The Intra-arterial Vasospasm Trial - A Multi-center Randomized Study

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- A Multicenter Randomized Study

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1. SYNOPSIS

Study Title: The Intra-arterial Vasospasm Trial - A Multicenter Randomized Study

Objectives: The primary objective of the study is to determine the optimal intra-arterial drug treatment regimen for arterial lumen restoration after cerebral vasospasm following aneurysmal subarachnoid hemorrhage.

The secondary objective is to evaluate clinical outcome 90 days after patient discharge following in-hospital optimal intra-arterial drug treatment for cerebral vasospasm.

Design: This study is a prospective multicenter randomized trial.

Outcome variables: The primary outcome measure is the post-infusion improvement ratio (PIIR) assessed 10 minutes after completion of the intra-arterial infusion. PIIR is a measure of arterial lumen diameter pre- and post-intra-arterial drug infusion in the presenting vasospasmic blood vessel.

Modified Rankin Scale (mRS) at 3 months post-hospital discharge will be recorded as a secondary outcome to assess overall clinical outcome.

Interventions: The interventions in this study are part of the routine standard of care (SOC) procedures for cerebral vasospasm treatment. Following surgical or endovascular intervention for aneurysmal subarachnoid hemorrhage (aSAH) if patients develop cerebral vasospasm refractory to maximal medical management, endovascular treatment by intra-arterial drug infusion of a single drug agent or a cocktail of drug agents will be initiated.

Study participants will be randomly assigned to one of the three treatment groups where one single drug agent or a cocktail of drug agents will be intra-arterially administered. *Group 1* will be treated with nicardipine. *Group 2* will be treated with verapamil and *Group 3* will be treated with the combination of verapamil, nitroglycerin and nicardipine. Pre- and post-infusion vasospasmic vessel diameters will be compared. The change in diameter will be quantified based on the mean percentage change. At three months post-hospital discharge, study participants will be followed up in clinic to evaluate clinical outcomes.

Duration: The total duration for study participation required is the standard hospital stay for post-aSAH vasospasm treatment and one follow-up clinic visit at 3 months following hospital discharge.

Sample Size: The study will require a maximum of 330 patients, 110 in each of the three treatment regimens. Subjects will be randomized equally into one of three treatment groups.

Population: The patient population will be hospitalized patients presenting with cerebral vasospasm post-aneurysmal subarachnoid hemorrhage.

Study time frame: The total study time frame is 24 months (18 months for enrollment + 3 months follow up and ± 3 months to accommodate any scheduling conflict and data gathering).

2. STUDY OBJECTIVES

Primary Objective: The primary objective of the study is to determine the optimal intra-arterial drug treatment regimen for arterial lumen restoration after cerebral vasospasm following aneurysmal subarachnoid hemorrhage.
We hypothesize that a cocktail of drug agents via infusion will likely improve treatment efficacy compared to single agents.

Secondary Objective: The secondary objective is to evaluate clinical outcome 90-days after patient discharge following in-hospital optimal intra-arterial drug treatment for cerebral vasospasm

3. BACKGROUND

Rationale & Supporting Data:
Cerebral vasospasm is a devastating health problem that is a major contributor to poor outcome following subarachnoid hemorrhage (SAH). The estimated case fatality following a SAH is 25-50% with a large proportion of these being secondary to the deleterious consequences of delayed cerebral vasospasm[1, 2]. Up to 70% of patients who survive the initial SAH develop signs of vasospasm, which, if untreated, can lead to devastating strokes [1,3,4]. To this date, the armamentarium available for predicting, preventing, and optimizing outcomes following severe vasospasm remains limited.

The reason for this poor result is, in part, that the complex pathogenesis of vasospasm has not been completely explicated. What is clear though is that between 3 and 21 days after SAH, severe vasoconstriction of the intracranial arteries frequently occurs, leading to delayed ischemia and commonly devastating strokes.

Despite improved microsurgical and endovascular techniques used to treat aneurysms, we have not made significant strides in treating cerebral vasospasm. The traditional therapy acutely using hypertensive hypervolemic hemodilution, which has been adopted in clinical practice, presents considerable cardiopulmonary risks. Endovascular treatments such as angioplasty and intra-arterial drug delivery, particularly of calcium channel blockers, have been considered the quintessential treatment for minimizing potential devastating ischemic stroke resulting from delayed cerebral vasospasm.

Based on the results of a recent national survey conducted by the two PI's of this study through the joint AANS/CNS cerebrovascular section, there is considerable variability in how intra-arterial of cerebral vasospasm is treated. This has led to variable outcomes.
The commonly used intra-arterial drugs for treating vasospasm are used as single agents, among them being verapamil[5], nicardipine[6, 7] and nitroglycerin. The clinical result is generally considered unsatisfactory. There has been no literature that conclusively recommends an optimal intra-arterial infusion agent or combination of agents for treating cerebral vasospasm, particularly when balloon angioplasty is not feasible for the involved arteries. The end result of treatment is thus generally unsatisfactory.

A retrospective study[8] was recently conducted in consecutive patients treated for cerebral vasospasm at The University of Texas Medical School, Memorial Hermann Hospital at the Texas Medical Center, a tertiary treatment center in Houston. Two cohorts were involved. Group 1 (N=47 patients, 116 vessels) was treated between 2008-2011 with a single agent; Group 2 (N=69 patients, 106 vessels) was treated between 2010-2013 with a cocktail of multiple agents (nitroglycerin, verapamil, nicardipine). Patient demographics, age, and modified Rankin score (mRS) at discharge and at 3 months were collected in the cerebrovascular database. Arterial luminal diameters were measured in cerebral angiograms both pre-infusion (PrID) and post-infusion (PoID). The Improvement Ratio (IR) = (PoID - PrID/PrID) x 100 was calculated and statistically compared among groups. This study results showed, Group 2 demonstrated a significantly greater improvement IR 45.8% (SD 36.6) than Group 1 IR 10.9% (SD 12.0), $P<0.001$. Multiple agent infusion resulted in an average of 34.9% greater vessel diameter improvement than single agent therapy. Comparison of the IR between different single agents within Group 1 (nicardipine and verapamil) demonstrated no difference in vessel diameter change. Patient age had no effect on efficacy in either group.
The conclusion of this study is that treatment of cerebral vasospasm with an IA cocktail of nitroglycerine, verapamil, and nicardipine provides significantly better angiographic improvement of vasospasm than does single agent therapy. (This study has been presented at the International Stroke Conference 2014, in San Diego, CA).

