AAST multi-center prospective, observational study on immune dysfunction in subjects who present with traumatic brain injury and receive beta adrenergic receptor blockers.

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Title	AAST multi-center prospective, observational study on immune dysfunction in subjects who present with traumatic brain injury and receive beta adrenergic receptor blockers.
Short Title	Early beta blockers after traumatic brain injury improve immune dysfunction
Protocol Number	Institutionally dependent
Methodology	Prospective, observational
Study Duration	Upon enrollment, study will last during the length of the hospitalization or 30 days, whichever is shorter.
Study Center(s)	Multi-Center
Objectives	To determine the effect of early propranolol treatment on immune dysfunction in subjects who present with traumatic brain injury.
Number of Subjects	Institutionally dependent
Diagnosis and Main Inclusion Criteria	Inclusion criteria include patients' ages 18 to 100 years who present after blunt trauma with evidence of brain injury on CT and require ICU admission.
Study Product, Dose, Route, Regimen	Data and outcomes will be observational and involve no therapeutic interventions or alterations from standard patient care.
Duration of administration	Data and outcomes will be observational and involve no therapeutic interventions or alterations from standard patient care.
Reference therapy	Standard Therapy
Statistical Methodology	Prospective, observational

Study Summary

This prospective, multi-center observational study will collect data on blunt trauma patients who present with CT evidence of brain injury to determine how early beta blocker affect mortality and immune dysfunction. Institutions and providers will conduct standard patient management without interference from this study. Data and outcomes are observational and involve no therapeutic interventions or alterations from standard patient care. Beta blockers, if provided, will be at the discretion of the physicians at the enrolling institution. We hypothesize that patients who receive early beta blockers after TBI will have improved outcomes and that propranolol will be superior to other available beta blockers.

Significance

Advances in health care offer trauma patients life-saving medical and surgical therapies, but limited pharmacologic options for head injury continue to contribute to treatment challenges. Thus far, therapeutics aimed at inhibiting patient deterioration after brain injuryhave made little impact in clinical practice. More than 21 multi-center clinical trials, designed to assess the value of various treatments for TBI, have been conducted since 1985 and none demonstrate a convincing benefit for TBI directed-therapy.

Several retrospective trauma database analyses demonstrate decreased mortality when patients who presented with TBI were treated with beta adrenergic receptor blockers. One study on patients with moderate to severe TBI identified β-blocker after admission was associated with reduced mortality (adjusted odds ratio: 0.54; 95% CI, 0.33 to 0.91; p<0.01). Another study demonstrated beta blocker therapy was associated with a significant survival advantage in moderate to severe TBI patients with elevated cardiac troponins (OR: 0.38; p = 0.03). When the type of beta blocker was compared, lowest mortality was observed in TBI patients who received propranolol. In sum, retrospective data demonstrates reduced morbidity and mortality when TBI patients receive beta blockers and the use of propranolol appears to be superior to other beta blockers.

Animal models of TBI offer mechanistic explanations of brain injury pathophysiology as well as potential pharmacologic options. A murine TBI model with microPET imaging demonstrated increased cerebral perfusion with beta adrenergic blockade suggesting that beta blockers reduce brain inflammation after injury. Related immunohistochemistry demonstrated significant improvement in mean cerebral perfusions and reduction in hypoxia. Brain infarct areas are reduced and neurological outcome improved in both mice lacking the beta adrenergic receptor and in wild type mice pretreated with a beta adrenergic antagonist. In a rat model of brain injury Il6, a key marker of the TBI related immune response, are increased in the CSF; beta adrenergic blockade reduced levels of Il6. Among TBI immune marker IL6 has the highest specificity and the most powerful predictive value of outcome. Therefore, preclinical data suggests that beta adrenergic receptor inhibition alters the immune response after TBI leading to reduced CNS immune dysfunction.

Most recently, early intravenous propranolol administration to severely injured trauma patients improved bone marrow dysfunction. This data indicates that a reduction in precursor cell inflammatory response may improve immune function after major trauma. Taken together, preclinical and clinical data indicate that beta blockers after TBI may improve immune function, reduce related complications and increase survival.

Hypothesis

We hypothesize that patients who receive early beta blockers after TBI will have improved outcomes. We further hypothesize that propranolol, a nonselective, beta-adrenergic receptor-blocking agent, will be superior among available beta blockers.

