;30(12):2166-2169.

80. Abi-Saab WM, Maggs DG, Jones T, et al. Striking differences in glucose and lactate levels between brain extracellular fluid and plasma in conscious human subjects: effects of hyperglycemia and hypoglycemia. *J Cereb Blood Flow Metab.* Mar 2002;22(3):271-279.
81. Zazulia AR, Videen TO, Powers WJ. Transient focal increase in perihematomal glucose metabolism after acute human intracerebral hemorrhage. *Stroke.* May 2009;40(5):1638-1643.
82. Hlatky R, Valadka AB, Goodman JC, Contant CF, Robertson CS. Patterns of energy substrates during ischemia measured in the brain by microdialysis. *J Neurotrauma.* Jul 2004;21(7):894-906.
83. Schulz MK, Wang LP, Tange M, Bjerre P. Cerebral microdialysis monitoring: determination of normal and ischemic cerebral metabolisms in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg.* Nov 2000;93(5):808-814.
84. Sarrafzadeh A, Haux D, Kuchler I, Lanksch WR, Unterberg AW. Poor-grade aneurysmal subarachnoid hemorrhage: relationship of cerebral metabolism to outcome. *J Neurosurg.* Mar 2004;100(3):400-406.