This encouraging result has led us to pursue this proposed prospective evaluation of the efficacy of cocktail drug agent infusion therapy versus the current standard of care single agent therapy that is used by the majority of neuro-interventionists throughout the United States.

The goal of this study is to determine the optimal intra-arterial drug treatment regimen for treating cerebral vasospasm.

Given that each of currently commonly used intra-arterial vasodilators (verapamil, nitroglycerin and nicardipine) has its own mechanisms of action despite some of them belonging to the same drug category [9], combining these medications for intra-arterial infusion potentially provides synergistic effects of cerebral vasodilation while minimizing cardiovascular instability induced by high doses of single agent treatment.
Based on single center retrospective data from the PI's center, we hypothesize that infusions of cocktail drug agents will improve treatment efficacy compared to single drug agent infusion.

Hypothesis: Intra-arterial (IA) infusion of cocktail drug agents is more efficacious than single drug agent treatment for cerebral vasospasm therapy.

4. STUDY DESIGN

This is a prospective multicenter randomized controlled clinical trial. Endovascular treatment will be initiated on hospitalized patients who present with cerebral vasospasm within 3-21 days following surgical or endovascular intervention for aneurysmal subarachnoid hemorrhage (aSAH). Endovascular treatment will consist of:

1. Diagnostic angiogram to locate the spasmic blood vessel/vessels.

2. Pharmacological cerebral angioplasty to treat presenting spasm in one or two the following arterial vessel territories (if all three territories need treatment: the patient is excluded from participation in the study)
   a. Right Carotid Artery Territory: to treat Vasospasm in R Carotid, R ACA, R MCA & its branches
   b. Left Carotid Artery Territory: to treat Vasospasm in L Carotid, L ACA, L MCA & its branches
   c. Vertebral-Basilar Territory

3. Post-treatment angiogram.

4. Balloon angioplasty may be done if vasodilators fail to produce response or show insufficient improvement.

Please refer to Appendix IV Study flow chart for the detailed study design & Flow

Randomization:

Study participants will be randomly assigned to one of three treatment groups. Randomization will be pre-determined and specific to each participating center. At each center only the Research Coordinator/Nurse will have access to the randomization pattern.

Treating physicians will not be blinded by the randomization scheme and will know the drug group assigned to the study subject ***only after the first diagnostic angiogram has been performed, when he/she confirms the need for drug treatment.***

However, the subjects enrolled in the trial will be blinded and will not know the treatment group to which they have been assigned.

TREATMENT CRITERIA

1. Symptomatic vasospasm - clinical symptoms, with or without Trans-cranial Doppler (TCD) study.

2. 50% or more stenosis seen on diagnostic angiogram in asymptomatic patients

DRUG DOSE: Patients who qualify for endovascular treatment post aSAH will be randomly assigned to one of three treatment groups:

Group 1: **Nicardipine (Cardene)**: 5 mg per circulation in 25 mL 5% Dextrose.
Infusion rate: 1.25 mL/minute over a period of 20 minutes

Group 2: **Verapamil**: 10 mg per circulation in 10 ml saline.
Infusion rate: 1 mL/minute over a period of 10 minutes.

Group 3:
Verapamil 10 mg in 10 mL saline, Infusion rate: 1 mL/minute over a period of 10 minutes + **Nitroglycerin** (200 mcg in 4 mL 5% dextrose, Infusion rate: 0.5 mL/min over 8 minutes + **Nicardipine** 5 mg in 25 mL 5% Dextrose, Infusion rate 1.25 mL/min over 20 minutes per circulation (USE DIFFERENT SYRINGES FOR EACH DRUG. DO NOT MIX DRUGS IN THE SAME SYRINGE.)

Perform post-treatment angiogram run minimally 10 minutes after completion of infusion.
Angiographic Imaging should be recorded 10 minutes after infusion.

ONLY ONE TREATMENT SESSION is permitted per day.

Drug Dosage: Maximum intra-arterial dose allowed within 24-hour period is, **nicardipine 10 mg**, **verapamil 20 mg**, **cocktail (verapamil 20 mg, nitroglycerin 400 mcg & nicardipine 10 mg)**

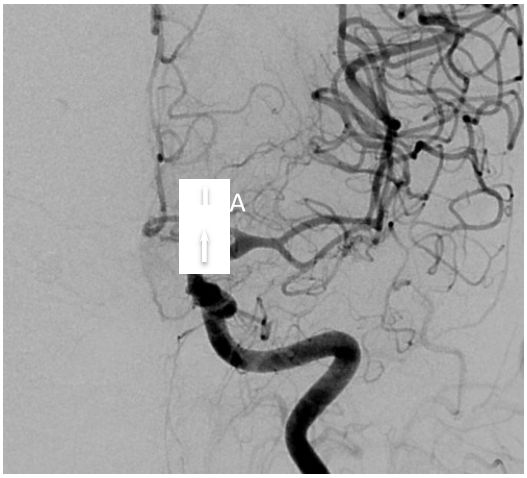
Please refer to Appendix V & VI for detailed drug dosage tabulations.

If the study subject needs another treatment after the first treatment session, use the same drug for each repeat treatment.
Additional doses can be given per the treating physician's discretion up to the maximum allowed dose as per the protocol; please record the additional doses and treatment given in the data collection forms.
Balloon angioplasty can be performed if drug infusions show insufficient improvement per the treating physician's discretion.

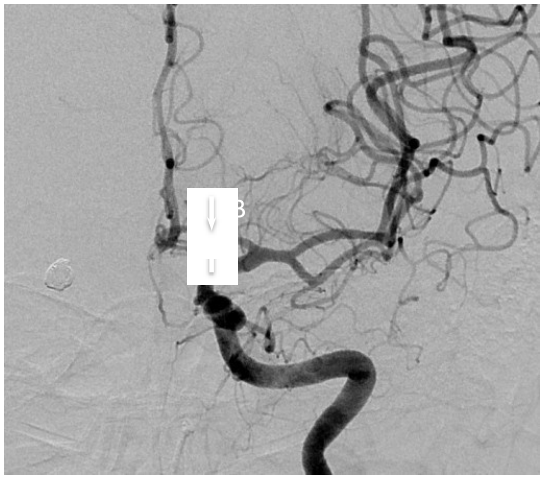
A central core laboratory will perform radiographic data assessment and assessors will be blinded to treatment group assignment.
The diameters of the same spasm vessel(s) will be compared before (pre-) and after (post-) infusion of the agent/agents, (see figure below).

