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Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

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Abstract

Introduction

Delayed cerebral ischemia due to cerebral vasospasm remains the foremost contributor to morbidity and mortality following aneurysmal subarachnoid hemorrhage. Past effort in preventing and treating delayed cerebral ischemia have failed to make any significant progress. To date, our most effective treatment involves the use of nimodipine, a calcium channel blocker. Recent studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent cerebral vasospasm. Thus far, no study has evaluated the effect of cilostazol plus nimodipine on the rate of delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of ICU stay, and long-term functional and quality of life outcomes will be recorded. All data will be collected with the aim of demonstrating that the use of cilostazol plus nimodipine will not only safely decrease the incidence of delayed cerebral ischemia, but decrease the rates of both radiographic and symptomatic vasospasm with subsequent improvement in long-term functional and quality-of-life outcomes when compared to nimodipine alone.

Ethics and Dissemination

Ethical approval was obtained at all participating hospitals by the institutional review board. The results of this study will be submitted for publication in peer-reviewed journals.

Article Summary

Strengths and limitations of this study:

- First randomized controlled trial in the US to evaluate the effect of cilostazol and nimodipine on delayed cerebral ischemia and cerebral vasospasm
- Adequately powered study
- Primary outcome improvement may not lead to secondary clinical outcome improvement

Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

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Registry: NCT04148105

Study Dates: November 2019 – October 2023

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Investigators: Research Site: Investigators and their subsequent roles are detailed in the authors' contributions section. Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating condition which affects approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been made in the treatment of ruptured aneurysms, however, there has been little progress in the treatment and prevention of delayed cerebral ischemia (DCI) due to cerebral vasospasm (cVS).[1,2] Cerebral vasospasm and subsequent DCI remain to be the most prominent cause of

morbidity and mortality following aSAH.[3] Although the mechanism and pathogenesis of cVS is not fully understood, it is considered a vital underlying mechanism in DCI.[4,5] Cerebral vasospasm is known to take effect between days 3 and 21 post-aSAH with a peak incidence between days 6 and 10.[2] Current therapy includes definitive treatment of the ruptured aneurysm through either open clipping or endovascular therapy followed by a 21-day course of nimodipine after the onset of SAH.[6–8] Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postprocedural treatment of aneurysmal subarachnoid hemorrhage (aSAH) for the prevention of cerebral vasospasm.[8,9] This regimen has shown long-term outcome improvement following aSAH.[7,10] Multiple other modalities have been investigated for the treatment and/or prevention of cVS including mechanical removal of blood, cisternal irrigation, Rho kinase inhibitors, triple-H therapy, and numerous endovascular treatments – all of which demonstrated minimal efficacy or limited use.[11–18] Despite years of investigation and improvement, the risk of symptomatic and radiographic vasospasm remains unacceptably high between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23] This also continues to be prevalent at our institution as we observed rates of symptomatic vasospasm and DCI to be 40% and 60%, respectively.

Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26] Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30] In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated the combined application of nimodipine and cilostazol. This combination therapy of nimodipine and cilostazol with possible synergistic effect require further investigation.[31]

Our randomized superiority trial seeks to investigate the combined effect of cilostazol plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when compared to nimodipine alone.

Study Goals and Objectives

Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients with aSAH.

Primary Objective

- To demonstrate that the combined use of cilostazol plus nimodipine when compared to nimodipine alone will decrease the rate of DCI in patients following aSAH

Secondary Objectives

- To demonstrate that the combined use of cilostazol plus nimodipine is not associated with increased drug-related serious adverse events
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of symptomatic and radiographic vasospasm
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the average length of intensive care unit (ICU) stay
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- To demonstrate that the combined use of cilostazol plus nimodipine will improve Modified Rankin Scores (mRS) and Quality-of-life (QoL) outcomes at 6-months.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow chart.

Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This protocol was approved by our Institutional Review Board (IRB) and published on ClinicalTrials.gov.

Over a three-year period, consecutive adult patients over the age of 18 who present to our tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT

angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). After satisfying inclusion/exclusion criteria, patients/family members are consented for full participation in the trial. Once consented, patients are randomized to receive either placebo or intervention with a centralized treatment allocation mechanism and block randomization to assure the two arms achieve equal proportion of patients over time.

All patients, treatment providers, investigators, and statisticians are blinded to the allocation. Blinding is achieved by allocation sequence being concealed to personnel involved in the enrolling, care and evaluation of the patient. The study coordinator will keep the randomization schedule in a cloud-based, secure and encrypted database. Only the study coordinator who monitors the trial, the pharmacist who executes the allocation, the supervising investigator who is not involved in the patients' care or enrollment will have access to the randomization schedule. Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will conceal the identity of the medications.

All participating patients, after undergoing treatment of their ruptured aneurysm (open clipping vs. endovascular coiling) and confirmation of a stable head CT will be randomized and scheduled to receive their allocation within 48 hours of surgery/intervention for a total of 14 days. In addition to their randomized allocation, all patients will receive a standard aSAH treatment protocol,[7] including 21 days of nimodipine as endorsed by the Congress of Neurological Surgeons. The standardized treatment regimen is summarized in Table 2. Each patient is followed according to the data collection schedule (Figure 2). While in the hospital, the patients are monitored frequently (every hour while in the ICU and every 4 hours while on the floor) throughout the day for any adverse/serious adverse events (Table 3). Adverse and serious adverse events (SAE) are defined using a validated classification scheme (Table 4).[33] SAE are defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the study medication will be recorded and reported immediately to the principal investigator and the IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in which knowledge of the allocation will aid in the clinical management of the patient and therefore warrant unblinding of the allocation.

The primary outcome will be defined as low-density areas on CT or signal changes on MRI performed at 1-week and 1-month following initial presentation determined by blinded neuroradiologists. Secondary outcomes including length of ICU stay, QoL, and mRS at 1-month, 3-months, & 6-months postoperatively will be prospectively collected. Length of ICU stay will be determined by standardized discharge criteria. Rates of symptomatic vasospasm will be collected and defined as development of a new focal or global neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[34] which was not explained by initial hemorrhage, re-bleeding, hydrocephalus, surgical complications, fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT scanning or MRI and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or CTA.[14,35,36] Radiographic vasospasm will be assessed by either CTA or DSA between 7 and 10 days postoperatively. Radiographic vasospasm with be defined as arterial narrowing not attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of stenosis compared to previous baseline CTA or DSA as determined by blinded neuroradiologists.[14] In each patient, the smallest diameters of 10 arterial segments of the bilateral distal internal carotid arteries (ICA), M1 and M2 segments of the middle cerebral artery (MCA), and A1 and A2 segments of the anterior cerebral artery (ACA) will be measured. Severity of the radiographic vasospasm will categorized as none or mild (0%-25% decrease in vessel diameter from baseline), moderate (25%-50% decrease in vessel diameter from baseline), or severe (greater than 50% decrease in vessel diameter from baseline). The most affected segment will be used to determine severity of radiographic vasospasm.

To demonstrate superiority, an 80% power is used to minimize chances of false negatives. Assuming an effect size of 50% with the use of cilostazol and a baseline rate of DCI of 60%, a total sample size was estimated to be 100 patients with an alpha of 0.05. In anticipation for any unforeseen events and those lost to follow-up, we plan to enroll a total of 120 patients.

Patient and Public Involvement

At the time of 1-month postoperative follow-up, patients or their families will be asked to participate as study advisers in our data monitoring and safety committee. There will be 2-4 patient advisers at any given time during the study period, each with a term of 6 months. These

patient advisers will share their experience regarding the recruitment process, surgery, and postoperative care in order to help ensure patient safety and satisfaction throughout the study.

Trial Status

At the time of manuscript submission, the trial is ongoing.

Safety Considerations

All study-related adverse events (AE) are recorded and reported immediately to the principal investigator and subsequently to the IRB within 24 hours of the event as previously stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical safety of the study and review adverse events reported to the IRB to determine risk and benefits. Any SAE related to the study medication represents a circumstance under which unblinding is permissible in order to ensure the safety of the participant. At that time, the intervention will be stopped, and any clinical intervention required at the discretion of the attending surgeon will ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be surgeons and related experts who will meet to review the results and any adverse events biannually to evaluate study safety.

Follow-up

Postoperatively, patients will be followed according to the data collection schedule (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be designated at the discretion of the treating attending physician.

Data Management and Statistical Analysis

During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will observe all the steps of the intervention and data collection to ensure proper execution. The progress of data entry, follow-up and recruitment are logged and monitored regularly by the CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and

the database will be maintained to within one week of the data collection. CRC will coordinate the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month and 6-months.

Comparability between groups will be evaluated by descriptive and univariate analyses. Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-value less than or equal to 0.05 will be considered statistically significant. Bonferroni's correction will be applied when appropriate. Descriptive statistics will be used in each arm for proportion who did not receive allocated intervention, lost to follow-up, excluded from primary analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses will be performed. An interim analysis will be conducted after 50 patients (25 per arm) have been enrolled and completed study procedures. This is a superiority trial. Early discontinuation of the study will be dependent on overwhelming positive results for the primary outcome. We will discontinue the trial if we achieve $p<0.001$ threshold at the time of interim analysis.[37]

Quality Assurance

Standardized medication orders will conceal the treatment allocation. The study coordinator will be responsible for managing the quality of patient data recorded in the study. All participating research staff will be trained and given written copies of a standard operating procedure to ensure consistency during recruitment, consent, handling of data, and follow-up evaluation. The study coordinator along with the PI will check weekly the content of the forms and database to ensure accurate and timely entry. Compliance at all study timepoints including enrollment, randomization, intervention, data, and outcome collection will be documented daily on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered into a cloud-based, secure and encrypted database by the research staff. Access to the database will be restricted. Data validation tool has been embedded in the database. Data entered will undergo monthly verification with the source document.

Expected Outcome of the Study

This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally,

we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and radiographic vasospasm.

Duration of the Project

Given our institutional volume, we anticipate a study period of 1-3 years assuming 50% of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment and subject to discontinuation if all previously defined criteria are met.

Project Management

Neurosurgery staff will counsel and recruit subjects according to their initial screening to participate in this trial. The neurosurgery staff will check for eligibility using inclusion and exclusion criteria listed in Table 1. They will also explain the study principles, including the detailed experimental in-hospital & postoperative protocol, investigational treatment, potential risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed in a cloud-based, secure, and encrypted database. The designated lead pharmacists will execute the randomized allocation assignment according to the block randomization schedule to maintain masking of allocation. The neuroscience ICU charge nurse will be responsible for overseeing and monitoring administration of the study medication. The neuroscience trained intensive care nursing staff will administer the study medication to the study participants. The PI and support staff will record all perioperative and postoperative data including study-related adverse events. The study coordinator will ensure and maintain follow-up visits for postoperative secondary outcomes. The neuroradiologists will evaluate and determine primary and secondary outcomes of DCI and vasospasm, respectively. The clinical research methodologist will function as the CRC, supervise the overall execution of the study, and participate in the writing of the protocol and manuscript.

Ethics and Dissemination

The study will be conducted according to the Helsinki Declaration[38], the NIH human subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good Clinical Practice.[39] This protocol is written following the SPIRIT 2013 guidelines and was

approved by the hospital IRB. The results of this study will be submitted for publication in peer-reviewed journals and the key findings will be presented at national conferences.

Author Contribution

TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this trial including organization and execution over two hospital campuses. DS contributed to the design and execution of the study drug protocol including randomization, blinding and placebo. MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard operating procedures, and maintaining quality assurance among study participants and their subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT contributed to the drafting of the original manuscript, participated in critically revising the manuscript and agree to be accountable for all aspects of the work.

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Disclaimer

This project is not an industry-sponsored study. The investigators are solely responsible for the protocol design, data collection, analysis and interpretation, writing of the report, or decision to submit this publication.

Competing Interests

None declared.

