COMparison of Postcraniotomy blood pressurE Target Effectiveness (COMPETE)

Statistical Analysis Plan

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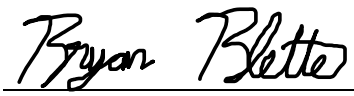

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Introduction

Over 160,000 craniotomies are performed annually in the United States. Up to 85% of patients undergoing a craniotomy may experience an acute elevation in blood pressure during emergence from anesthesia, a phenomenon known as post-craniotomy emergence hypertension (PCEH).[1]Hypertension is believed to increase the risk of postoperative intracranial hemorrhage (ICH), which is responsible for approximately one third of post-craniotomy surgical mortality.[2] This perceived risk has led to widespread practice of imposing post-operative systolic blood pressure (SBP) limits. There is limited retrospective evidence to guide the selection of an appropriate target SBP for this patient population. Although a more liberal goal (SBP<160) may theoretically increase the risk of ICH, an intensive goal (SBP<140) may pose a risk of end-organ hypoperfusion, acute kidney injury, myocardial injury, stroke, or prolonged ICU stay. In this study, we aim to address the comparative effectiveness of SBP<140mmHg or SBP<160mmHg as a perioperative SBP goal, providing high-quality, patient-centered evidence to support clinical practice.

Population and design considerations

Study Population:

This study will be performed in the Neurological Intensive Care Unit (ICU) at Vanderbilt University Medical Center. The population of this study is all adult patients undergoing a craniotomy for resection of an intradural brain tumor. The inclusion and exclusion criteria for the study are as follows:

Inclusion:

- Age ≥ 18 years old
- Undergoes craniotomy for resection of an intradural brain tumor scheduled using any of the following CPT codes:

CPT	Description
61304	Craniectomy or craniotomy, exploratory; supratentorial
61305	Craniectomy or craniotomy, exploratory; infratentorial (posterior fossa)
61330	Decompression of orbit only, transcranial approach
61333	Exploration of orbit (transcranial approach); with removal of lesion
61510	Craniectomy, trephination, bone flap craniotomy; for excision of brain tumor, supratentorial, except meningioma
61512	Craniectomy, trephination, bone flap craniotomy; for excision of meningioma, supratentorial
61516	Craniectomy, trephination, bone flap craniotomy; for excision or fenestration of cyst, supratentorial
61518	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; except meningioma, cerebellopontine angle tumor, or midline tumor at base of skull
61519	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; meningioma
61520	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; cerebellopontine angle tumor

61521	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; midline tumor at base of skull
61524	Craniectomy, infratentorial or posterior fossa; for excision or fenestration of cyst
61526	Craniectomy, bone flap craniotomy, transtemporal (mastoid) for excision of cerebellopontine angle tumor
61530	Craniectomy, bone flap craniotomy, transtemporal (mastoid) for excision of cerebellopontine angle tumor tumor; combined with middle/posterior fossa craniotomy/craniectomy
61545	Craniotomy with elevation of bone flap; for excision of craniopharyngioma
61546	Craniotomy for hypophysectomy or excision of pituitary tumor, intracranial approach
61580	Craniofacial approach to anterior cranial fossa; extradural, including lateral rhinotomy, ethmoidectomy, sphenoidectomy, without maxillectomy or orbital exenteration
61581	Craniofacial approach to anterior cranial fossa; extradural, including lateral rhinotomy, orbital exenteration, ethmoidectomy, sphenoidectomy and/or maxillectomy
61582	Craniofacial approach to anterior cranial fossa; extradural, including unilateral or bifrontal craniotomy, elevation of frontal lobe(s), osteotomy of base of anterior cranial fossa
61583	Craniofacial approach to anterior cranial fossa; intradural, including unilateral or bifrontal craniotomy, elevation or resection of frontal lobe, osteotomy of base of anterior cranial fossa
61584	Orbitocranial approach to anterior cranial fossa, extradural, including supraorbital ridge osteotomy and elevation of frontal and/or temporal lobe(s); without orbital exenteration
61585	Orbitocranial approach to anterior cranial fossa, extradural, including supraorbital ridge osteotomy and elevation of frontal and/or temporal lobe(s); with orbital exenteration
61586	Bicoronal, transzygomatic and/or LeFort I osteotomy approach to anterior cranial fossa with or without internal fixation, without bone graft
61590	Infratemporal pre-auricular approach to middle cranial fossa (parapharyngeal space, infratemporal and midline skull base, nasopharynx), with or without disarticulation of the mandible, including parotidectomy, craniotomy, decompression and/or mobilization of the facial nerve and/or petrous carotid artery
61591	Infratemporal post-auricular approach to middle cranial fossa (internal auditory meatus, petrous apex, tentorium, cavernous sinus, parasellar area, infratemporal fossa) including mastoidectomy, resection of sigmoid sinus, with or without decompression and/or mobilization of contents of auditory canal or petrous carotid artery
61592	Orbitocranial zygomatic approach to middle cranial fossa (cavernous sinus and carotid artery, clivus, basilar artery or petrous apex) including osteotomy of zygoma, craniotomy, extra- or intradural elevation of temporal lobe