The diameters will be measured at the following locations:
ICA supraclinoid segment, MCA M1, MCA M2, ACA A1, ACA A2 & Basilar

The pre-treatment diameter measurement will be at the narrowest spot as is shown in the figure below. The post-treatment diameter measurement will be at the same location as the one prior to the infusion treatment.



Pre-infusion



Post-infusion

The changes will be quantitated based on the ratio percentage as shown in the following formula.

Post-infusion improvement ratio (PIIR) = (B – A)/ A

Example: A = 1 mm
B = 1.2 mm

PIIR % = (1.2 – 1)/ 1 = 20%

If balloon angioplasty is performed, the artery diameter will still be measured and the measurement documented.

Clinical data, that will be collected and entered in REDCap are as follows:

- Patient demographics (age, gender, BMI, race)
- Patient medical and surgical history
- Patient's current medications
- The length of time from aneurysm rupture to time of surgical intervention
- Time in between vasodilator applications
- Number of drug applications used
- Dose of drug applications
- Pre- and post-procedure intracranial pressure measurements (ICPs)
- Cardiovascular instability (SBP changes in mm Hg, requirement of intravenous [IV] pressors)
- New strokes on CT
- Modified Rankin Scale, NIHSS (before treatment, at discharge, and at 3 months after discharge)

Patients will have a 3-month follow-up clinic visit as per standard of care after discharge from the hospital.

5. SELECTION AND ENROLLMENT OF SUBJECTS

Inclusion Criteria: Only adult patients ≥ 18 years with ruptured aneurysms requiring surgery or endovascular therapy and who experience vasospasm post-operatively (3-21 days post-procedure) will be enrolled in this study.
Informed consent will be obtained either from the patient or the patient's legal representative.
The institutional PI/Co-PI will determine the **eligibility of the patients** for the study on the basis of the following:

- Adult patient, age 18 – 80 years old, with ruptured aneurysm(s) who experience vasospasm postoperatively within 3-21 days.
- Symptomatic vasospasm (clinical or TCD)
- For centers that perform a routine day 7 angiogram post-aneurysm treatment – 50% or more stenosis seen on diagnostic angiogram for asymptomatic patients.

Exclusion Criteria:

- Inability to obtain consent from patient or patient's family
- Pregnant women (confirmed by a positive pregnancy test)
- Hunt Hess (HH) grade 5
- Intra-arterial drug treatment in all 3 arterial territories

Study Centers:
The University of Texas Medical School at Houston
University of Illinois College of Medicine – Chicago
Geisinger Health System,
North Shore University Hospital – Northwell Health

Study Enrollment Procedures:
Institutional PI & Co-PI will determine a patient's eligibility based on SOC testing and procedures used in treating patients with aneurysms.
For patients who develop vasospasm during their hospital stay due to aSAH, the PI and members of his research team will approach them to request participation in the clinical study. The study procedures will be explained to the patient or his/her legal representative in detail and consent forms for the study will be explained in detail. Any questions or concerns the participants have will be answered in detail, before the patient or his/her representative signs the consent forms and the potential participants will be given ample time to make an informed decision. For women who have to be excluded from participating in the study on the basis of a suspected pregnancy, a pregnancy test needs to be performed to confirm the pregnancy.
The study coordinator at each site will maintain a log sheets of all the enrolled participants and potential participants approached for the study, eligible participants who refuse to participate & reasons for nonparticipation.
The University of Texas Medical School at Houston is the primary center and will maintain records from all other participating centers.

6. STUDY INTERVENTIONS

Interventions, Administration, and Study Duration:
All study interventions done in this trial are standard of care procedures for cerebral vasospasm treatment. After obtaining informed consent, a clinical examination will be done to assess patient's neurological status pre-infusion. The patient will be taken to the Interventional Radiology suite where he/she will be assigned to one of the three treatment groups based on the center specific randomization scheme for endovascular intra-arterial drug infusion.
Infusions can be given for a total of two times during the same procedure time slot. A post-infusion angiogram will be done minimally10 minutes after the treatment to check for improvement in the spasmic blood vessel. Balloon angioplasty can be performed if the post-treatment angiogram run shows insufficient improvement as per the treating physician's discretion. Post-infusion clinical status will be noted. Three months post-discharge from hospital, study participants will be followed up in clinic to evaluate their functional clinical outcome. If, for any reason, the patient cannot come back for a follow-up visit, the PI/Co-PI's will contact the patient via phone/email to gather the required data. A minimum of mRS and NIHSS should be gathered for follow-up data.

Handling of Study Interventions:
Each participating study center will use its available hospital pharmacy services to acquire the drugs to be used in the study as per their current standard procedures. The study coordinator at each site will maintain a log for study randomization, enrollment and withdrawal.
Concomitant Interventions:
Balloon angioplasty can be done if the drugs used fail to improve the spasm in the blood vessels. The vessel diameter will still be recorded at the end of the study.

7. CLINICAL AND LABORATORY EVALUATIONS

For this clinical trial no additional clinical or laboratory evaluations are required apart from the standard hospital routine care procedures. The required evaluations are listed below:

Schedule of Evaluations

Table 1.

Evaluation	Screening	Pre-Vasospasm Treatment	Post – Vasospasm Treatment	3 months Follow up
Informed Consent	Y			
Pregnancy Test	Y			
Clinical examination mRS, NIHSS, (24-hr window)	Y	Y	Y	Y
NON-contrast CT scan (24-hr window)	Y	Y	Y	Y
TCD (Lindegaard Index)	Y	Y	Y	
Pharmacological angioplasty	Intervention			

Balloon angioplasty	Concomitant intervention			
Intracranial pressure	Y	Y	Y	
Enter Clinical DATA in REDCAP	ENTER within 1 week of discharge & F/U			

Time Frame:
Pre-vasospasm treatment: 24 hours prior to procedure
Post-vasospasm treatment: within 24 hours of the procedure
3-month follow-up visit: +/- 2 weeks
Core Lab Image upload: Please upload all angiogram and CT scan images of the patients enrolled each month to the core lab website by the 7th calendar day of the preceding month.