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Figure Legend:

Figure 1. Study Design CONSORT Flow Diagram

Figure 2. Data Collection Schedule & Timeline

Table 1. Inclusion, Exclusion, and Withdrawal Criteria

Inclusion	Exclusion
18 years of age or older	Non-aneurysmal subarachnoid hemorrhage
Anterior circulation aneurysm	Multiple ruptured aneurysms
Patients who have undergone surgical intervention	Patients with congestive heart failure
Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan	Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)
Consent to study participation	Active pathological bleeding
	Allergy to cilostazol
	Positive pregnancy test
	Coagulopathy not caused by anti-coagulant use
	History of hemorrhagic complications (gastrointestinal bleeding, etc.)
	Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol
	Patients requiring anticoagulant/antiplatelet treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm)

Criteria for discontinuing follow-up:
Subject wishing to terminate participation in the study at any time throughout his/her participation
CT, computed tomography

Table 2. Standardized Treatment Regimen

Location	Treatment
NSICU and floor	**Intervention group:** • 60 mg nimodipine Q4H for 21 days • 100 mg cilostazol b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]
	Control group: • 60mg nimodipine Q4H for 21 days • Cilostazol placebo b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]

NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography

Table 3. List of Adverse or Serious Adverse Events

Cilostazol		Nimodipine	
Adverse events		**Adverse events**	
	Headache		Hypotension (mild)
	Diarrhea		Diarrhea
	Abnormal Stools		Dyspepsia
	Palpitations		Rash
	Dizziness		Headache
	Peripheral Edema		Flushing
	Dyspepsia		
	Abdominal pain		
	Tachycardia		
Serious adverse events		**Serious adverse events**	
	Hypotension		Hypotension (severe)
	Bleeding		EKG changes
	Stevens Johnson		CHF
	Syndrome		Thromboembolism
	Anaphylaxis		Thrombocytopenia
	Hypersensitivity		Anemia
	Reaction		GI bleeding
	Leukopenia		Ileus
	Thrombocytopenia		Intestinal obstruction
	Tachyarrhythmias		
	Myocardial		
	Infarction		
	Angina		

EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal

Table 4. Definition and Classification of Surgical Complications

Grade	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic, or radiological intervention
3a)	Intervention not under general anesthesia
3b)	Intervention under general anesthesia
Grade 4	Life-threatening complication (including CNS complications)* requiring IC/ICU management
4a)	Single organ dysfunction (including dialysis)
4b)	Multiorgan dysfunction
Grade 5	Death of a patient
Suffix	If the patient suffers from a complication at the time of discharge, the suffix "d" is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

*Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

Figure 1. CONSORT flow diagram

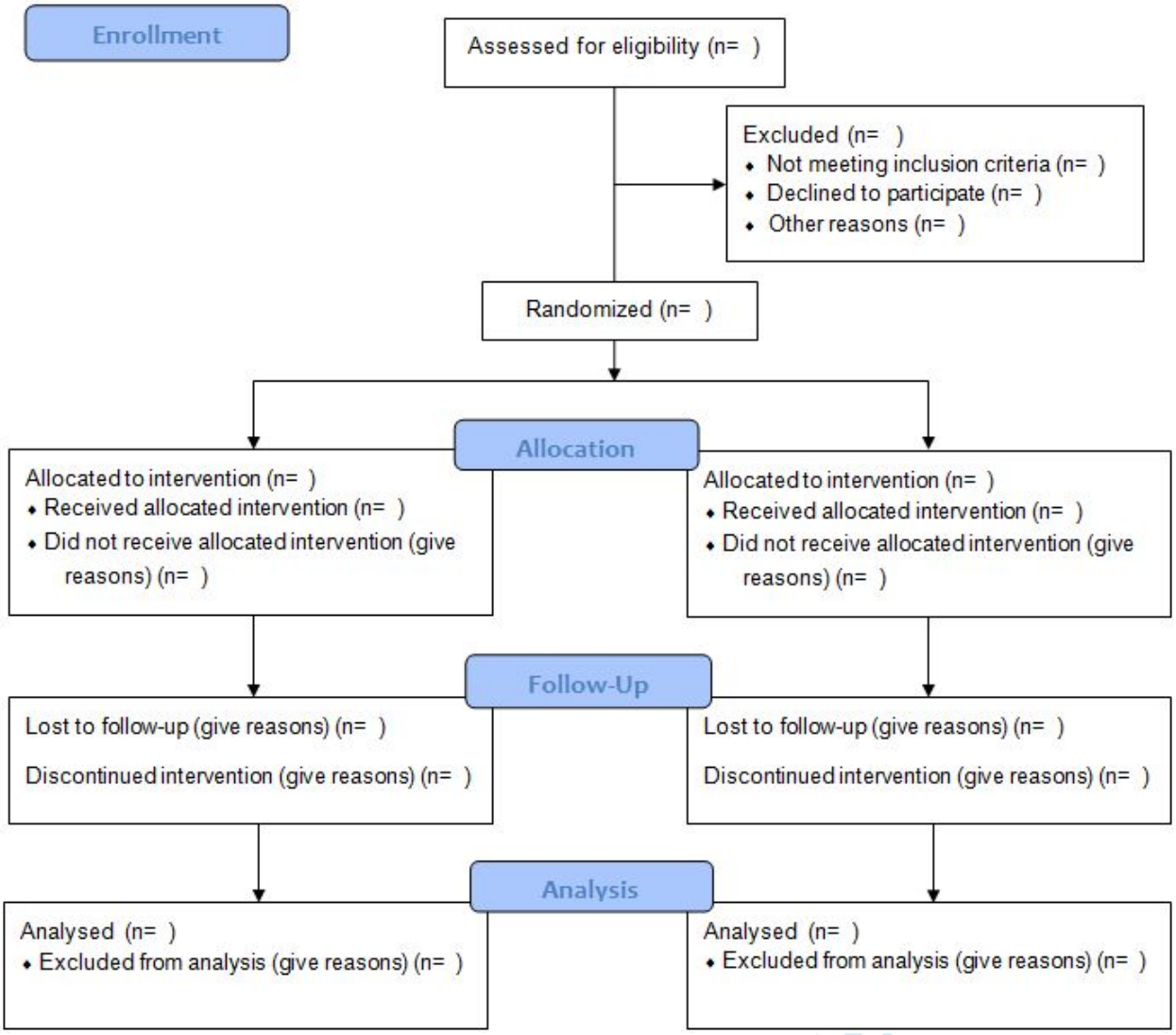

Figure 2. Data Collection Schedule

	PreOp	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D/C
Eligibility			X																					
Recruit			X																					
Consent			X																					
Clinical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
mFisher		X																						
Hunt Hess		X																						
EKG/ECHO	X																							
Pregnancy	X																							
Randomise			X																					
Cilostazol /Placebo			X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Nimodipine		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CT Scan		X	X						X															
DSA/CTA		X								X	X	X												
Coiling		X																						
All AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
mRS		X																						
EVD (Y/N)																								
Symptomatic Vasospasm? (Mark "Y")																								

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
	6b	Explanation for choice of comparators	3, 4
Objectives	7	Specific objectives or hypotheses	4, 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6 Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5, 6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5, 6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5, 6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, 7, 8, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8, 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8, 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6, 7, 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

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Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

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Abstract

Introduction

Delayed cerebral ischemia (DCI) due to cerebral vasospasm (cVS) remains the foremost contributor to morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH). Past efforts in preventing and treating DCI have failed to make any significant progress. To date, our most effective treatment involves the use of nimodipine, a calcium channel blocker. Recent studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent cVS. Thus far, no study has evaluated the effect of cilostazol plus nimodipine on the rate of DCI following aSAH.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of intensive care unit (ICU) stay, and long-term functional and quality of life outcomes will be recorded. All data will be collected with the aim of demonstrating that the use of cilostazol plus nimodipine will not only safely decrease the incidence of delayed cerebral ischemia, but decrease the rates of both radiographic and symptomatic vasospasm with subsequent improvement in long-term functional and quality-of-life (QoL) outcomes when compared to nimodipine alone.

Ethics and Dissemination

Ethical approval was obtained at all participating hospitals by the Ascension Providence Hospital Institutional Review Board (IRB). The results of this study will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04148105

Article Summary

Strengths and limitations of this study:

- First randomized controlled trial in the US to evaluate the effect of cilostazol and nimodipine on delayed cerebral ischemia and cerebral vasospasm
- Adequately powered study
- Includes both objective outcomes (DCI and angiographic vasospasm) and subjective patient-reported-outcomes.
- We limited the study population to anterior circulation aSAH, thereby limiting the generalizability of the results to other patient populations

Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

FDA IND Application: Approved on 4/5/2019 (FDA IND# 143368) for off-label use

Trial Registration Number: NCT04148105

Study Dates: November 2019 – October 2023

Institutional Approvals: The protocol was approved by the Ascension Providence Hospital Institutional Review Board (IRB)

Funding Agency: This study is supported by the Ascension Providence Hospital Institutional research grant. This project is not an industry-sponsored study. The investigators are solely responsible for the protocol design, data collection, analysis and interpretation, writing of the report, or decision to submit this publication

Investigators: Research Site: Investigators and their subsequent roles are detailed in the authors' contributions section. Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine

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Introduction

Aneurysmal subarachnoid hemorrhage is a devastating condition which affects approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been made in the treatment of ruptured aneurysms, however, there has been little progress in the

treatment and prevention of DCI due to cVS.[1,2] Cerebral vasospasm and subsequent DCI remain to be the most prominent cause of morbidity and mortality following aSAH.[3] Although the mechanism and pathogenesis of cVS is not fully understood, it is considered a vital underlying mechanism in DCI.[4,5] Cerebral vasospasm is known to take effect between days 3 and 21 post-aSAH with a peak incidence between days 6 and 10.[2] Current therapy includes definitive treatment of the ruptured aneurysm through either open clipping or endovascular therapy followed by a 21-day course of nimodipine after the onset of SAH.[6–8] Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postprocedural treatment of aSAH for the prevention of DCI.[8,9] This regimen has shown long-term outcome improvement following aSAH.[7,10] Multiple other modalities have been investigated for the treatment and/or prevention of cVS including mechanical removal of blood, cisternal irrigation, Rho kinase inhibitors, triple-H therapy, and numerous endovascular treatments – all of which demonstrated minimal efficacy or limited use.[11–18] Despite years of investigation and improvement, the risk of symptomatic and radiographic vasospasm remains unacceptably high between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23] This also continues to be prevalent at our institution as we observed rates of symptomatic vasospasm and DCI to be 40% and 60%, respectively.

Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26] Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30] In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated the combined application of nimodipine and cilostazol. This combination therapy of nimodipine and cilostazol with possible synergistic effect require further investigation.[31]

Our randomized superiority trial seeks to investigate the combined effect of cilostazol plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when compared to nimodipine alone.

Study Goals and Objectives

Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients with aSAH.

Primary Objective

- To demonstrate that the combined use of cilostazol plus nimodipine when compared to nimodipine alone will decrease the rate of DCI in patients following aSAH

Secondary Objectives

- To demonstrate that the combined use of cilostazol plus nimodipine is not associated with increased drug-related serious adverse events
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of symptomatic and radiographic vasospasm
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the average length of ICU stay
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- To demonstrate that the combined use of cilostazol plus nimodipine will improve Modified Rankin Scores (mRS) and QoL outcomes at 6-months.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow chart.

Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This protocol was approved by the Ascension Providence Hospital IRB and published on ClinicalTrials.gov.

Over a three-year period, consecutive adult patients over the age of 18 who present to our tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). Patients with posterior circulation aSAH are known to be lower risk for developing symptomatic vasospasm and were therefore excluded to avoid bias.[33] After satisfying inclusion/exclusion criteria, patients/family members are consented for full participation in the trial. Once consented, patients are randomized to receive either placebo or intervention with a centralized treatment allocation mechanism and block randomization to assure the two arms achieve equal proportion of patients over time.

All patients, treatment providers, investigators, and statisticians are blinded to the allocation. Blinding is achieved by allocation sequence being concealed to personnel involved in the enrolling, care and evaluation of the patient. The study coordinator will keep the randomization schedule in a cloud-based, secure and encrypted database. Only the study coordinator who monitors the trial, the pharmacist who executes the allocation, the supervising investigator who is not involved in the patients' care or enrollment will have access to the randomization schedule. Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will conceal the identity of the medications.

All participating patients, after undergoing treatment of their ruptured aneurysm (open clipping vs. endovascular coiling) and confirmation of a stable head CT 24-hours post-intervention will be randomized and scheduled to receive their allocation within 48 hours of surgery/intervention for a total of 14 days. In addition to their randomized allocation, all patients will receive a standard aSAH treatment protocol,[7] including 21 days of nimodipine as endorsed by the Congress of Neurological Surgeons. The standardized treatment regimen is summarized in Table 2. Each patient is followed according to the data collection schedule (Figure 2). While in the hospital, the patients are monitored frequently (every hour while in the ICU and every 4 hours while on the floor) for any adverse/serious adverse events (Table 3). Adverse and serious

adverse events (SAE) are defined using a validated classification scheme (Table 4).[34] SAE are defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the study medication will be recorded and reported immediately to the principal investigator and the IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in which knowledge of the allocation will aid in the clinical management of the patient and therefore warrant unblinding of the allocation.