61595	Transtemporal approach to posterior cranial fossa, jugular foramen or midline skull base, including mastoidectomy, decompression of sigmoid sinus and/or facial nerve, with or without mobilization
61596	Transcochlear approach to posterior cranial fossa, jugular foramen or midline skull base, including labyrinthectomy, decompression, with or without mobilization of facial nerve and/or petrous carotid artery
61597	Transcondylar (far lateral) approach to posterior cranial fossa, jugular foramen or midline skull base, including occipital condylectomy, mastoidectomy, resection of C1-C3 vertebral body(s), decompression of vertebral artery, with or without mobilization
61598	Transpetrosal approach to posterior cranial fossa, clivus or foramen magnum, including ligation of superior petrosal sinus and/or sigmoid sinus
61600	Resection or excision of neoplastic, vascular or infectious lesion of base of anterior cranial fossa; extradural
61601	Resection or excision of neoplastic, vascular or infectious lesion of base of anterior cranial fossa; intradural, including dural repair, with or without graft
61605	Resection or excision of neoplastic, vascular or infectious lesion of infratemporal fossa, parapharyngeal space, petrous apex; extradural
61606	Resection or excision of neoplastic, vascular or infectious lesion of infratemporal fossa, parapharyngeal space, petrous apex; intradural, including dural repair, with or without graft
61607	Resection or excision of neoplastic, vascular or infectious lesion of parasellar area, cavernous sinus, clivus or midline skull base; extradural
61608	Resection or excision of neoplastic, vascular or infectious lesion of parasellar area, cavernous sinus, clivus or midline skull base; intradural, including dural repair, with or without graft
61615	Resection or excision of neoplastic, vascular or infectious lesion of base of posterior cranial fossa, jugular foramen, foramen magnum, or C1-C3 vertebral bodies; extradural
61616	Resection or excision of neoplastic, vascular or infectious lesion of base of posterior cranial fossa, jugular foramen, foramen magnum, or C1-C3 vertebral bodies; intradural, including dural repair, with or without graft

Exclusion:

- Declines to consent
- Attending decisions based on intraoperative findings leading to lack of clinical equipoise
- Patient is a prisoner
- Patient is known to be pregnant

Study Design:

This study is a pragmatic, single center, randomized, comparative effectiveness trial comparing clinical outcomes of imposing a target SBP <140 mmHg versus a target SBP <160 mmHg over the first 24 hours following craniotomy for resection of an intradural brain tumor.

Randomization:

Randomization of this population will be performed at a 1:1 ratio on the level of the individual patient. A secondary endpoint of interest in this study is Neurological ICU length of stay, which is heavily influenced by the end time of a patient's surgical procedure. In an effort to ensure that this variable is equally distributed between the two study arms, randomization will be stratified into two groups by time of postoperative order entry. The two groups are defined as those with postoperative orders entered prior to 3:00pm and those with postoperative orders entered after 3:00pm, based on baseline data reporting the distribution of postoperative order entry for eligible craniotomies performed at VUMC.

Sample Size Considerations:
To approximate necessary sample size, we consider outcome data captured previously from a similar patient population at VUMC. Because VUMC currently uses a SBP<140 mmHg perioperative goal, we will assume this data is reflective of the treatment arm which will be assigned to this strategy. Using a Mann-Whitney Test comparing untransformed length of stay across the trial arms and a simulation based on resampling of prior data, we calculated that enrolling 250 patients per arm, for a total sample size of 500 patients, would give 80% power to detect a ~16% decrease in hospital length of stay.