Evaluations:

Screening & Pre-entry: Screening & pre-entry evaluations may occur simultaneously. Any patient who presents with cerebral vasospasm within 3-21 days after aneurysmal SAH and has an intervention done for aneurysm rupture is eligible for this clinical trial assuming other inclusion criteria are met.

Entry: On confirming patient eligibility and informed consent process, the patient will be randomly assigned to one of the three treatment groups for intra-arterial infusion of study drugs.

On-Study/On-Intervention Evaluations: Pharmacological angioplasty

Intervention Discontinuation Evaluations: If for any reason the PI or the Co-PI discontinue the intervention on a patient, the data will still be collected and entered into the data sheet; patients will still receive all medical & surgical care they need as per routine hospital care procedures. During analysis data from discontinued participants will be factored in.

On Study/Off-Intervention Evaluations: Before discharge from hospital after intervention, patient's neurological status will be noted using Modified Rankin scale and NIH Stroke Scale [NIHSS]. Any new changes on CT scan should be noted, ICP should be noted, and any procedure complications or delayed procedure complications should be noted.

Off-Study Requirements: Study participants will be followed up in clinic at 3 months post-discharge from hospital. All participants will receive this follow-up visit, even if the study intervention was discontinued.

Informed Consent: Informed consent process will take place in a private room where the PI/Co-PI and or the study coordinator will explain the study trial and enrollment process to the potential participants. They will be given ample time to understand the study and to be asked if they have any questions or concerns.

The Informed Consent form is attached in the appendix below.

Documentation of vasospasm: By clinical symptoms, transcranial doppler ultrasound, CT-angiogram & cerebral angiogram.

Clinical Assessments: A complete neurological examination will be done & Modified Rankin score (mRS), NIHSS will be noted. At 3-month follow-up appointment, there will be a recording taken during the mRS evaluation. This recording will contain only the Subject ID and the mRS questions and answers.

8. MANAGEMENT OF ADVERSE EVENTS

This protocol presents minimal risks to the subjects, and adverse events or other problems apart from those expected during standard hospital care for this condition are not anticipated.
In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the institutional review board of the institution involved [IRB], using the current procedures followed at each participating center. The primary site should also be informed of such an event within 48 hours. All appropriate funding and regulatory agencies will be notified there after by the study coordinator
The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project via email as they are reviewed by the principal investigator. The protocol's research monitor(s), e.g., study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of serious adverse events within 5 days of the event becoming known to the principal investigator:

Adverse effects of cerebral angiogram:
BLEEDING FROM GROIN
FEMORAL ARTERY OCCLUSION
STROKE SYMPTOMS (SLURRED SPEECH, WEAKNESS AND/OR LOSS OF SENSATION IN FACE, ARMS & LEGS)
ALLERGIC REACTION TO CONTRAST AGENT
KIDNEY DAMAGE
SEVERE HEADACHE

Details of adverse events, management & monitoring plan for adverse events is listed in appendices

9. CRITERIA FOR INTERVENTION DISCONTINUATION

The PI & Co-PI can discontinue study intervention(s) based on their clinical judgment & patient's best interest. All the data that needs to be entered in the Case Report Form (CRF) will be collected and data from discontinued study participants will be factored in in the analysis.

10. STATISTICAL CONSIDERATIONS

Design:
The clinical trial will be conducted under a common umbrella protocol developed by the primary site (UTH) with the intention of combining data from all satellite centers for analysis. Each investigational site will give utmost importance to follow the study protocol to maintain consistency in study execution at all centers. Patients will be randomly assigned to 3 treatment groups in a 1:1:1 allocation ratio. The three therapeutic regimens to be considered are:
Group 1: nicardipine (Cardene) 5 mg per circulation in 25 mL of 5% Dextrose,
Group 2: verapamil 10 mg per circulation in 10 mL saline
Group 3: Cocktail agents: 5 mg in 25 mL 5% Dextrose + verapamil 10 mg in 10 mL saline + nitroglycerin 200 mcg in 4 cc of D5W per circulation.

A maximum of 330 subjects, 110 per treatment arm, will be randomized. The trial includes interim analyses that may reduce the maximal sample size if clear differences emerge among the arms during the conduct of the trial.

Interim Analyses:
Interim analyses will be performed to allow for discontinuing enrollment to treatment arms due to futility. After approximately 90 subjects have been randomized, 30 per arm, interim analyses will begin at the next quarterly Data and Safety Monitoring Board (DSMB) meeting. Subsequent interim analyses will be performed to coincide with DSMB meetings, which will occur after 40 subjects, 70 subjects, 110 subjects, 165 subjects, and 248 subjects have completed the study, and at the conclusion of the study (330 subjects).

At each interim analysis, an Analysis of Variance (ANOVA) will be performed to compare the PIIR results across treatment arms. If the overall treatment effect is significant with a p-value<0.05, then pairwise treatment comparisons will be performed. If any pairwise comparison is significant at a Tukey's adjusted two-sided p-value of 0.02 ($p< 0.02$), the poor performing arm will be dropped from the randomization scheme. If multiple arms are dropped and only one treatment arm remains open for randomization, that arm will be declared as best, and the clinical trial will end. Pairwise comparisons will only be performed if the overall treatment effect in the ANOVA is significant.

A maximum of 110 subjects will be randomized to each treatment arm, for a total sample size of 330. If an arm or arms are dropped early, the final sample size will be less than 330. For example, suppose an interim analysis is performed after 70 subjects are randomized to the 3 treatment arms (total sample size 210). Suppose further, at the interim analysis one arm is dropped, and the remaining two arms continue to enroll to completion. The final sample size will be 290, i.e., 70 subjects in the dropped treatment arm, and 110 in each of the remaining treatment arms.

Enrollment will continue while the interim analyses are performed

Final Analyses:
All patients will be included in analyses utilizing the Intent-to-Treat approach that includes all subjects randomized in their randomized treatment arm regardless of treatment received.