The primary outcome will be defined as new ischemic areas on CT performed at 1-month following initial presentation and not observed on postoperative CT (24-hours post-intervention) determined by blinded neuroradiologists.[35] Ischemic areas or low-density areas on CT performed the day after intervention will be defined as rupture-related or procedural-related infarctions and/or brain injury (such as ventriculostomy tract, craniotomy changes, etc.). Secondary outcomes including symptomatic vasospasm, angiographic vasospasm, length of ICU stay, QoL, and mRS at 1-month, 3-months, & 6-months postoperatively will be prospectively collected. Length of ICU stay will be determined by standardized discharge criteria. Rates of symptomatic vasospasm will be collected and defined as development of a new focal or global neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[36] which was not explained by initial hemorrhage, re-bleeding, hydrocephalus, surgical complications, fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT scanning or MRI and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or CTA.[14,37,38] Radiographic vasospasm will be assessed by either CTA or DSA between 7 and 10 days postoperatively. Radiographic vasospasm with be defined as arterial narrowing not attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of stenosis compared to previous baseline CTA or DSA as determined by blinded neuroradiologists.[14] In each patient, the smallest diameters of 10 arterial segments of the bilateral distal internal carotid arteries (ICA), M1 and M2 segments of the middle cerebral artery (MCA), and A1 and A2 segments of the anterior cerebral artery (ACA) will be measured. Severity of the radiographic vasospasm will be categorized as none or mild (0%-25% decrease in vessel diameter from baseline), moderate (25%-50% decrease in vessel diameter from baseline), or severe (greater than 50% decrease in vessel diameter from baseline). The most affected segment will be used to determine severity of radiographic vasospasm.

To demonstrate superiority, an 80% power is used to minimize chances of false negatives. Assuming an relative effect size of 25% and absolute effect size of 16% with the use of cilostazol and a baseline rate of DCI of 50%, a total sample size was estimated to be 126 patients with an alpha of 0.05. In anticipation for any unforeseen events and those lost to follow-up, we plan to enroll a total of 138 patients.

Patient and Public Involvement

At the time of 1-month postoperative follow-up, patients or their families will be asked to participate as study advisers in our data monitoring and safety committee. There will be 2-4 patient advisers at any given time during the study period, each with a term of 6 months. These patient advisers will share their experience regarding the recruitment process, surgery, and postoperative care in order to help ensure patient safety and satisfaction throughout the study.

Trial Status

At the time of manuscript submission, the trial is ongoing.

Safety Considerations

All study-related adverse events (AE) are recorded and reported immediately to the principal investigator and subsequently to the IRB within 24 hours of the event as previously stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical safety of the study and review adverse events reported to the IRB to determine risk and benefits. Any SAE related to the study medication represents a circumstance under which unblinding is permissible in order to ensure the safety of the participant. At that time, the intervention will be stopped, and any clinical intervention required at the discretion of the attending surgeon will ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be surgeons and related experts who will meet to review the results and any adverse events biannually to evaluate study safety.

Follow-up

Postoperatively, patients will be followed according to the data collection schedule (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be designated at the discretion of the treating attending physician.

Data Management and Statistical Analysis

During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will observe all the steps of the intervention and data collection to ensure proper execution. The progress of data entry, follow-up and recruitment are logged and monitored regularly by the CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and the database will be maintained to within one week of the data collection. CRC will coordinate the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month and 6-months.

Comparability between groups will be evaluated by descriptive and univariate analyses. Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-value less than or equal to 0.05 will be considered statistically significant. Bonferroni's correction will be applied when appropriate. Descriptive statistics will be used in each arm for proportion who did not receive allocated intervention, lost to follow-up, excluded from primary analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses will be performed. An interim analysis will be conducted quarterly during the trial, i.e. after a total of 35, 70, and 105 patients have been enrolled. This is a superiority trial. Early discontinuation of the study will be dependent on overwhelming positive results for the primary outcome. We will discontinue the trial if we achieve $p<0.001$ threshold at the time of interim analysis.[39]

Quality Assurance

Standardized medication orders will conceal the treatment allocation. The study coordinator will be responsible for managing the quality of patient data recorded in the study. All participating research staff will be trained and given written copies of a standard operating procedure to ensure consistency during recruitment, consent, handling of data, and follow-up

evaluation. The study coordinator along with the PI will check weekly the content of the forms and database to ensure accurate and timely entry. Compliance at all study timepoints including enrollment, randomization, intervention, data, and outcome collection will be documented daily on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered into a cloud-based, secure and encrypted database by the research staff. Access to the database will be restricted. Data validation tool has been embedded in the database. Data entered will undergo monthly verification with the source document.

Expected Outcome of the Study

This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally, we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and radiographic vasospasm.

Duration of the Project

Given our institutional volume, we anticipate a study period of 1-3 years assuming 50% of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment and subject to discontinuation if all previously defined criteria are met.

Project Management

Neurosurgery staff will counsel and recruit subjects according to their initial screening to participate in this trial. The neurosurgery staff will check for eligibility using inclusion and exclusion criteria listed in Table 1. They will also explain the study principles, including the detailed experimental in-hospital & postoperative protocol, investigational treatment, potential risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed in a cloud-based, secure, and encrypted database. The designated lead pharmacists will execute the randomized allocation assignment according to the block randomization schedule to maintain masking of allocation. The neuroscience ICU charge nurse will be responsible for overseeing and monitoring administration of the study medication. The neuroscience trained intensive care nursing staff will administer the study medication to the study participants. The PI and support

staff will record all perioperative and postoperative data including study-related adverse events. The study coordinator will ensure and maintain follow-up visits for postoperative secondary outcomes. The neuroradiologists will evaluate and determine primary and secondary outcomes of DCI and vasospasm, respectively. The clinical research methodologist will function as the CRC, supervise the overall execution of the study, and participate in the writing of the protocol and manuscript.

Ethics and Dissemination

The study will be conducted according to the Helsinki Declaration[40], the NIH human subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good Clinical Practice.[41] This protocol is written following the SPIRIT 2013 guidelines and was approved by the hospital IRB. The results of this study will be submitted for publication in peer-reviewed journals and the key findings will be presented at national conferences.

Author Contribution

TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this trial including organization and execution over two hospital campuses. DS contributed to the design and execution of the study drug protocol including randomization, blinding and placebo. MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard operating procedures, and maintaining quality assurance among study participants and their subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT contributed to the drafting of the original manuscript, participated in critically revising the manuscript and agree to be accountable for all aspects of the work.

Funding

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Disclaimer

This project is not an industry-sponsored study. The investigators are solely responsible for the protocol design, data collection, analysis and interpretation, writing of the report, or decision to submit this publication.

Competing Interests

None declared.

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Figure Legend:

Figure 1. Study Design CONSORT Flow Diagram

Figure 2. Data Collection Schedule & Timeline

Table 1. Inclusion, Exclusion, and Withdrawal Criteria

Inclusion	Exclusion
18 years of age or older	Non-aneurysmal subarachnoid hemorrhage
Anterior circulation aneurysm rupture	Multiple ruptured aneurysms
Patients who have undergone surgical intervention	Patients with congestive heart failure
Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan	Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)
Consent to study participation	Active pathological bleeding
	Allergy to cilostazol
	Positive pregnancy test
	Coagulopathy not caused by anti-coagulant use
	History of hemorrhagic complications (gastrointestinal bleeding, etc.)
	Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol
	Patients requiring anticoagulant/antiplatelet treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm)

Criteria for discontinuing follow-up:
Subject wishing to terminate participation in the study at any time throughout his/her participation
CT, computed tomography

Table 2. Standardized Treatment Regimen

Location	Treatment
NSICU and floor	**Intervention group:** • 60 mg nimodipine Q4H for 21 days • 100 mg cilostazol b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]
	Control group: • 60mg nimodipine Q4H for 21 days • Cilostazol placebo b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]

NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PO, post-operative; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography

Table 3. List of Adverse or Serious Adverse Events

Cilostazol		Nimodipine	
Adverse events		**Adverse events**	
	Headache		Hypotension (mild)
	Diarrhea		Diarrhea
	Abnormal Stools		Dyspepsia
	Palpitations		Rash
	Dizziness		Headache
	Peripheral Edema		Flushing
	Dyspepsia		
	Abdominal pain		
	Tachycardia		
Serious adverse events		**Serious adverse events**	
	Hypotension		Hypotension (severe)
	Bleeding		EKG changes
	Stevens Johnson		CHF
	Syndrome		Thromboembolism
	Anaphylaxis		Thrombocytopenia
	Hypersensitivity		Anemia
	Reaction		GI bleeding
	Leukopenia		Ileus
	Thrombocytopenia		Intestinal obstruction
	Tachyarrhythmias		
	Myocardial		
	Infarction		
	Angina		

EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal

Table 4. Definition and Classification of Surgical Complications

Grade	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic, or radiological intervention
3a)	Intervention not under general anesthesia
3b)	Intervention under general anesthesia
Grade 4	Life-threatening complication (including CNS complications)* requiring IC/ICU management
4a)	Single organ dysfunction (including dialysis)
4b)	Multiorgan dysfunction
Grade 5	Death of a patient
Suffix	If the patient suffers from a complication at the time of discharge, the suffix "d" is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

*Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

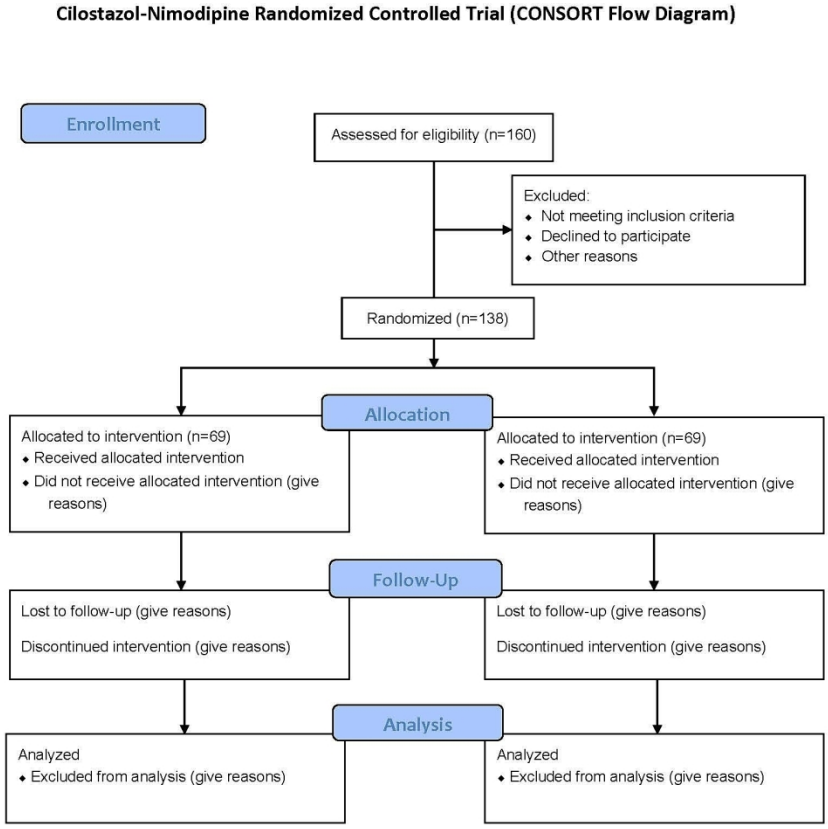

Figure 1. Study Design CONSORT Flow Diagram

143x186mm (300 x 300 DPI)

Figure 2. Data Collection Schedule

	PreOp	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D/C
Eligibility			X																					
Recruit			X																					
Consent			X																					
Clinical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
mFisher		X																						
Hunt Hess		X																						
EKG/ECHO	X																							
Pregnancy	X																							
Randomise			X																					
Cilostazol /Placebo			X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Nimodipine		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CT Scan		X	X						X															
DSA/CTA		X								X	X	X												
Coiling		X																						
All AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
mRS		X																						
EVD (Y/N)																								
Symptomatic Vasospasm? (Mark "Y")																								

Figure 2. Data Collection Schedule & Timeline

181x117mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
	6b	Explanation for choice of comparators	3, 4
Objectives	7	Specific objectives or hypotheses	4, 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6 Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5, 6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5, 6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5, 6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, 7, 8, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8, 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8, 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6, 7, 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

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Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

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Abstract

Introduction

Delayed cerebral ischemia (DCI) due to cerebral vasospasm (cVS) remains the foremost contributor to morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH). Past efforts in preventing and treating DCI have failed to make any significant progress. To date, our most effective treatment involves the use of nimodipine, a calcium channel blocker. Recent studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent cVS. Thus far, no study has evaluated the effect of cilostazol plus nimodipine on the rate of DCI following aSAH.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of intensive care unit (ICU) stay, and long-term functional and quality of life outcomes will be recorded. All data will be collected with the aim of demonstrating that the use of cilostazol plus nimodipine will not only safely decrease the incidence of delayed cerebral ischemia, but decrease the rates of both radiographic and symptomatic vasospasm with subsequent improvement in long-term functional and quality-of-life (QoL) outcomes when compared to nimodipine alone.