Specific aims

The study's specific aims are:
1. To determine the occurrence of pneumonia, sepsis, and mortality in TBI patients
2. To determine ICU and hospital length of stay in TBI patients
3. To determine if variations in specific beta blockers impact rates of pneumonia, sepsis and mortality
4. To determine if variations in specific beta blockers impact ICU and hospital length of stay
4. To determine if beta blockers in combination with other medical therapeutics including vitamin C alter pneumonia, sepsis and mortality

Study design

This is a prospective multi-center observational study of blunt trauma patients who present with CT evidence of brain injury and require ICU admission. Data and outcomes are observational and involve no therapeutic interventions or alterations from standard patient care. Institutions and providers will conduct normal diagnosis and management procedures without interference from this study. Beta blockers, if provided, will be at the discretion of the physicians at the enrolling institution. Beta blockers may be provided per protocol at admission, for example propranolol 1mg IV q6 hour or metoprolol 5 mg IV q6 hours. Or targeted to heart rate, such as propranolol 1 mg IV q6h, increase by 0.5mg for heart greater than 100 or esmolol IV drip titrate to heart rate 60 to 100. Beta blockers are sometimes dosed only for hypertension, for example, labetalol 10mg IV prn systolic blood pressure greater than 180mmHg. If beta blockers are continued by mouth then propranolol 40mg PO TID or metoprolol 25 mg PO TID are common choices. In general beta blockers require hold parameters for heart rate less than 60 or systolic blood pressure less than 100mHg. Dosing of beta blockers will be left up to the individual institutions and their physicians. Data will be collected whether or not the patient receives beta blockers.

Inclusion Criteria: The following criteria must be met for patients to be eligible for this study:
1) Blunt trauma patients who present with CT evidence of brain injury and require ICU admission
2) Inter-facility transfers will be eligible for inclusion if injury sustained within 12 hours of transfer
3) Age ≥18 years

Exclusion Criteria
1) Patients <18years of age
2) TBI patients who do not require ICU admission

Data collection will include*:
1) Demographics
2) Medications
3) Initial CT findings and surgical interventions
4) Outcomes such as pneumonia, UTI or DVT

*Please see data collection sheet for further details

Patient consent

This is an observational study that will not alter institutional management protocols or patient care. Enrollment in this study will pose no additional medical risk to participants. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers thus posing minimal risk of breach of confidentiality.

Data entry and Analysis

All adult patients aged 18 years and older who require ICU admission after blunt trauma for brain injury will be captured in this prospective, multicenter database. Patients must have a computed tomography (CT) scan of the brain which demonstrates injury in order to be included. If transferred from another hospital, injury must have been sustained 12 hours prior to arrival. Demographic data including age, sex, Injury Severity Score (ISS), head AIS score, Glasgow Coma Scale (GCS) score, admission systolic blood pressure (SBP), will be examined for all patients and related to beta blocker use. Our primary outcome measure will be in-hospital mortality. Secondary outcome measures will be rates on pneumonia, sepsis, and hospital length of stay. Descriptive statistics such as rates, means, standard deviations, medians and interquartile ranges (IQR) will be used to describe the basic features of the data under study. Student's t tests and its non-parametric version (e.g. Wilcoxon-Mann-Whitney test) will be used to evaluate patient-level differences according to the outcome of mortality. Similarly, Chi-square tests or Fisher's exact tests (small sample size) will be used to assess associations in categorical data and the outcome of mortality. Associations between patient-level characteristics and the outcome of mortality will ultimately be analyzed using a multivariate logistic regression model. In this confounder adjusted model factors such as age, sex, head AIS score of 4 or greater, GCS score of 8 or less, ISS of 25 or greater, admission SBP of less than 90 mm Hg, and beta blocker administration will be adjusted for whenever found to be significant (at alpha level 0.02) in the univariate analysis. Adjusted odds ratio (AORs) of mortality and 95% confidence intervals (CIs) will be calculated. A p value of 0.05 will be considered as a statistically significant finding. If we assume a mortality of 10% and power the study for a reduction by 0.2 to a mortality of 8%, a sample size of 2165 achieves 90% power to detect a difference of 0.02 using a two-sided binomial test. The target significance level is 0.0500. The actual significance level achieved by this test is 0.0488. These results assume that the population mortality rate under the null hypothesis is 10% (0.10) and the alternative rate is 8% (0.08).

Timeline

This study will be completed over a 44 month period
        1) Recruitment of centers and IRB approval 6 months
        2) Enrollment of patients 36 months
        3) Data analysis and manuscript preparation 2 months