At the final analysis, the primary outcome measure, PIIR will be compared between treatment arms using an ANOVA model. All data will be used in the final analysis, including any arms that may have been dropped from the randomization. If the overall treatment effect in the ANOVA model is significant at the two-sided, 5% level, then pairwise comparisons among treatment arms will be conducted using Tukey's adjusted p-values with $p<0.0330$ declared as statistically significant. This value controls global type I error (mistakenly claiming any pairwise difference when all treatments are equal) accounting for 6 interim analyses at the anticipated accrual rate of 2 years. If accrual significantly deviates from the anticipated accrual rate, further trial simulations will be conducted to determine an appropriate adjustment for the actual number of interim analyses conducted.

Descriptive statistics, means, medians, and standard deviations, will be reported for PIIR in each treatment arm. The two-sided 95% confidence interval will also be presented for the PIIR in each treatment arm.

The key secondary outcome, mRS (Modified Rankin Scale) at 3-months post-treatment, will be summarized by treatment arm by reporting the counts and proportions in each mRS category. Comparisons among treatment groups will be made using a Chi-square test.

Additional secondary outcomes include SAE (severe adverse event) occurrences and the rate of treatment failure with balloon angioplasty. These outcomes will be summarized descriptively by presenting rates and proportions. Exploratory analyses comparing outcomes between treatment arms will be made using a Chi-square test.

Additional exploratory multivariable linear regression models will be created for the PIIR outcome, adjusting for treatment groups and additional baseline factors.

The analyses for the secondary outcomes are considered exploratory and no adjustments for the multiple tests and multiple comparisons will be made. Results will be interpreted cautiously understanding the some results may be significant at the 5% level due to chance alone.

Sample Size Justification:
Simulations were performed to estimate the power of the study for the primary outcome measure, PIIR, with a maximum sample size of 330 (110 per treatment arm) and the interim analyses for possible early arm dropping. A range of scenarios of PIIR were examined; the key scenarios used to power the trial are presented in Table 2.

Table 2.

Scenario	Treatment Arm 1: Nicardipine (N)	Treatment Arm 2: Verapamil (V)	Treatment Arm 3: Combination (C)
Combo 20	0.10	0.10	0.30
Mixed 1530	0.10	0.15	0.30

Note that the scenarios are both in favor of Verapamil over Nicardipine, but the results are symmetric if Nicardipine and Verapamil were reversed.

The trial will make every pairwise comparison:

- N versus V
- N versus C
- V versus C

The simulations focused on the V>N, C>N, and C>V comparisons. The following table presents the expected (mean) sample size and probability that the combination treatment regimen is better than the verapamil regimen, i.e., Pr(C>V), the main comparison of interest. Power is defined as the probability of identifying the superiority of the best dose over the other two doses.

Table 3.

Scenario	Expected N	Power Pr(C>V)
Combo 20	177	0.95
Mixed 1530	211	0.77

Table 3 demonstrates, that for a hypothesized scenario of "Combo 20" where the combination therapy PIIR is 0.30 compared to 0.10 in Nicardipine and Verapamil, the study will have over 90% power and an expected sample size of 177. Both the Nicardipine and Verapamil arms would have been dropped at interim analyses before they reached their maximum enrollment of 110. If the scenario of "Mixed 1530" is observed, a situation where the Nicardipine arm PIIR is 0.10, the Verapamil arm PIIR is 0.15 and the combination arm is 0.30, the study will have 77% power and an expected sample size of 211. Again, both the Nicardipine and Verapamil arms would have been dropped at interim analyses before they reached their maximum enrollment of 110.

Missing Data and Dropout Rate: We do not anticipate missing data for the primary outcome PIIR as the angiogram will be performed 10 minutes post-infusion. For the secondary outcome, mRS at 3-months, based on previous studies, we estimate up to a 20% loss follow-up. Efforts will be made to keep all patients in the study through the 3-month follow-up visit. Substantial efforts will be made to ensure complete follow-up. Rates of missing data and loss to follow-up will be reported by treatment arm. We will attempt to document maximum amount of information regarding the status of these

patients who drop out. This procedure will help to compare characteristics of those patients who completed the study with those who did not.

Data and Safety Monitoring:
In order to ensure patient safety and integrity of data collection, data and safety monitoring during this trial will include both internal and external mechanisms. The PI has developed an internal monitoring system, which will be implemented after each enrolled patient and on a monthly basis at the host site, University of Texas Health Science Center Houston. The study team will perform internal monitoring. In addition, on a yearly basis, a monitor will be asked to review study and safety data for all participating centers. Monitoring of participating centers will occur on a yearly basis, or following the completion of the study for each additional two subjects at each center, whichever occurs first. Monitoring may occur in person, or remote. Lastly, the Data and Safety Monitoring Board will independently review the accumulating data, assess the risk to benefit ratio, and can consider halting the trial if the risk to benefit ratio is deemed unacceptable. The external monitor and the DSMB will also monitor protocol compliance, safety, and on-schedule study progress.

11. DATA COLLECTION, SITE MONITORING AND ADVERSE EVENT REPORTING

Data collection: detailed clinical information will be gathered using an established method approved by UT Health for abstracting information from electronic database and by the approved established method at each participating site.
Each participating center will use REDCap data software an online secure web application to enter the data in the central REDCap database managed by UT-Houston.

All the radiographic images will be evaluated and analyzed by a single CORE LAB (at The University of California – Los Angeles) centrally in blind fashion. The radiographic images will be submitted via VPN with security and with federal Health Insurance Portability and Accountability Act (HIPPA) compliance.

The patient's demographics (gender, age, race, BMI, co-morbidity, tobacco use, cocaine/illicit drug use history), aneurysm treatment modality, days after the SAH and aneurysm treatment, vasodilator(s) used (Group #) and numbers of the treatment sessions will be submitted via REDCap. Summaries will be provided quarterly to the DSMB members.

Records to Be Kept: All patient data will be de-identified and CRFs will be stored on password protected cloud drive

Data and Safety Monitoring Plan & Quality Assurance:
The Data and Safety Monitoring Board (DSMB) is responsible for conducting on going safety reviews of the trial. The first meeting will be held when approximately 40 subjects have completed the study and subsequent meetings will be held at following each of the following study timepoints, or every 6 months, whichever occurs first.