Ethics and Dissemination

Ethical approval was obtained at all participating hospitals by the Ascension Providence Hospital Institutional Review Board (IRB). The results of this study will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04148105

Article Summary

Strengths and limitations of this study:

- First randomized controlled trial in the US to evaluate the effect of cilostazol and nimodipine on delayed cerebral ischemia and cerebral vasospasm
- Adequately powered study
- Includes both objective outcomes (DCI and angiographic vasospasm) and subjective patient-reported-outcomes.
- We limited the study population to anterior circulation aSAH, thereby limiting the generalizability of the results to other patient populations

Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

FDA IND Application: Approved on 4/5/2019 (FDA IND# 143368) for off-label use

Trial Registration Number: NCT04148105

Study Dates: November 2019 – October 2023

Institutional Approvals: The protocol was approved by the Ascension Providence Hospital Institutional Review Board (IRB)

Funding Agency: This study is supported by the Ascension Providence Hospital Institutional research grant. This project is not an industry-sponsored study. The investigators are solely responsible for the protocol design, data collection, analysis and interpretation, writing of the report, or decision to submit this publication

Investigators: Research Site: Investigators and their subsequent roles are detailed in the authors' contributions section. Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine

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Introduction

Aneurysmal subarachnoid hemorrhage is a devastating condition which affects approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been made in the treatment of ruptured aneurysms, however, there has been little progress in the

treatment and prevention of DCI due to cVS.[1,2] Cerebral vasospasm and subsequent DCI remain to be the most prominent cause of morbidity and mortality following aSAH.[3] Although the mechanism and pathogenesis of cVS is not fully understood, it is considered a vital underlying mechanism in DCI.[4,5] Cerebral vasospasm is known to take effect between days 3 and 21 post-aSAH with a peak incidence between days 6 and 10.[2] Current therapy includes definitive treatment of the ruptured aneurysm through either open clipping or endovascular therapy followed by a 21-day course of nimodipine after the onset of SAH.[6–8] Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postprocedural treatment of aSAH for the prevention of DCI.[8,9] This regimen has shown long-term outcome improvement following aSAH.[7,10] Multiple other modalities have been investigated for the treatment and/or prevention of cVS including mechanical removal of blood, cisternal irrigation, Rho kinase inhibitors, triple-H therapy, and numerous endovascular treatments – all of which demonstrated minimal efficacy or limited use.[11–18] Despite years of investigation and improvement, the risk of symptomatic and radiographic vasospasm remains unacceptably high between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23] This also continues to be prevalent at our institution as we observed rates of symptomatic vasospasm and DCI to be 40% and 60%, respectively.

Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26] Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30] In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated the combined application of nimodipine and cilostazol. This combination therapy of nimodipine and cilostazol with possible synergistic effect require further investigation.[31]

Our randomized superiority trial seeks to investigate the combined effect of cilostazol plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when compared to nimodipine alone.

Study Goals and Objectives

Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients with aSAH.

Primary Objective

- To demonstrate that the combined use of cilostazol plus nimodipine when compared to nimodipine alone will decrease the rate of DCI in patients following aSAH

Secondary Objectives

- To demonstrate that the combined use of cilostazol plus nimodipine is not associated with increased drug-related serious adverse events
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of symptomatic and radiographic vasospasm
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the average length of ICU stay
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- To demonstrate that the combined use of cilostazol plus nimodipine will improve Modified Rankin Scores (mRS) and QoL outcomes at 6-months.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow chart.

Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This protocol was approved by the Ascension Providence Hospital IRB and published on ClinicalTrials.gov.

Over a three-year period, consecutive adult patients over the age of 18 who present to our tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). Patients with posterior circulation aSAH are known to be lower risk for developing symptomatic vasospasm and were therefore excluded to avoid bias.[33] After satisfying inclusion/exclusion criteria, patients/family members are consented for full participation in the trial. Once consented, patients are randomized to receive either placebo or intervention with a centralized treatment allocation mechanism and block randomization to assure the two arms achieve equal proportion of patients over time.

All patients, treatment providers, investigators, and statisticians are blinded to the allocation. Blinding is achieved by allocation sequence being concealed to personnel involved in the enrolling, care and evaluation of the patient. The study coordinator will keep the randomization schedule in a cloud-based, secure and encrypted database. Only the study coordinator who monitors the trial, the pharmacist who executes the allocation, the supervising investigator who is not involved in the patients' care or enrollment will have access to the randomization schedule. Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will conceal the identity of the medications.

All participating patients, after undergoing treatment of their ruptured aneurysm (open clipping vs. endovascular coiling) and confirmation of a stable head CT 24-hours post-intervention will be randomized and scheduled to receive their allocation within 48 hours of surgery/intervention for a total of 14 days. In addition to their randomized allocation, all patients will receive a standard aSAH treatment protocol,[7] including 21 days of nimodipine as endorsed by the Congress of Neurological Surgeons. The standardized treatment regimen is summarized in Table 2. Each patient is followed according to the data collection schedule (Figure 2). While in the hospital, the patients are monitored frequently (every hour while in the ICU and every 4 hours while on the floor) for any adverse/serious adverse events (Table 3). Adverse and serious

adverse events (SAE) are defined using a validated classification scheme (Table 4).[34] SAE are defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the study medication will be recorded and reported immediately to the principal investigator and the IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in which knowledge of the allocation will aid in the clinical management of the patient and therefore warrant unblinding of the allocation.

The primary outcome will be defined as new ischemic areas on CT performed at 1-month following initial presentation and not observed on postoperative CT (24-hours post-intervention) determined by blinded neuroradiologists.[35] Ischemic areas or low-density areas on CT performed the day after intervention will be defined as rupture-related or procedural-related infarctions and/or brain injury (such as ventriculostomy tract, craniotomy changes, etc.). Secondary outcomes including symptomatic vasospasm, angiographic vasospasm, length of ICU stay, QoL, and mRS at 1-month, 3-months, & 6-months postoperatively will be prospectively collected. Length of ICU stay will be determined by standardized discharge criteria. Rates of symptomatic vasospasm will be collected and defined as development of a new focal or global neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[36] which was not explained by initial hemorrhage, re-bleeding, hydrocephalus, surgical complications, fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT scanning or MRI and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or CTA.[14,37,38] Radiographic vasospasm will be assessed by either CTA or DSA between 7 and 10 days postoperatively. Radiographic vasospasm with be defined as arterial narrowing not attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of stenosis compared to previous baseline CTA or DSA as determined by blinded neuroradiologists.[14] In each patient, the smallest diameters of 10 arterial segments of the bilateral distal internal carotid arteries (ICA), M1 and M2 segments of the middle cerebral artery (MCA), and A1 and A2 segments of the anterior cerebral artery (ACA) will be measured. Severity of the radiographic vasospasm will be categorized as none or mild (0%-25% decrease in vessel diameter from baseline), moderate (25%-50% decrease in vessel diameter from baseline), or severe (greater than 50% decrease in vessel diameter from baseline). The most affected segment will be used to determine severity of radiographic vasospasm.

To demonstrate superiority, an 80% power is used to minimize chances of false negatives. Assuming a relative effect size of 15% with the use of cilostazol and a baseline rate of DCI of 50%, a total sample size was estimated to be 349 patients with an alpha of 0.05. In anticipation for any unforeseen events and those lost to follow-up, we plan to enroll a total of 390 patients.

Patient and Public Involvement

At the time of 1-month postoperative follow-up, patients or their families will be asked to participate as study advisers in our data monitoring and safety committee. There will be 2-4 patient advisers at any given time during the study period, each with a term of 6 months. These patient advisers will share their experience regarding the recruitment process, surgery, and postoperative care in order to help ensure patient safety and satisfaction throughout the study.

Trial Status

At the time of manuscript submission, the trial is ongoing.

Safety Considerations

All study-related adverse events (AE) are recorded and reported immediately to the principal investigator and subsequently to the IRB within 24 hours of the event as previously stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical safety of the study and review adverse events reported to the IRB to determine risk and benefits. Any SAE related to the study medication represents a circumstance under which unblinding is permissible in order to ensure the safety of the participant. At that time, the intervention will be stopped, and any clinical intervention required at the discretion of the attending surgeon will ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be surgeons and related experts who will meet to review the results and any adverse events biannually to evaluate study safety.

Follow-up

Postoperatively, patients will be followed according to the data collection schedule (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome

and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be designated at the discretion of the treating attending physician.

Data Management and Statistical Analysis

During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will observe all the steps of the intervention and data collection to ensure proper execution. The progress of data entry, follow-up and recruitment are logged and monitored regularly by the CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and the database will be maintained to within one week of the data collection. CRC will coordinate the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month and 6-months.

Comparability between groups will be evaluated by descriptive and univariate analyses. Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-value less than or equal to 0.05 will be considered statistically significant. Bonferroni's correction will be applied when appropriate. Descriptive statistics will be used in each arm for proportion who did not receive allocated intervention, lost to follow-up, excluded from primary analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses will be performed. An interim analysis will be conducted quarterly during the trial, i.e. after a total of 75, 150, and 250 patients have been enrolled. This is a superiority trial. Early discontinuation of the study will be dependent on overwhelming positive results for the primary outcome. We will discontinue the trial if we achieve $p<0.001$ threshold at the time of interim analysis.[39]

Quality Assurance

Standardized medication orders will conceal the treatment allocation. The study coordinator will be responsible for managing the quality of patient data recorded in the study. All participating research staff will be trained and given written copies of a standard operating procedure to ensure consistency during recruitment, consent, handling of data, and follow-up evaluation. The study coordinator along with the PI will check weekly the content of the forms and database to ensure accurate and timely entry. Compliance at all study timepoints including

enrollment, randomization, intervention, data, and outcome collection will be documented daily on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered into a cloud-based, secure and encrypted database by the research staff. Access to the database will be restricted. Data validation tool has been embedded in the database. Data entered will undergo monthly verification with the source document.

Expected Outcome of the Study

This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally, we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and radiographic vasospasm.

Duration of the Project

Given our institutional volume, we anticipate a study period of 1-3 years assuming 50% of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment and subject to discontinuation if all previously defined criteria are met.

Project Management

Neurosurgery staff will counsel and recruit subjects according to their initial screening to participate in this trial. The neurosurgery staff will check for eligibility using inclusion and exclusion criteria listed in Table 1. They will also explain the study principles, including the detailed experimental in-hospital & postoperative protocol, investigational treatment, potential risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed in a cloud-based, secure, and encrypted database (see supplementary text). The designated lead pharmacists will execute the randomized allocation assignment according to the block randomization schedule to maintain masking of allocation. The neuroscience ICU charge nurse will be responsible for overseeing and monitoring administration of the study medication. The neuroscience trained intensive care nursing staff will administer the study medication to the study participants. The PI and support staff will record all perioperative and postoperative data including study-related adverse events. The study coordinator will ensure and maintain follow-up

visits for postoperative secondary outcomes. The neuroradiologists will evaluate and determine primary and secondary outcomes of DCI and vasospasm, respectively. The clinical research methodologist will function as the CRC, supervise the overall execution of the study, and participate in the writing of the protocol and manuscript.

Ethics and Dissemination

The study will be conducted according to the Helsinki Declaration[40], the NIH human subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good Clinical Practice.[41] This protocol is written following the SPIRIT 2013 guidelines and was approved by Ascension Providence Hospital IRB. The results of this study will be submitted for publication in peer-reviewed journals and the key findings will be presented at national conferences.

Author Contribution

TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this trial including organization and execution over two hospital campuses. DS contributed to the design and execution of the study drug protocol including randomization, blinding and placebo. MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard operating procedures, and maintaining quality assurance among study participants and their subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT contributed to the drafting of the original manuscript, participated in critically revising the manuscript and agree to be accountable for all aspects of the work.

Funding

This trial is supported by the Ascension Providence Hospital Institutional research grant.

Disclaimer

This project is not an industry-sponsored study. The investigators are solely responsible for the protocol design, data collection, analysis and interpretation, writing of the report, or decision to submit this publication.