This study will be executed in two stages, outlined as follows. Stage 1 will evaluate the fidelity measurements (patient blood pressure values for the first 24 hours post-craniotomy, and antihypertensive use (nicardipine, hydralazine, or labetalol) in the first 24 hours post-craniotomy) for an anticipated 10% of the total sample size (50 patients). This initial stage is designed to determine feasibility and separation between groups. Group separation in antihypertensive use is defined as the difference in proportions of patients receiving antihypertensives by arm, from ICU admission to the earlier of ICU discharge or 24 hours after ICU admission. Group separation in blood pressure values is defined as the absolute difference between arms in mean SBP from ICU admission to the earlier of ICU discharge or 24 hours after ICU admission (contrasting means within study arms of the mean SBPs of individuals within each arm). Additional versions of the fidelity endpoints will be reported as outlined in **Endpoints** below. The following separations between groups, during Stage 1, would then determine trial progression to Stage 2.

Difference in mean SBP*	Proportion of patients receiving antihypertensives**	Conclusion
>10mmHg	>20%	Study continues
>10mmHg	<20% and >10%	Study continues
>10mmHg	<10%	Study continues
<10mmHg and >5mmHg	>20%	Study continues
<10mmHg and >5mmHg	<20% and >10%	Study continues
<10mmHg and >5mmHg	**<10%**	**Study does not continue**
<5mmHg	>20%	Study continues
<5mmHg	**<20% and >10%**	**Study does not continue**
<5mmHg	**<10%**	**Study does not continue**

*Absolute difference in mean SBP from ICU admission to the earlier of ICU discharge or 24 hours after ICU admission.
**Absolute difference in proportion of patients receiving antihypertensive therapy from ICU admission to the earlier of ICU discharge or 24 hours after ICU admission.

We are explicitly examining the separation between groups for the fidelity measurements at Stage 1 and have outlined the trial progression scenarios. It is anticipated that all patients will have the same data collected and will be included in the analyses for the primary, secondary, and exploratory outcomes.

Interventions
Patients in each arm will undergo regular and frequent blood pressure measurements, using an arterial line (placed during surgery), or a non-invasive blood pressure (NIBP) measurement if the patient does not have a functional arterial line.

Arm 1: SBP Target < 160 mmHg

The neuro-intensive care team will monitor the patient's SBP and treat with antihypertensive medications to achieve an SBP<160mHg. Selection of the appropriate PO or IV medication is at the discretion of the neuro-ICU team; most frequently used agents include nicardipine, labetalol, and hydralazine. Selection of the appropriate agent is based on other clinical elements including severity of hypertension, heart rate, patients' home medication regimens, and any medication interactions or allergies. The blood pressure goal will be continued throughout the hospitalization. The arterial line will be removed at the discretion of the neurosurgery team, typically on the morning of the first day after surgery.

Arm 2: SBP Target < 140 mmHg

The neuro-intensive care team will monitor the patient's SBP and treat with antihypertensive medications to achieve an SBP<140mHg. Selection of the appropriate PO or IV medication is at the discretion of the neuro-ICU team, as described above for Arm 1. The blood pressure goal will be maintained until the neurosurgery team chooses to 'liberalize' the blood pressure goal to higher SBP levels. The arterial line will be removed when the blood pressure goal is liberalized, typically on the morning of the first day after surgery.

Endpoints
Primary Endpoint

- Hospital length of stay, from enrollment to discharge (days), with mortality equals longest observed length of stay plus 1 day

Secondary Endpoint(s)

- ICU length of stay, from enrollment to transfer from the ICU (hours)
- Intracranial hemorrhage requiring return to the operating room within 7 days following surgery
- Routinely collected Patient Reported Outcome Measure (PROMIS10, FACT-Br) at post-operative neurosurgery clinic follow-up visit(s) between enrollment and 90 days following enrollment
- Composite of adverse events potentially related to antihypertensive use through duration of hospital stay

- Inpatient mortality
- AKI (serum creatinine increase ≥ 0.3 mg/dL or 1.5x max value over 48 hour time period while in hospital)
- BNP elevation (>900 pg/mL) ever during index hospitalization
- Myocardial infarction (>14 ng/l troponin T for female patients and >22 ng/l troponin T for male patients using high-sensitivity troponin assay, or >0.029 ng/mL troponin T OR >0.045 ng/mL troponin I using standard troponin assay) – ever during index hospitalization

Exploratory Endpoint(s)

- Mannitol use during hospital stay
- Hypertonic saline use during hospital stay

Fidelity Endpoint

- Patient blood pressure values for the first 24 hours post-craniotomy
  - Highest SBP value in first 24 hours
  - Number of SBP values above target threshold during the first 24 hours
  - Area under the curve of SBP values
- Antihypertensive use (nicardipine, hydralazine, or labetalol) in the first 24 hours post-craniotomy
  - Proportion of patients receiving antihypertensives in the first 24 hours
  - Total dose of nicardipine over first 24 hours (total dose of all antihypertensives will be reported but not used as a fidelity endpoint)

Estimands and Analysis Framework

We will target treatment-policy estimands using an intent-to-treat approach to answer the effectiveness question posed. That is, participants will be evaluated by treatment group as assigned regardless of what was delivered. All eligible participants will be included.