- 70 subjects completed the study
- 110 subjects completed the study
- 165 subjects completed the study
- 248 subjects completed the study
- 330 subjects completed the study

(Subject completion of the study will be defined as a subject having a completed 90-day follow up and completed analysis of study imaging by the corelab)

Frequency of the meetings may be changed by the Chair based on need. Meetings may be in person, via teleconference, or a combination of the two. A quorum must occur for the meeting to proceed.

During the review process the DSMB will evaluate whether the study should continue unchanged, require modification/amendment or be closed to enrollment and will inform the trial co-PIs of the study.
The trial co-PIs are responsible for communicating with DSMB at each time point listed above regarding potential safety issues and whether the study should continue unchanged,

require modification/amendment, or be closed to enrollment. These will be further communicated with the individual participating local PIs.

The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

Data Safety Monitoring Board
Dr. David Langer;
Dr. Kevin Cockroft.
Dr. Juliana Tolles

12. HUMAN SUBJECTS

Institutional Review Board (IRB) Review and Informed Consent:
This protocol, the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject. For subjects who cannot consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

Subject Confidentiality:
All records that leave any study site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee. All data will be digitally stored on a UT Z100 password protected cloud drive.

Study Modification/Discontinuation:
The study may be modified or discontinued at any time by the PI, IRB, the NINDS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

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APPENDIX

I. List of Participating Centers:

1. The University of Texas Medical School at Houston
2. University of Illinois in Chicago
3. Geisinger Health System
4. North Shore University Hospital – Northwell Health
5. Memorial Hermann Hospital- At The Woodlands

II. Drug Information: The dose of the each medication set in this study is based on the limited clinical data available for each agent.

1) Nicardipine: a dihydrophyridine calcium channel blocker, the therapeutic effect is believed to be related to the selective inhibition of transmembrane calcium ion influx into vascular smooth muscle, resulting in a reduction of free calcium ions in these cells and disruption of actin-myosin interaction essential to muscle contraction [9]. The dose used frequently in IA therapy is ranges 2 – 25 mg/each arterial territory, mean dose 5.7 +/- 4.3 mg [6]. High dose IA nicardipine results hypotension, in some cases, even dose ranging from 4 to 7.5mg.

2) Verapamil: a phenylalkylamin calcium channel blocker that inhibits voltage-gated calcium channels in the arterial wall smooth muscle cells and results in vasodilation. It has been observed that there were no significant changes in BP, HR or ICP after administration of more than 20mg of IA verapamil [5].

3) Nitroglycerin: has been used in cerebral vasospasm treatment for a couple of decades. It has been reported dose of single vascular territory used up to 700 mcg without major hemodynamic instability.

III. Adverse events:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational drugs. NOTE 1 This definition includes events related to the investigational drugs. NOTE 2 This definition includes events related to the procedures involved.
Adverse drug effect	Any AE related to the use of an investigational drug.
Serious adverse event	Any AE that a) led to death, b) led to serious deterioration in the health of the subject that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by this Protocol, without serious deterioration in health, is **not** considered a serious adverse event. (ISO 14155, 2011)
Technical Event	A study procedure related event.
Stroke	New Stroke event, worsening of motor, sensory or speech function. Cant be explained by cerebral vasospasm and or pre-existing aSAH Clinically and radiographically.
Neurologic Death	For the purposes of study endpoints, neurologic death is defined as any death determined to be of **neurologic** cause. This definition excludes: death due to rupture of a nonindex aneurysm or as a consequence of treatment of a nonindex aneurysm.
Death	For the purposes of study endpoints, death excludes death of accidental causes or death due to rupture of a nonindex aneurysm or as a consequence of treatment of a nonindex aneurysm.

*Study procedure related **Minor complications** might include*:

Nausea and/or vomiting (post-anesthesia)
Mild headache
Groin discomfort: mild pain and or bruising at the incision site

Study Procedure related ***Significant complications*** *(catheter induced: different from pre-existing cerebral vasospasm & SAH induced ischemia):*
Intra-cranial catheter induced spasm of the treated segment of artery or branches
Stroke (ischemic, hemorrhagic, TIA)
Hemiplegia
Aphasia
Visual impairment or blindness
Intra cranial artery tear (hemorrhage)
Femoral artery occlusion due to catheter

Study Procedure related Very Rare side effects may include:
Death
Renal failure due to dye induced
Seizure
Infection
Blood vessel or nerve damage
Decreased blood flow in the leg on the side of the groin puncture
A pseudoaneurysm may develop as a result of injury to all the layers of a vessel wall resulting in a hematoma
Air embolism
Mental status changes
Total occlusion of the treated blood vessel segment or other blood vessels.

DRUG RELATED adverse events & overdose effects:
NOTE: All drug related adverse events & overdose effects listed below are excerpts from the package inserts. The package inserts used as a reference are for IV doses since no data is available on Intra-arterial package inserts

1. NICARDIPINE

ADVERSE EVENTS:
Body as a Whole: headache, fever, neck pain
Cardiovascular: hypertension, tachycardia, angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep vein thrombophlebitis
Digestive: nausea, vomiting, dyspepsia
Hemic and Lymphatic: thrombocytopenia
Metabolic and Nutritional: hypophosphatemia, peripheral edema
Nervous: confusion, hypertonia
Respiratory: respiratory disorder
Special Senses: conjunctivitis, ear disorder, tinnitus
Urogenital: urinary frequency
Sinus node dysfunction and myocardial infarction, which may be due to disease progression, have been seen in patients on chronic therapy with orally administered nicardipine.

OVERDOSAGE:
Several overdosages with orally administered nicardipine have been reported, IA overdoses are not known as yet.
One adult patient allegedly ingested 600 mg of nicardipine [standard (immediate-release) capsules], and another patient, 2160 mg of the sustained-release formulation of nicardipine.
Symptoms included marked hypotension, bradycardia, palpitations, flushing, drowsiness, confusion and slurred speech. All symptoms resolved without sequelae.
An over dosage occurred in a one-year-old child who ingested half of the powder in a 30 mg nicardipine standard capsule. The child remained asymptomatic.
Based on results obtained in laboratory animals, lethal overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block.
Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.
For treatment of overdosage, implement standard measures including monitoring of cardiac and respiratory functions. Position the patient so as to avoid cerebral anoxia. Use vasopressors for patients exhibiting profound hypotension.