Competing Interests

None declared.

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Figure Legend:

Figure 1. Study Design CONSORT Flow Diagram

Figure 2. Data Collection Schedule & Timeline

Table 1. Inclusion, Exclusion, and Withdrawal Criteria

Inclusion	Exclusion
18 years of age or older	Non-aneurysmal subarachnoid hemorrhage
Anterior circulation aneurysm rupture	Multiple ruptured aneurysms
Patients who have undergone surgical intervention	Patients with congestive heart failure
Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan	Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)
Consent to study participation	Active pathological bleeding
	Allergy to cilostazol
	Positive pregnancy test
	Coagulopathy not caused by anti-coagulant use
	History of hemorrhagic complications (gastrointestinal bleeding, etc.)
	Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol
	Patients requiring anticoagulant treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm) ***Exception***: patients who require the use of aspirin as determined by the staff member performing the coil embolization for thromboembolic event protection due to a small amount of coil extrusion from the aneurysm neck with be allowed to be included into the trial
Criteria for discontinuing follow-up:	
Subject wishing to terminate participation in the study at any time throughout his/her participation	
CT, computed tomography	

Table 2. Standardized Treatment Regimen

Location	Treatment
NSICU and floor	**Intervention group:** • 60 mg nimodipine Q4H for 21 days • 100 mg cilostazol b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]
	Control group: • 60mg nimodipine Q4H for 21 days • Cilostazol placebo b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]

NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PO, post-operative; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography

Table 3. List of Adverse or Serious Adverse Events

Cilostazol		Nimodipine	
Adverse events		**Adverse events**	
	Headache		Hypotension (mild)
	Diarrhea		Diarrhea
	Abnormal Stools		Dyspepsia
	Palpitations		Rash
	Dizziness		Headache
	Peripheral Edema		Flushing
	Dyspepsia		
	Abdominal pain		
	Tachycardia		
Serious adverse events		**Serious adverse events**	
	Hypotension		Hypotension (severe)
	Bleeding		EKG changes
	Stevens Johnson		CHF
	Syndrome		Thromboembolism
	Anaphylaxis		Thrombocytopenia
	Hypersensitivity		Anemia
	Reaction		GI bleeding
	Leukopenia		Ileus
	Thrombocytopenia		Intestinal obstruction
	Tachyarrhythmias		
	Myocardial		
	Infarction		
	Angina		

EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal

Table 4. Definition and Classification of Surgical Complications

Grade	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic, or radiological intervention
3a)	Intervention not under general anesthesia
3b)	Intervention under general anesthesia
Grade 4	Life-threatening complication (including CNS complications)* requiring IC/ICU management
4a)	Single organ dysfunction (including dialysis)
4b)	Multiorgan dysfunction
Grade 5	Death of a patient
Suffix	If the patient suffers from a complication at the time of discharge, the suffix "d" is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

*Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

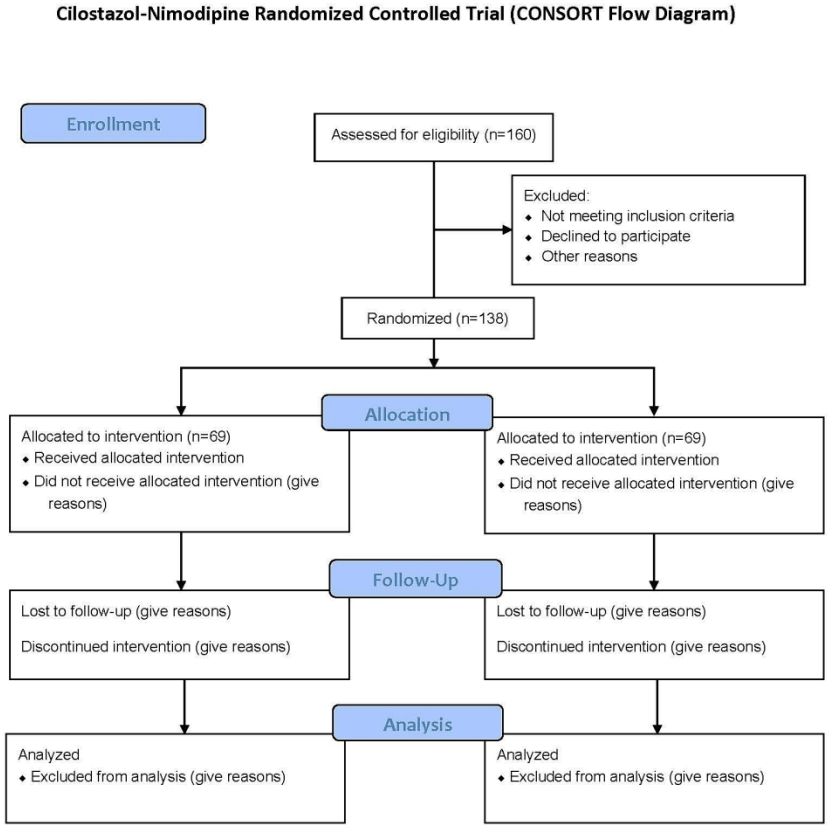

Figure 1. Study Design CONSORT Flow Diagram

143x186mm (300 x 300 DPI)

Figure 2. Data Collection Schedule

	PreOp	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D/C
Eligibility			X																					
Recruit			X																					
Consent			X																					
Clinical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
mFisher		X																						
Hunt Hess		X																						
EKG/ECHO	X																							
Pregnancy	X																							
Randomise			X																					
Cilostazol /Placebo			X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Nimodipine		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CT Scan		X	X						X															
DSA/CTA		X								X	X	X												
Coiling		X																						
All AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
mRS		X																						
EVD (Y/N)																								
Symptomatic Vasospasm? (Mark "Y")																								

Figure 2. Data Collection Schedule & Timeline

181x117mm (300 x 300 DPI)

Ascension Providence Hospital
16001 West Nine Mile Road, Southfield, MI

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

AND

AUTHORIZATION TO USE OR DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH TO BE CONDUCTED AT PROVIDENCE HOSPITAL, PROVIDENCE PARK HOSPITAL AND MEDICAL CENTERS

Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage (SAH): A Multicenter, Randomized, Double-blinded, Placebo-controlled Trial

Principal Investigator:

Boyd Richards D.O. Neurological Surgery

Co-Investigators:

Doris Tong, MD; Chad F. Claus; Sina Rajamand, DO; Ascher Kaufmann, MD; Troy Dawley, DO; Prashant Kelkar, DO; Teck M Soo, MD

Office Phone: (248) 569-7745

Please read the following material to ensure that you are informed of the nature of this clinical research study and how you will participate in it. Signing this form will indicate that you have been informed and that you give your consent to participate in a free manner. Federal regulations require written informed consent prior to participation in this clinical research study.

INTRODUCTION

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and any applicable risks. Your signature on this form also means that you want to take part in this study. This is a randomized multi-center double-blinded controlled clinical trial. Your doctor will explain the clinical research study to you. Research studies or clinical trials only include people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you recently underwent either a surgical or endovascular intervention for the treatment of intracranial hemorrhage and are being seen at Ascension Providence Hospital.

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BACKGROUND

This research study is designed to evaluate the effects of the combination between Cilostazol and Nimodipine on delayed cerebral ischemia due to cerebral vasospasm after anterior circulation aneurysmal subarachnoid hemorrhage. Cilostazol is a selective phosphodiesterase-3 inhibitor which exerts a vasodilatory and antithrombotic effect. Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postoperative treatment of aneurysmal subarachnoid hemorrhage. We seek to compare the incidence of delayed cerebral ischemia when treated with Cilostazol and Nimodipine versus when treated with Nimodipine alone. The researchers will compare two different groups. With your consent, you will be randomly assigned to a group who receives conventional post-intervention treatment with Nimodipine or to a group who receives conventional post-intervention treatment with Nimodipine in addition to 100mg Cilostazol twice daily for 14 days after your intervention. Your chances of being in one group are 1 in 2, much like flipping a coin. This is a double-blind study, which means neither you nor your doctor will know which group you are in until the study is completed.

Imaging will be taken 1 day after your intervention, 7 ± 2 days after your intervention, approximately 1 month and 6 months after discharge as part of your standard of care. More imaging, including but not limited to CTA or MRI scans, may be needed depending on the individual care management plan.

PURPOSE OF THE STUDY

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will decrease the rate of delayed cerebral ischemia during your hospital stay

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will not lead to significant increase in bleeding disorders

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone, will lead to significant improvement in the following:
    - The rates of symptomatic vasospasm
    - The rates of angiographic vasospasm
    - Quality-of-life outcomes: Modified Rankin Scores (mRS) at Pre, 1, 3 and 6 months postoperatively and SF-12 at 1, 3 and 6 months postoperatively
    - Length of hospitalization
    - Length of stay in the intensive care unit (ICU)
    - Duration of ventriculostomy use

How many people will take part in this study?

Approximately 120 men and/or women of at least 18 years of age will be in this study.

How long will I be in this study?

You will participate in this study for 6 months. Your part in the study is completed once you have completed your 6-month follow-up visit with your surgeon including completion of the modified Rankin Scores and SF-12 questionnaires.

What will happen if I take part in this research study?

You have recently undergone either a surgical or endovascular intervention for the treatment of intracranial hemorrhage and your surgeon has determined that you meet eligibility criteria to participate in this research study.

After your enrollment, you will receive the necessary post-intervention care. If you are randomly selected into the treatment group, you will receive the drug Cilostazol in addition to your standard care regimen. If you are not, you will receive the standard care regimen plus a placebo. However, your knowledge of which group you are assigned to, as well as the administration of that drug will not be known to you. Throughout your hospital stay, data will be collected including any Cilostazol-related adverse events, occurrence of symptomatic vasospasm, and length of stay, among others. This all will be collected from either your electronic medical record or directly from you by a blinded member our staff. You will follow-up in clinic with your surgeon for standard post-interventional evaluation which includes 1, 3, and 6-month follow-up visit along with completion of modified Rankin Score and SF-12 questionnaires.

Risk to patients

Important risks and side effects of 100mg Cilostazol may include:

Frequent side effects:
- Headche
- Abnormal stools
- Diarrhea

Infrequent side effects:
- Abdominal pain
- Back pain
- Infection
- Palpitation
- Tachycardia
- Flatulence
- Nausea
- Peripheral edema
- Myalgia
- Dizziness
- Cough increased
- Pharyngitis
- Rhinitis

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Rare side effects:

- Chills
- Vertigo
- Other rare side effects

***Frequent* (occurs in 10-25% of people – 10 to 25 out of 100 people)**
***Infrequent* (occurs in 1-10% of people – 1 to 10 out of 100 people)**
***Rare* (occurs in less than 1% of people – less than 1 out of 100 people)**

Every effort will be made to minimize any discomfort and these risks. There may be other risks that are unknown at this time.

You should tell the person obtaining your consent if you are currently participating in any other medical research studies.

What are the benefits of the study?

There may be no direct benefit to you in participating in the study. However, it is possible that you may have less chance of delayed cerebral ischemia or symptomatic and angiographic cerebral vasospasm following your surgery. You may also experience an improvement in postoperative quality-of-life. In the future, other patients may benefit from the results of this study, when they become known.

What other options are there?

One option is to not participate. You do not have to participate in this research study in order to continue receiving treatment for your condition. Electing to not participate in this study will not affect your care whatsoever.

Do I have to participate in this study?

Your participation in this study is voluntary. Your refusal to participate will cause no penalty or loss of benefits which you would otherwise receive. If you decide to participate, you may change your mind about being in the study and may quit at any time without penalty of loss of benefits regarding your future care. If new information becomes available during the study that may affect your willingness to continue in the study, your doctor and/or his/her associate will discuss this information with you. Also, your doctor may stop your participation at any time if he/she feels it is in your best interest.

Will it cost anything to participate?

We do not expect there to be any additional costs to you if you participate in this study. Besides the drug treatment, the additional care you would receive during this study is considered standard of care and would not otherwise be different.

Compensation to patients – None

There is no compensation or pay offered for your medical care if you are injured as a result of participating in this study. You and/or your medical insurance may have to pay for your medical care if you are injured as a result of participating in this study. You are not giving up any of your legal rights by signing this consent form.

Confidentiality of Records

The principal investigators will have access to your medical records and your test results. While absolute confidentiality cannot be guaranteed, all research material which could identify you will be kept as confidential as possible within the state and federal laws. You should be aware that your medical records could be examined by the study staff, the Institutional Review Board (a group of people who review the research to protect your rights), or government agencies in order to verify the data collected during this research study. If the results of this study are presented in any public forum, you will not be personally identified.