Statistical Approach

Descriptive Analysis

To characterize the study sample, baseline demographic and clinical data will be described overall and by study arm. Categorical variables will be described using frequencies and proportions, and continuous variables will be described using medians and interquartile ranges. Missingness will be reported for each variable. Graphical summaries using box plots, violin plots, and/or histograms may be used to describe the data graphically. At a minimum, the following variables will be described at time of enrollment:

- Age (years)
- Sex (male, female, unknown)
- Race (African American, Asian/Pacific Islander, Caucasian, Multiple, Native American, Other, Unknown)
- Ethnicity (Hispanic, Non-Hispanic, Unknown)
- Patient comorbidities
  - Hypertension (Yes/No)

    - Coagulopathy (Yes/No)
    - Renal failure (Yes/No)
- At home medications
    - Home anti-hypertensive medications
    - Home anticoagulant medications
    - Home antiplatelet medications

Main Analysis
We will describe all the outcome variables overall and grouped by study arm using the same approach as for the demographic data. Summary statistics and graphical representations may be displayed, and missingness will be reported for each variable.

The primary analysis will be a Mann-Whitney U Test comparing the hospital length of stay across arms. This test is robust to potential right-skew in the primary outcome and will be reported alongside a probabilistic index and 95% bootstrap confidence interval. To enhance interpretability, supplementary analyses will consider a t-test and corresponding difference in average length of stay across arms, as well as an ordinal regression model which adjusts for the baseline covariates age, sex, composite race/ethnicity, hypertension, coagulopathy, renal failure, at-home medications, and the stratification factor used during randomization. The model will be assessed using a P-residual plot. The adjusted odds ratio will be reported with a 95% confidence interval. G-computation will then be used to further estimate the marginal mean difference and ratio of means in hospital length of stay across study arms. All treatment effect estimates will be reported with 95% confidence intervals and p-values under a null hypothesis of no difference between the two arms. All analyses will be performed in R version 4.4 or later.

Secondary and Exploratory Outcome Analysis
ICU length of stay will be analyzed in the same manner as the primary outcome but may be measured and reported using hours or a continuous time scale. Intracranial hemorrhage requiring return to the operating room will be treated as a binary outcome and assessed using logistic regression (reporting the adjusted odds ratio). The composite of adverse events potentially related to antihypertensive use defined earlier will be analyzed similarly; the components of the composite will be reported across arms descriptively. PROMIS-10 and FACT-BR for survivors will be analyzed using t-tests and adjusted linear regressions for outcomes measured at 2-3 weeks and 90 days post-baseline. Baseline values will be adjusted for when available. The two time points will be analyzed separately; we do not expect a high enough rate of completers to perform longitudinal models. As the anticipated mortality rate is low, these analyses will be performed in a survivors-only framework. Sensitivity analyses will consider whether effects change under potential informative missingness (i.e., inability to complete score questions due to functional impairment) and an additional sensitivity analysis will repeat the tests and models in only the patients with available baseline measurements. Mannitol and hypertonic saline use during hospital stay will be analyzed using adjusted logistic regression. All model results will be summarized with point estimates and 95% confidence intervals (CIs), which will be emphasized over p-values when reporting the results for secondary and implementation outcomes. No adjustments for multiplicity will be made. The adjustment set of covariates may be model-specific if certain covariates are more or less relevant for particular outcomes.

Missing Data

In our study design, we do not expect missingness in our primary outcome. If there are individual with missing covariates, these individuals will not be excluded from adjusted models; we will use multiple imputation with predictive mean matching to account for missingness under a missing at random assumption, conditional on other available covariates. Prevalence of missingness for each key variable will be reported as described in the descriptive analysis plan.

Heterogeneity of Treatment Effect

To determine whether effects of treatment on the primary endpoint depends on any of the baseline characteristics, we will test the interaction between the baseline characteristics and treatment effect in the ordinal regression model. The prespecified potential interacting factors are as follows:

- Age
- Sex
- Prior hypertension
- Prior coagulopathy
- Prior renal failure

Any non-specified interactions that are explored (including any explored for secondary outcomes) will be reported as post-hoc. Differential treatment effects will be reported using a forest plot of subgroup effects as well as interaction odds ratios, both with relevant 95% confidence intervals.