2. VERAPAMIL

ADVERSE EVENTS:
The following reactions were reported with verapamil hydrochloride injection used in

controlled U.S. clinical trials involving 324 patients:
Cardiovascular: Symptomatic hypotension (1.5%); bradycardia (1.2%); severe tachycardia (1.0%).
The worldwide experience in open clinical trials in more than 7,900 patients was similar.
Central Nervous System Effects: Dizziness (1.2%); headache (1.2%). Occasional cases of seizures during verapamil injection have been reported.
Gastrointestinal: Nausea (0.9%); abdominal discomfort (0.6%).
In rare cases of hypersensitive patients, broncho/laryngeal spasm accompanied by itch and urticarial has been reported.
The following reactions have been reported at low frequency: emotional depression, rotary nystagmus, sleepiness, vertigo, muscle fatigue, diaphoresis, and respiratory failure.

OVERDOSAGE
Treatment of over dosage should be supportive and individualized. Beta-adrenergic stimulation and/or parenteral administration of calcium injections may increase calcium ion flux across the slow channel, and have been effectively used in treatment of deliberate over dosage with oral verapamil hydrochloride.
Verapamil cannot be removed by hemodialysis.
Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including isoproterenol hydrochloride, other vasopressor agents, or cardiopulmonary resuscitation.

3. NITROGLYCERIN

Adverse reactions to nitroglycerin are generally dose-related and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy.
Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.
Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred.

OVERDOSE:
The ill effects of nitroglycerin overdose are generally the results of Nitroglycerin’s capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

Methemoglobinemia- The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously

Monitoring Plan:
During the Intra-Arterial Drug infusion Treatment all patients will be under General Anesthesia (GA). Neuro- Anesthetist will manage & monitor these patients during the treatment procedure, pre & post procedure they will be closely monitored & managed in Neurological Intensive Care unit (ICU) by ICU team.
Data will be collected at 12-hour intervals pre & post procedure.
Intra procedure data to be collected is Vital signs (Blood Pressure, Heart Rate), ECG, arterial pressure, Intra-cranial Pressure.
If any drug related complications occur the medications will be stopped immediately.
The following conditions would warrant for immediate stopping of the study drug:
Marked hypotension, bradycardia, severe tachycardia, high degree AV-block, asystole, crescendo angina & methemoglobinemia

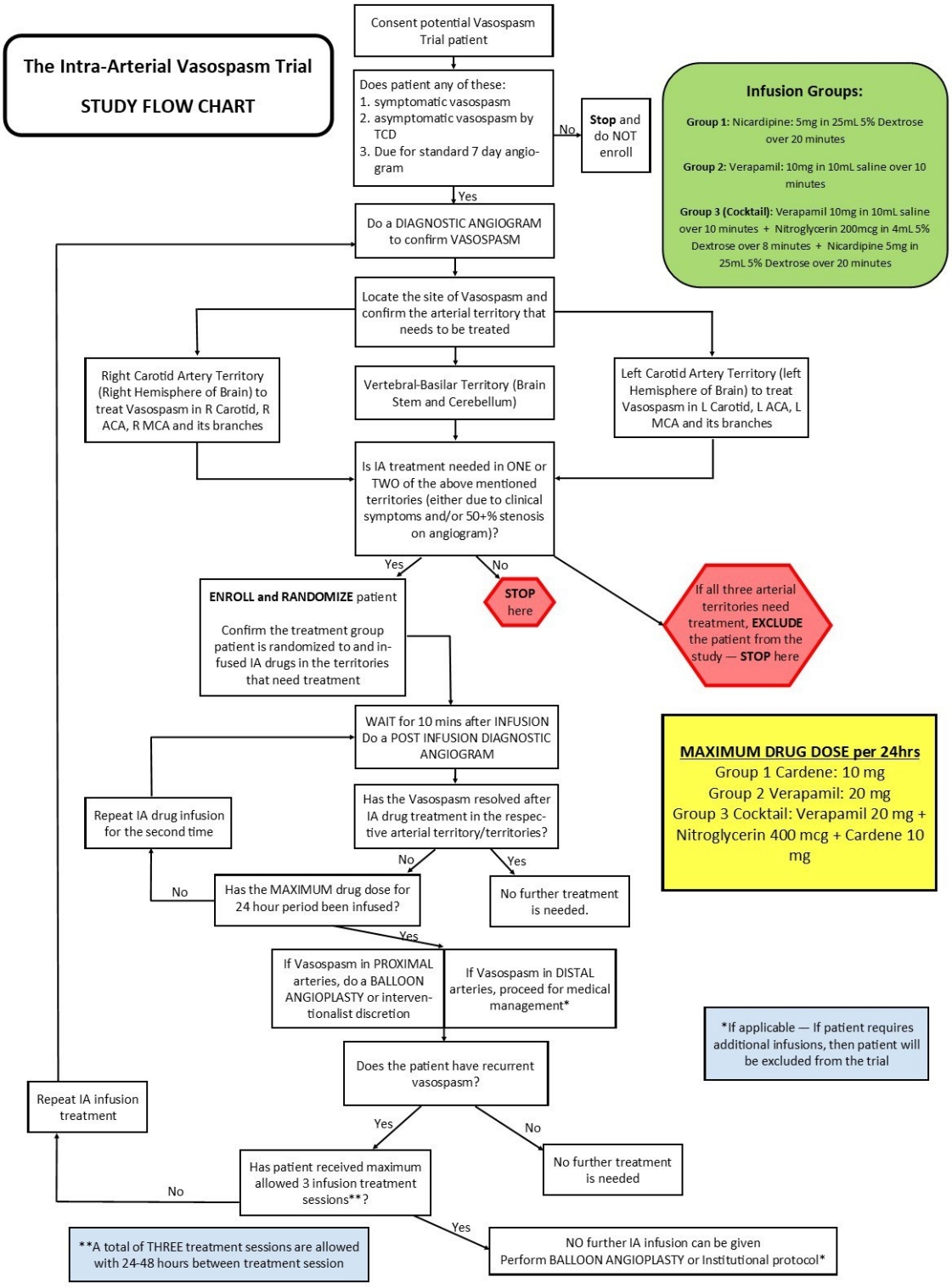
A protocol deviation is defined as any study action taken by the investigator or site personnel in conflict with the study protocol. The investigator and/or sponsor will characterize deviation severity as per the following Table.