Participant HIPAA Authorization to Use and Disclose Protected Health Information (PHI)

Your participation in this study will require the use and disclosure of certain medical and other information about you. The information that may be used or disclosed includes any and all health care records such as: laboratory, pathology and/or radiology results, CT scans, MRI, and Protected Health Information (PHI) previously collected for research purposes.

Your PHI will be used in the following ways: To conduct the research and to ensure that the research meets legal, institutional or accreditation requirements.

Your authorization to use and disclose the above information has no expiration date.

Your PHI may be seen, used or disclosed to the following:

- The researchers and members of the research team
- Other health care providers or employees of Ascension Providence Hospital
- Representatives of the Institutional Review Board (IRB), the FDA (Food and Drug Administration), or other governmental agencies involved in research monitoring.
- Other agencies as required by law.

You have the right to review your PHI. However, if you agree to participate in the research study and sign below, you will not be able to look at your research information until the research study is completed.

You do not have to sign this authorization. If you decide not to sign the authorization it will not affect your treatment or eligibility for health benefits. However, if you do not sign this authorization you may not participate in this study.

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You may withdraw your authorization at any time by notifying the principal investigator in writing, but the withdrawal will not affect any information already disclosed. However, you need to be aware that your written withdrawal of this Authorization may result in the termination of the research-related treatment being provided to you.

This study and more information will be available at ClinicalTrials.gov which is a registry and results database of publicly and privately supported research studies conducted in the United States and around the world. Sponsors or investigators of certain clinical trials are required by U.S. law to register their trials on and submit summary results to ClinicalTrials.gov. Each study record includes a summary of the study protocol, including the purpose, recruitment status, and eligibility criteria. Study locations and specific contact information are listed to assist with enrollment. You can visit ClinicalTrials.gov for more information regarding this study.

Who do I call with questions about the study or to report an injury?

If you have any questions regarding a research-related injury, you can contact:
Troy Dawley, DO
22250 Providence Dr Ste 601, Southfield, MI 48075
(214) 886-6111

If you have any questions about your rights as a subject in this clinical research study, you may contact the IRB representative at 248-849-8889 at Ascension Providence Hospital.

CONSENT

You have had the opportunity to fully discuss the purpose of this clinical research study and how it will be carried out. Your questions have been answered. Your participation in this study is fully voluntary and you may withdraw at any time.

Your signature below acknowledges that you voluntarily agree to participate in this clinical research study, and you will receive a signed copy of this form.

_____
Printed Name of Research Subject

_____ _____
Signature of Research Subject Date

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Legally Authorized Representative (if applicable):

_____

Printed Name of Legally Authorized Representative

_____ _____

Signature of Legally Authorized Representative Date

Check Relationship to Subject:*

☐ Legal Guardian or Legally Authorized Representative for Medical Care (LARM)
☐ Spouse

☐ Adult Son or Daughter ☐ Mother or Father ☐ Adult Brother or Sister ☐ Other, explain:

Reason subject is unable to sign for self:

**If a Legal Guardian or Legally Authorized Representative for Medical Care (LARM) has not been appointed, then consent should be obtained from the closest next of kin (in the order listed above). When that individual is unavailable or refuses to act the next in order should be contacted.*
** If there is a disagreement among next of kin regarding the appropriateness of the treatment plan, Clinical Safety Risk Management may be contacted. Outside of business hours, Clinical Safety Risk Management can be contacted through any St. John Hospital operator.*

_____

Printed Name of Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
	6b	Explanation for choice of comparators	3, 4
Objectives	7	Specific objectives or hypotheses	4, 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6 Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5, 6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5, 6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5, 6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, 7, 8, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8, 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8, 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6, 7, 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

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Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial Protocol

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Abstract

Introduction

Delayed cerebral ischemia (DCI) due to cerebral vasospasm (cVS) remains the foremost contributor to morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH). Past efforts in preventing and treating DCI have failed to make any significant progress. To date, our most effective treatment involves the use of nimodipine, a calcium channel blocker. Recent studies have suggested that cilostazol, a platelet aggregation inhibitor, may prevent cVS. Thus far, no study has evaluated the effect of cilostazol plus nimodipine on the rate of DCI following aSAH.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial investigating the effect of cilostazol on delayed cerebral ischemia. Data concerning rates of delayed cerebral ischemia, symptomatic & radiographic vasospasm, length of intensive care unit (ICU) stay, and long-term functional and quality of life outcomes will be recorded. All data will be collected with the aim of demonstrating that the use of cilostazol plus nimodipine will not only safely decrease the incidence of delayed cerebral ischemia, but decrease the rates of both radiographic and symptomatic vasospasm with subsequent improvement in long-term functional and quality-of-life (QoL) outcomes when compared to nimodipine alone.

Ethics and Dissemination

Ethical approval was obtained at all participating hospitals by the Ascension Providence Hospital Institutional Review Board (IRB). The results of this study will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04148105

Article Summary

Strengths and limitations of this study:

- First randomized controlled trial in the US to evaluate the effect of cilostazol and nimodipine on delayed cerebral ischemia and cerebral vasospasm
- Adequately powered study
- Includes both objective outcomes (DCI and angiographic vasospasm) and subjective patient-reported-outcomes.
- We limited the study population to anterior circulation aSAH, thereby limiting the generalizability of the results to other patient populations

Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

FDA IND Application: Approved on 4/5/2019 (FDA IND# 143368) for off-label use

Trial Registration Number: NCT04148105

Study Dates: November 2019 – October 2023

Institutional Approvals: The protocol was approved by the Ascension Providence Hospital Institutional Review Board (IRB)

Funding Agency: This study is supported by the Ascension Providence Hospital Institutional research grant (1478832-5). This project is not an industry-sponsored study. The investigators are solely responsible for the protocol design, data collection, analysis and interpretation, writing of the report, or decision to submit this publication

Investigators: Research Site: Investigators and their subsequent roles are detailed in the authors' contributions section. Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine

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Introduction

Aneurysmal subarachnoid hemorrhage is a devastating condition which affects approximately 9 in 100,000 people annually around the world.[1,2] Much advance has been made in the treatment of ruptured aneurysms, however, there has been little progress in the

treatment and prevention of DCI due to cVS.[1,2] Cerebral vasospasm and subsequent DCI remain to be the most prominent cause of morbidity and mortality following aSAH.[3] Although the mechanism and pathogenesis of cVS is not fully understood, it is considered a vital underlying mechanism in DCI.[4,5] Cerebral vasospasm is known to take effect between days 3 and 21 post-aSAH with a peak incidence between days 6 and 10.[2] Current therapy includes definitive treatment of the ruptured aneurysm through either open clipping or endovascular therapy followed by a 21-day course of nimodipine after the onset of SAH.[6–8] Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postprocedural treatment of aSAH for the prevention of DCI.[8,9] This regimen has shown long-term outcome improvement following aSAH.[7,10] Multiple other modalities have been investigated for the treatment and/or prevention of cVS including mechanical removal of blood, cisternal irrigation, Rho kinase inhibitors, triple-H therapy, and numerous endovascular treatments – all of which demonstrated minimal efficacy or limited use.[11–18] Despite years of investigation and improvement, the risk of symptomatic and radiographic vasospasm remains unacceptably high between 20%-50%[11,19–21] and as high as 80%, respectively.[11,21–23] This also continues to be prevalent at our institution as we observed rates of symptomatic vasospasm and DCI to be 40% and 60%, respectively.

Cilostazol, a platelet aggregation inhibitor used for the treatment of symptomatic intermittent claudication, is a selective phosphodiesterase-3 inhibitor that exerts a vasodilatory and antithrombotic effect.[9] This vasodilatory effect has been demonstrated on healthy cerebral arteries[24], and shown to prevent cerebral vasospasm in SAH animal models.[25,26] Subsequent human trials have demonstrated cilostazol to be safe and effective at decreasing both radiographic and symptomatic cerebral vasospasm, with no serious adverse reactions.[9,27–30] In addition, two recent systematic reviews and meta-analyses both concluded that cilostazol effectively reduced incidences of vasospasm, new cerebral infarction, and poor outcomes in patients following aSAH.[31,32] However, to date, no randomized controlled trial has evaluated the combined application of nimodipine and cilostazol. This combination therapy of nimodipine and cilostazol with possible synergistic effect require further investigation.[31]

Our randomized superiority trial seeks to investigate the combined effect of cilostazol plus nimodipine on cerebral vasospasm, rates of DCI, and functional neurologic outcome when compared to nimodipine alone.

Study Goals and Objectives

Our goal is to demonstrate that cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients with aSAH.

Primary Objective

- To demonstrate that the combined use of cilostazol plus nimodipine when compared to nimodipine alone will decrease the rate of DCI in patients following aSAH

Secondary Objectives

- To demonstrate that the combined use of cilostazol plus nimodipine is not associated with increased drug-related serious adverse events
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease rates of symptomatic and radiographic vasospasm
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the average length of ICU stay
- To demonstrate that the combined use of cilostazol plus nimodipine will decrease the incidence of secondary endovascular intervention (intra-arterial verapamil or angioplasty)
- To demonstrate that the combined use of cilostazol plus nimodipine will improve Modified Rankin Scores (mRS) and QoL outcomes at 6-months.

Methods and Analysis

This is a multicenter, double-blinded, randomized, placebo-controlled superiority trial in adults in accordance with SPIRIT guidelines. This study will have a two-arm parallel design without cross-over and equal randomization per arm. Figure 1 outlines the CONSORT flow chart.

Table 1 provides details to the inclusion, exclusion criteria, and withdrawal criteria. This protocol was approved by the Ascension Providence Hospital IRB and published on ClinicalTrials.gov.

Over a three-year period, consecutive adult patients over the age of 18 who present to our tertiary care institution with aSAH diagnosed on computerized tomography (CT) and CT angiography (CTA) will be assessed for eligibility. Recruitment of participants is based on those adults who are diagnosed with aSAH due to ruptured anterior circulation aneurysm(s). Patients with posterior circulation aSAH are known to be lower risk for developing symptomatic vasospasm and were therefore excluded to avoid bias.[33] After satisfying inclusion/exclusion criteria, patients/family members are consented for full participation in the trial. Once consented, patients are randomized to receive either placebo or intervention with a centralized treatment allocation mechanism and block randomization to assure the two arms achieve equal proportion of patients over time.

All patients, treatment providers, investigators, and statisticians are blinded to the allocation. Blinding is achieved by allocation sequence being concealed to personnel involved in the enrolling, care and evaluation of the patient. The study coordinator will keep the randomization schedule in a cloud-based, secure and encrypted database. Only the study coordinator who monitors the trial, the pharmacist who executes the allocation, the supervising investigator who is not involved in the patients' care or enrollment will have access to the randomization schedule. Pharmacy will prepare identical appearing tablets/capsules/syringes as placebo which will conceal the identity of the medications.

All participating patients, after undergoing treatment of their ruptured aneurysm (open clipping vs. endovascular coiling) and confirmation of a stable head CT 24-hours post-intervention will be randomized and scheduled to receive their allocation within 48 hours of surgery/intervention for a total of 14 days. In addition to their randomized allocation, all patients will receive a standard aSAH treatment protocol,[7] including 21 days of nimodipine as endorsed by the Congress of Neurological Surgeons. The standardized treatment regimen is summarized in Table 2. Each patient is followed according to the data collection schedule (Figure 2). While in the hospital, the patients are monitored frequently (every hour while in the ICU and every 4 hours while on the floor) for any adverse/serious adverse events (Table 3). Adverse and serious

adverse events (SAE) are defined using a validated classification scheme (Table 4).[34] SAE are defined as a grade 2 or higher (Table 4). All unexpected SAE related or possibly related to the study medication will be recorded and reported immediately to the principal investigator and the IRB within 24 hours. In addition to cessation of the intervention, SAEs may present a situation in which knowledge of the allocation will aid in the clinical management of the patient and therefore warrant unblinding of the allocation.

The primary outcome will be defined as new ischemic areas on CT performed at 1-month following initial presentation and not observed on postoperative CT (24-hours post-intervention) determined by blinded neuroradiologists.[35] Ischemic areas or low-density areas on CT performed the day after intervention will be defined as rupture-related or procedural-related infarctions and/or brain injury (such as ventriculostomy tract, craniotomy changes, etc.). Secondary outcomes including symptomatic vasospasm, angiographic vasospasm, length of ICU stay, QoL, and mRS at 1-month, 3-months, & 6-months postoperatively will be prospectively collected. Length of ICU stay will be determined by standardized discharge criteria. Rates of symptomatic vasospasm will be collected and defined as development of a new focal or global neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[36] which was not explained by initial hemorrhage, re-bleeding, hydrocephalus, surgical complications, fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT scanning or MRI and angiographic vasospasm on diagnostic cerebral angiogram (DSA) or CTA.[14,37,38] Radiographic vasospasm will be assessed by either CTA or DSA between 7 and 10 days postoperatively. Radiographic vasospasm with be defined as arterial narrowing not attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia as a ratio of stenosis compared to previous baseline CTA or DSA as determined by blinded neuroradiologists.[14] In each patient, the smallest diameters of 10 arterial segments of the bilateral distal internal carotid arteries (ICA), M1 and M2 segments of the middle cerebral artery (MCA), and A1 and A2 segments of the anterior cerebral artery (ACA) will be measured. Severity of the radiographic vasospasm will be categorized as none or mild (0%-25% decrease in vessel diameter from baseline), moderate (25%-50% decrease in vessel diameter from baseline), or severe (greater than 50% decrease in vessel diameter from baseline). The most affected segment will be used to determine severity of radiographic vasospasm.

To demonstrate superiority, an 80% power is used to minimize chances of false negatives. Assuming a relative effect size of 29% with the use of cilostazol and a baseline rate of DCI of 50%, a total sample size was estimated to be 100 patients with an alpha of 0.05. In anticipation for any unforeseen events and those lost to follow-up, we plan to enroll a total of 120 patients.

Patient and Public Involvement

At the time of 1-month postoperative follow-up, patients or their families will be asked to participate as study advisers in our data monitoring and safety committee. There will be 2-4 patient advisers at any given time during the study period, each with a term of 6 months. These patient advisers will share their experience regarding the recruitment process, surgery, and postoperative care in order to help ensure patient safety and satisfaction throughout the study.

Trial Status

At the time of manuscript submission, the trial is ongoing.

Safety Considerations

All study-related adverse events (AE) are recorded and reported immediately to the principal investigator and subsequently to the IRB within 24 hours of the event as previously stated. All AE will be logged in an adverse outcome reporting log as needed. The institutional data safety monitoring board (DSMB) will be responsible for monitoring the clinical and surgical safety of the study and review adverse events reported to the IRB to determine risk and benefits. Any SAE related to the study medication represents a circumstance under which unblinding is permissible in order to ensure the safety of the participant. At that time, the intervention will be stopped, and any clinical intervention required at the discretion of the attending surgeon will ensue and documented and presented to the IRB and DSMB. Members of the DSMB will be surgeons and related experts who will meet to review the results and any adverse events biannually to evaluate study safety.

Follow-up

Postoperatively, patients will be followed according to the data collection schedule (Figure 2). Data will be prospectively collected using a standardized specific adverse outcome

and clinical report form (CRF). Once discharged from the hospital, patients will be scheduled follow-up visits at 1-month, 3-months, and 6-months. Any additional follow-up will be designated at the discretion of the treating attending physician.

Data Management and Statistical Analysis

During the first two weeks of the trial, the PI, clinical research coordinator (CRC) will observe all the steps of the intervention and data collection to ensure proper execution. The progress of data entry, follow-up and recruitment are logged and monitored regularly by the CRC. The CRF will be entered into the database within 24 hours of the patient's discharge and the database will be maintained to within one week of the data collection. CRC will coordinate the postoperative follow-up and evaluate the capture rate for QoL and mRS at 1-month, 3-month and 6-months.

Comparability between groups will be evaluated by descriptive and univariate analyses. Multivariate, stratified or subgroup analyses will be used in case of confounders imbalance. A p-value less than or equal to 0.05 will be considered statistically significant. Bonferroni's correction will be applied when appropriate. Descriptive statistics will be used in each arm for proportion who did not receive allocated intervention, lost to follow-up, excluded from primary analysis, and drug-related complications. Intention-to-treat, per-protocol and sensitivity analyses will be performed. An interim analysis will be conducted quarterly during the trial, i.e. after a total of 75, 150, and 250 patients have been enrolled. This is a superiority trial. Early discontinuation of the study will be dependent on overwhelming positive results for the primary outcome. We will discontinue the trial if we achieve $p<0.001$ threshold at the time of interim analysis.[39]

Quality Assurance

Standardized medication orders will conceal the treatment allocation. The study coordinator will be responsible for managing the quality of patient data recorded in the study. All participating research staff will be trained and given written copies of a standard operating procedure to ensure consistency during recruitment, consent, handling of data, and follow-up evaluation. The study coordinator along with the PI will check weekly the content of the forms and database to ensure accurate and timely entry. Compliance at all study timepoints including

enrollment, randomization, intervention, data, and outcome collection will be documented daily on a compliance monitoring sheet (CMS) by the investigator. The recorded data will be entered into a cloud-based, secure and encrypted database by the research staff. Access to the database will be restricted. Data validation tool has been embedded in the database. Data entered will undergo monthly verification with the source document.

Expected Outcome of the Study

This study is intended to demonstrate that the use of cilostazol plus nimodipine is safe and superior to nimodipine alone in the prevention of DCI in patients who have aSAH. We expect to identify any immediate drug-related adverse effects as listed in Table 3. Additionally, we aim to demonstrate that cilostazol plus nimodipine decreases rates of both symptomatic and radiographic vasospasm.

Duration of the Project

Given our institutional volume, we anticipate a study period of 1-3 years assuming 50% of eligible patients agree to participate. Interim analysis will be performed at 50% enrollment and subject to discontinuation if all previously defined criteria are met.

Project Management

Neurosurgery staff will counsel and recruit subjects according to their initial screening to participate in this trial. The neurosurgery staff will check for eligibility using inclusion and exclusion criteria listed in Table 1. They will also explain the study principles, including the detailed experimental in-hospital & postoperative protocol, investigational treatment, potential risks, and benefits. Subsequent detailed written consent will be obtained by the staff and placed in a cloud-based, secure, and encrypted database (see supplementary text). The designated lead pharmacists will execute the randomized allocation assignment according to the block randomization schedule to maintain masking of allocation. The neuroscience ICU charge nurse will be responsible for overseeing and monitoring administration of the study medication. The neuroscience trained intensive care nursing staff will administer the study medication to the study participants. The PI and support staff will record all perioperative and postoperative data including study-related adverse events. The study coordinator will ensure and maintain follow-up

visits for postoperative secondary outcomes. The neuroradiologists will evaluate and determine primary and secondary outcomes of DCI and vasospasm, respectively. The clinical research methodologist will function as the CRC, supervise the overall execution of the study, and participate in the writing of the protocol and manuscript.

Ethics and Dissemination

The study will be conducted according to the Helsinki Declaration[40], the NIH human subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good Clinical Practice.[41] This protocol is written following the SPIRIT 2013 guidelines and was approved by Ascension Providence Hospital IRB. The results of this study will be submitted for publication in peer-reviewed journals and the key findings will be presented at national conferences.

Author Contribution

TD, CFC, SR, BR, and DT contributed substantially to the conception and design of this trial including organization and execution over two hospital campuses. DS contributed to the design and execution of the study drug protocol including randomization, blinding and placebo. MB and LG contributed substantially to the acquisition of data, ensuring accurate and standard operating procedures, and maintaining quality assurance among study participants and their subsequent care over two hospital campuses. TD, CFC, SR, DS, MB, LG, PK, BR, TMS, and DT contributed to the drafting of the original manuscript, participated in critically revising the manuscript and agree to be accountable for all aspects of the work.

Funding

This trial is supported by the Ascension Providence Hospital Institutional research grant (1478832-5).

Disclaimer

This project is not an industry-sponsored study. The investigators are solely responsible for the protocol design, data collection, analysis and interpretation, writing of the report, or decision to submit this publication.

Competing Interests

None declared.

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Figure Legend:

Figure 1. Study Design CONSORT Flow Diagram

Figure 2. Data Collection Schedule & Timeline

Table 1. Inclusion, Exclusion, and Withdrawal Criteria

Inclusion	Exclusion
18 years of age or older	Non-aneurysmal subarachnoid hemorrhage
Anterior circulation aneurysm rupture	Multiple ruptured aneurysms
Patients who have undergone surgical intervention	Patients with congestive heart failure
Absence of rebleeding or new intracranial hemorrhage on postintervention CT scan	Severe aneurysmal subarachnoid hemorrhage (Hunt Hess Grade V)
Consent to study participation	Active pathological bleeding
	Allergy to cilostazol
	Positive pregnancy test
	Coagulopathy not caused by anti-coagulant use
	History of hemorrhagic complications (gastrointestinal bleeding, etc.)
	Uncontrolled or severe comorbidity that would qualify as an absolute contraindication for cilostazol
	Patients requiring anticoagulant treatment following intervention (e.g. stent-assisted coiling or flow-diverting stent obliteration of aneurysm) ***Exception***: patients who require the use of aspirin as determined by the staff member performing the coil embolization for thromboembolic event protection due to a small amount of coil extrusion from the aneurysm neck with be allowed to be included into the trial

Criteria for discontinuing follow-up:
Subject wishing to terminate participation in the study at any time throughout his/her participation
CT, computed tomography

Table 2. Standardized Treatment Regimen

Location	Treatment
NSICU and floor	**Intervention group:** • 60 mg nimodipine Q4H for 21 days • 100 mg cilostazol b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]
	Control group: • 60mg nimodipine Q4H for 21 days • Cilostazol placebo b.i.d. for 14 days • CT or MRI scheduled on POD 1, POD 7 ± 2, and PO 1 month ± 1 week • DSA or CTA performed between POD 7 – 10 to assess angiographic vasospasm • Standard subarachnoid hemorrhage treatment pathway [4]

NSICU, neurosurgical intensive care unit; Q4H, every 4 hours; b.i.d. twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PO, post-operative; POD, post-operative day; DSA, digital subtraction angiography; CTA, computed tomography angiography

Table 3. List of Adverse or Serious Adverse Events

Cilostazol		Nimodipine	
Adverse events		**Adverse events**	
	Headache		Hypotension (mild)
	Diarrhea		Diarrhea
	Abnormal Stools		Dyspepsia
	Palpitations		Rash
	Dizziness		Headache
	Peripheral Edema		Flushing
	Dyspepsia		
	Abdominal pain		
	Tachycardia		
Serious adverse events		**Serious adverse events**	
	Hypotension		Hypotension (severe)
	Bleeding		EKG changes
	Stevens Johnson		CHF
	Syndrome		Thromboembolism
	Anaphylaxis		Thrombocytopenia
	Hypersensitivity		Anemia
	Reaction		GI bleeding
	Leukopenia		Ileus
	Thrombocytopenia		Intestinal obstruction
	Tachyarrhythmias		
	Myocardial		
	Infarction		
	Angina		

EKG, electrocardiogram; CHF, congestive heart failure; GI, gastrointestinal

Table 4. Definition and Classification of Surgical Complications

Grade	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological or surgical, endoscopic, and radiological interventions
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parenteral nutrition are also included.
Grade 3	Requiring surgical, endoscopic, or radiological intervention
3a)	Intervention not under general anesthesia
3b)	Intervention under general anesthesia
Grade 4	Life-threatening complication (including CNS complications)* requiring IC/ICU management
4a)	Single organ dysfunction (including dialysis)
4b)	Multiorgan dysfunction
Grade 5	Death of a patient
Suffix	If the patient suffers from a complication at the time of discharge, the suffix "d" is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

*Cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

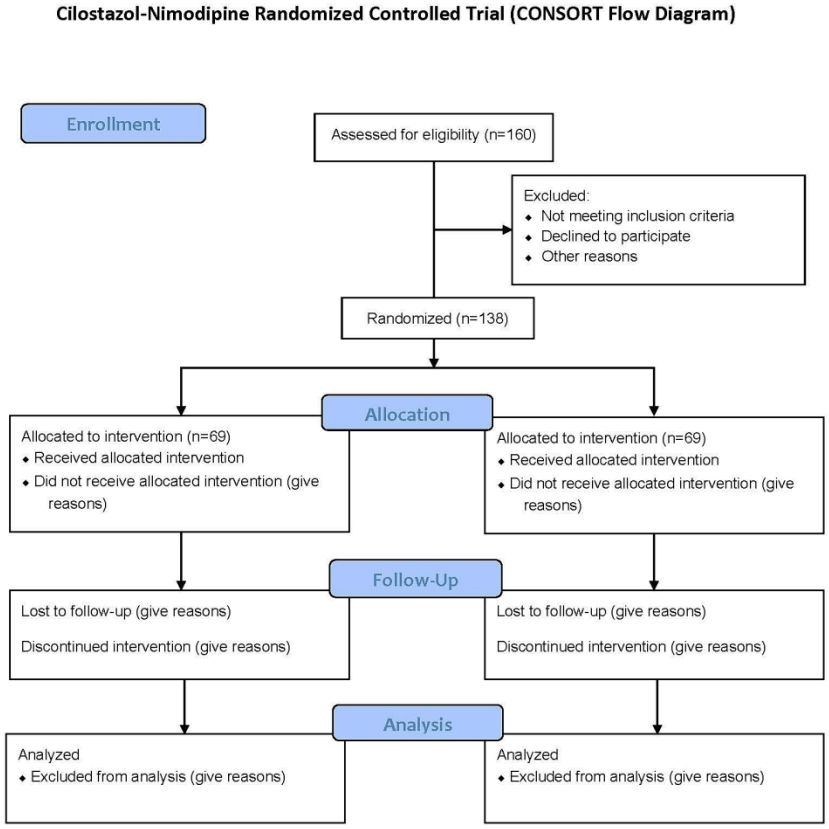

Figure 1. Study Design CONSORT Flow Diagram

143x186mm (300 x 300 DPI)

Figure 2. Data Collection Schedule

	PreOp	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D/C
Eligibility			X																					
Recruit			X																					
Consent			X																					
Clinical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
mFisher		X																						
Hunt Hess		X																						
EKG/ECHO	X																							
Pregnancy	X																							
Randomise			X																					
Cilostazol /Placebo			X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Nimodipine		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CT Scan		X	X						X															
DSA/CTA		X								X	X	X												
Coiling		X																						
All AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
mRS		X																						
EVD (Y/N)																								
Symptomatic Vasospasm? (Mark "Y")																								

Figure 2. Data Collection Schedule & Timeline

181x117mm (300 x 300 DPI)

Ascension Providence Hospital
16001 West Nine Mile Road, Southfield, MI

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

AND

AUTHORIZATION TO USE OR DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH TO BE CONDUCTED AT PROVIDENCE HOSPITAL, PROVIDENCE PARK HOSPITAL AND MEDICAL CENTERS

Title: Efficacy and Safety of Cilostazol-Nimodipine Combined Therapy on Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage (SAH): A Multicenter, Randomized, Double-blinded, Placebo-controlled Trial

Principal Investigator:

Boyd Richards D.O. Neurological Surgery

Co-Investigators:

Doris Tong, MD; Chad F. Claus; Sina Rajamand, DO; Ascher Kaufmann, MD; Troy Dawley, DO; Prashant Kelkar, DO; Teck M Soo, MD

Office Phone: (248) 569-7745

Please read the following material to ensure that you are informed of the nature of this clinical research study and how you will participate in it. Signing this form will indicate that you have been informed and that you give your consent to participate in a free manner. Federal regulations require written informed consent prior to participation in this clinical research study.

INTRODUCTION

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and any applicable risks. Your signature on this form also means that you want to take part in this study. This is a randomized multi-center double-blinded controlled clinical trial. Your doctor will explain the clinical research study to you. Research studies or clinical trials only include people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you recently underwent either a surgical or endovascular intervention for the treatment of intracranial hemorrhage and are being seen at Ascension Providence Hospital.

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BACKGROUND

This research study is designed to evaluate the effects of the combination between Cilostazol and Nimodipine on delayed cerebral ischemia due to cerebral vasospasm after anterior circulation aneurysmal subarachnoid hemorrhage. Cilostazol is a selective phosphodiesterase-3 inhibitor which exerts a vasodilatory and antithrombotic effect. Nimodipine is a dihydropyridine calcium channel blocker which is recommended for the postoperative treatment of aneurysmal subarachnoid hemorrhage. We seek to compare the incidence of delayed cerebral ischemia when treated with Cilostazol and Nimodipine versus when treated with Nimodipine alone. The researchers will compare two different groups. With your consent, you will be randomly assigned to a group who receives conventional post-intervention treatment with Nimodipine or to a group who receives conventional post-intervention treatment with Nimodipine in addition to 100mg Cilostazol twice daily for 14 days after your intervention. Your chances of being in one group are 1 in 2, much like flipping a coin. This is a double-blind study, which means neither you nor your doctor will know which group you are in until the study is completed.

Imaging will be taken 1 day after your intervention, 7 ± 2 days after your intervention, approximately 1 month and 6 months after discharge as part of your standard of care. More imaging, including but not limited to CTA or MRI scans, may be needed depending on the individual care management plan.

PURPOSE OF THE STUDY

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will decrease the rate of delayed cerebral ischemia during your hospital stay

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone will not lead to significant increase in bleeding disorders

- To demonstrate that the combined use of Cilostazol and Nimodipine when compared to Nimodipine alone, will lead to significant improvement in the following:
    - The rates of symptomatic vasospasm
    - The rates of angiographic vasospasm
    - Quality-of-life outcomes: Modified Rankin Scores (mRS) at Pre, 1, 3 and 6 months postoperatively and SF-12 at 1, 3 and 6 months postoperatively
    - Length of hospitalization
    - Length of stay in the intensive care unit (ICU)
    - Duration of ventriculostomy use

How many people will take part in this study?

Approximately 120 men and/or women of at least 18 years of age will be in this study.

How long will I be in this study?

You will participate in this study for 6 months. Your part in the study is completed once you have completed your 6-month follow-up visit with your surgeon including completion of the modified Rankin Scores and SF-12 questionnaires.

What will happen if I take part in this research study?

You have recently undergone either a surgical or endovascular intervention for the treatment of intracranial hemorrhage and your surgeon has determined that you meet eligibility criteria to participate in this research study.

After your enrollment, you will receive the necessary post-intervention care. If you are randomly selected into the treatment group, you will receive the drug Cilostazol in addition to your standard care regimen. If you are not, you will receive the standard care regimen plus a placebo. However, your knowledge of which group you are assigned to, as well as the administration of that drug will not be known to you. Throughout your hospital stay, data will be collected including any Cilostazol-related adverse events, occurrence of symptomatic vasospasm, and length of stay, among others. This all will be collected from either your electronic medical record or directly from you by a blinded member our staff. You will follow-up in clinic with your surgeon for standard post-interventional evaluation which includes 1, 3, and 6-month follow-up visit along with completion of modified Rankin Score and SF-12 questionnaires.

Risk to patients

Important risks and side effects of 100mg Cilostazol may include:

Frequent side effects:
- Headche
- Abnormal stools
- Diarrhea

Infrequent side effects:
- Abdominal pain
- Back pain
- Infection
- Palpitation
- Tachycardia
- Flatulence
- Nausea
- Peripheral edema
- Myalgia
- Dizziness
- Cough increased
- Pharyngitis
- Rhinitis

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Rare side effects:

- Chills
- Vertigo
- Other rare side effects

***Frequent* (occurs in 10-25% of people – 10 to 25 out of 100 people)**
***Infrequent* (occurs in 1-10% of people – 1 to 10 out of 100 people)**
***Rare* (occurs in less than 1% of people – less than 1 out of 100 people)**

Every effort will be made to minimize any discomfort and these risks. There may be other risks that are unknown at this time.

You should tell the person obtaining your consent if you are currently participating in any other medical research studies.

What are the benefits of the study?

There may be no direct benefit to you in participating in the study. However, it is possible that you may have less chance of delayed cerebral ischemia or symptomatic and angiographic cerebral vasospasm following your surgery. You may also experience an improvement in postoperative quality-of-life. In the future, other patients may benefit from the results of this study, when they become known.

What other options are there?

One option is to not participate. You do not have to participate in this research study in order to continue receiving treatment for your condition. Electing to not participate in this study will not affect your care whatsoever.

Do I have to participate in this study?

Your participation in this study is voluntary. Your refusal to participate will cause no penalty or loss of benefits which you would otherwise receive. If you decide to participate, you may change your mind about being in the study and may quit at any time without penalty of loss of benefits regarding your future care. If new information becomes available during the study that may affect your willingness to continue in the study, your doctor and/or his/her associate will discuss this information with you. Also, your doctor may stop your participation at any time if he/she feels it is in your best interest.

Will it cost anything to participate?

We do not expect there to be any additional costs to you if you participate in this study. Besides the drug treatment, the additional care you would receive during this study is considered standard of care and would not otherwise be different.

Compensation to patients – None

There is no compensation or pay offered for your medical care if you are injured as a result of participating in this study. You and/or your medical insurance may have to pay for your medical care if you are injured as a result of participating in this study. You are not giving up any of your legal rights by signing this consent form.

Confidentiality of Records

The principal investigators will have access to your medical records and your test results. While absolute confidentiality cannot be guaranteed, all research material which could identify you will be kept as confidential as possible within the state and federal laws. You should be aware that your medical records could be examined by the study staff, the Institutional Review Board (a group of people who review the research to protect your rights), or government agencies in order to verify the data collected during this research study. If the results of this study are presented in any public forum, you will not be personally identified.

Participant HIPAA Authorization to Use and Disclose Protected Health Information (PHI)

Your participation in this study will require the use and disclosure of certain medical and other information about you. The information that may be used or disclosed includes any and all health care records such as: laboratory, pathology and/or radiology results, CT scans, MRI, and Protected Health Information (PHI) previously collected for research purposes.

Your PHI will be used in the following ways: To conduct the research and to ensure that the research meets legal, institutional or accreditation requirements.

Your authorization to use and disclose the above information has no expiration date.

Your PHI may be seen, used or disclosed to the following:

- The researchers and members of the research team
- Other health care providers or employees of Ascension Providence Hospital
- Representatives of the Institutional Review Board (IRB), the FDA (Food and Drug Administration), or other governmental agencies involved in research monitoring.
- Other agencies as required by law.

You have the right to review your PHI. However, if you agree to participate in the research study and sign below, you will not be able to look at your research information until the research study is completed.

You do not have to sign this authorization. If you decide not to sign the authorization it will not affect your treatment or eligibility for health benefits. However, if you do not sign this authorization you may not participate in this study.

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You may withdraw your authorization at any time by notifying the principal investigator in writing, but the withdrawal will not affect any information already disclosed. However, you need to be aware that your written withdrawal of this Authorization may result in the termination of the research-related treatment being provided to you.

This study and more information will be available at ClinicalTrials.gov which is a registry and results database of publicly and privately supported research studies conducted in the United States and around the world. Sponsors or investigators of certain clinical trials are required by U.S. law to register their trials on and submit summary results to ClinicalTrials.gov. Each study record includes a summary of the study protocol, including the purpose, recruitment status, and eligibility criteria. Study locations and specific contact information are listed to assist with enrollment. You can visit ClinicalTrials.gov for more information regarding this study.

Who do I call with questions about the study or to report an injury?

If you have any questions regarding a research-related injury, you can contact:
Troy Dawley, DO
22250 Providence Dr Ste 601, Southfield, MI 48075
(214) 886-6111

If you have any questions about your rights as a subject in this clinical research study, you may contact the IRB representative at 248-849-8889 at Ascension Providence Hospital.

CONSENT

You have had the opportunity to fully discuss the purpose of this clinical research study and how it will be carried out. Your questions have been answered. Your participation in this study is fully voluntary and you may withdraw at any time.

Your signature below acknowledges that you voluntarily agree to participate in this clinical research study, and you will receive a signed copy of this form.

_____
Printed Name of Research Subject

_____ _____
Signature of Research Subject Date

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Legally Authorized Representative (if applicable):

_____

Printed Name of Legally Authorized Representative

_____ _____

Signature of Legally Authorized Representative Date

Check Relationship to Subject:*

☐ Legal Guardian or Legally Authorized Representative for Medical Care (LARM)
☐ Spouse

☐ Adult Son or Daughter ☐ Mother or Father ☐ Adult Brother or Sister ☐ Other, explain:

Reason subject is unable to sign for self:

**If a Legal Guardian or Legally Authorized Representative for Medical Care (LARM) has not been appointed, then consent should be obtained from the closest next of kin (in the order listed above). When that individual is unavailable or refuses to act the next in order should be contacted.*
** If there is a disagreement among next of kin regarding the appropriateness of the treatment plan, Clinical Safety Risk Management may be contacted. Outside of business hours, Clinical Safety Risk Management can be contacted through any St. John Hospital operator.*

_____

Printed Name of Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	11
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3, 4
	6b	Explanation for choice of comparators	3, 4
Objectives	7	Specific objectives or hypotheses	4, 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5, 6 Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5, 6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5, 6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5, 6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, 7, 8, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8, 9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, 9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9, 10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8, 9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6, 7, 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.