Deviation severity	**Definition**
Major deviation:	Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized drug use.
Minor deviation:	Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

Investigators must notify the Study Chairs & respective IRB within 24 hours if a deviation is required to protect subject safety. The Study Chairs may terminate investigators and/or investigative sites from the study if the rate of protocol deviations is deemed high or patient safety is in question.

During the DSMB reviews, occurring every 6 months at a minimum, the DSMB members will review all serious related AE's (catheter induced spasm, new ischemic stroke, hemiplegia, aphasia, visual impairment or blindness, Intra cranial artery tear) to adjudicate if the SAE's are procedure related, drug related or other. The DSMB members may terminate investigators and/or investigative sites from the study if the rate of protocol deviations is deemed high or patient safety is in question.

IV. STUDY FLOW CHART



V. DRUG DOSE TABULATION

NICARDIPINE		
Drug Label suggested dose	Maximum dose of 15 mg/hour (0.25 mg/minute) Until desired blood pressure reduction is achieved.	Reference: page 6 of package insert
Drug Label suggested infusion rate	75 mL/hour (1.25 mL/minute) Concentration: 0.2 mg/mL	Reference: page 7 of package insert
Revised drug dose per infusion	**5 mg in 25 mL 5% Dextrose** **Infused at the rate of 1.25 mL/ minute (i.e. 0.25 mg/minute) over a period of 20 minutes**	

VERAPAMIL		
Drug Label suggested dose	Initial dose: 5-10mg/2minutes (2.5-5 mg/minute) Repeat dose: 10mg, 30 minutes after the first dose if initial response not adequate.	Reference: page 7 of package insert
Drug Label suggested infusion rate	2.5 – 5mg/minute Concentration: 2.5 mg/mL	Reference: page 8 of package insert
Drug dose	**10 mg in 10 mL normal saline** **Infused at the rate of 1 mL/minute (i.e. 1 mg/minute) over a period of 10 minutes**	

NITROGLYCERIN		
Drug Label suggested dose	25 mcg/minute or more	Reference: page 6 of package insert
Drug Label suggested infusion rate	0.5 ml/minute Concentration: 50 mcg/mL	Reference: page 7 of package insert
Revised drug dose per infusion	**200 mcg in 4 mL 5% dextrose** **Infused at the rate of 0.5 mL/minute (i.e. 25mcg/minute) over a period of 8 minutes**	

VI. MAXIMUM POSSIBLE DRUG DOSES:

NICARDIPINE (Arm 1) DRUG DOSE SCENARIOS								
		Treatment Session 1		**Treatment Session 2** (24-48 hours after treatment session 1)		**Treatment Session 3** (24-48 hours after treatment session 2)		**All 3 Treatment Sessions**
No of arterial territory to be infused	Infusion	Drug Infusion Dose	Total maximum dose in 24 hour period	Drug Infusion Dose	Total maximum dose in 24 hour period	Drug Infusion Dose	Total maximum dose in 24 hour period	Total maximum dose for all treatments
One Arterial territory	Infusion 1	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	30 mg
	Repeat infusion	5 mg		5 mg		5 mg		
Two Arterial territories	Infusion in First arterial territory	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	30 mg
	Infusion in Second arterial territory	5 mg		5 mg		5 mg		

VERAPAMIL (Arm 2) DRUG DOSE SCENARIOS								
		Treatment Session 1		**Treatment Session 2** (24-48 hours after treatment session 1)		**Treatment Session 3** (24-48 hours after treatment session 2)		**All 3 Treatment Sessions**
No of arterial territory to be infused	Infusion	Drug Infusion Dose	Total maximum dose in 24 hour period	Drug Infusion Dose	Total maximum dose in 24 hour period	Drug Infusion Dose	Total maximum dose in 24 hour period	Total maximum dose for all treatments
One Arterial territory	Infusion 1	10 mg	20 mg	10 mg	20 mg	10 mg	20 mg	60 mg
	Repeat infusion	10 mg		10 mg		10 mg		
Two Arterial territories	Infusion in First arterial territory	10 mg	20 mg	10 mg	20 mg	10 mg	20 mg	60 mg
	Infusion in Second arterial territory	10 mg		10 mg		10 mg		

COCKTAIL DRUG (Arm 3) DOSE SCENARIOS (per each infusion: VERAPAMIL 10 mg + NITROGLYCERIN 200 mcg + CARDENE 5 mg)								
		Treatment Session 1		**Treatment Session 2** (24-48 hours after treatment session 1)		**Treatment Session 3** (24-48 hours after treatment session 2)		**All 3 Treatment Sessions**
No of Arterial territory to be infused	Infusion	Drug Infusion Dose	Total maximum dose in 24 hour period	Drug Infusion Dose	Total maximum dose in 24 hour period	Drug Infusion Dose	Total maximum dose in 24 hour period	Total maximum dose for all treatments
One Arterial territory	Infusion 1	10 mg + 200 mcg + 5 mg	20 mg + 400 mcg + 10 mg	10 mg + 200 mcg + 5 mg	20 mg + 400 mcg + 10 mg	10 mg + 200 mcg + 5 mg	20 mg + 400 mcg + 10 mg	60 mg + 1200 mcg + 30 mg
	Repeat infusion	10 mg + 200 mcg + 5 mg		10 mg + 200 mcg + 5 mg		10 mg + 200 mcg + 5 mg		
Two Arterial territories	Infusion in First arterial territory	10 mg + 200 mcg + 5 mg	20 mg + 400 mcg + 10 mg	10 mg + 200 mcg + 5 mg	20 mg + 400 mcg + 10 mg	10 mg + 200 mcg + 5 mg	20 mg + 400 mcg + 10 mg	60 mg + 1200 mcg + 30 mg
	Infusion in Second arterial territory	10 mg + 200 mcg + 5 mg		10 mg + 200 mcg + 5 mg		10 mg + 200 mcg + 5 mg		

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