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Clinical Trial of Sodium Nitrite for Out of Hospital Cardiac Arrest

Study protocol

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Original Study protocol (pg 2-13)

Clinical trial to determine the safety and efficacy of sodium nitrite for out-of-hospital cardiac arrest- phase 2

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Introduction:

Based on data from the phase 1 trial, we believe that 25 mg of nitrite is likely to produce a slightly lower than desired blood nitrite level and that the 60 mg dose may produces a slightly higher than targeted blood nitrite level (10-20 μM). Since pharmacodynamics (efficacy/toxicity based on levels) is unknown in humans, these targets are extrapolated from other preclinical study data. In these studies, higher nitrite levels (up to 100 μM) were not associated with harm and in healthy volunteers little change in hemodynamics was noted with blood levels up to 50 μM.

Our safety data do not suggest a significant safety signal with either the 25 mg or the 60 mg dose. However, the rate of re-arrest and pressor requirements tended to be higher for the 60 mg dose as compared to historical controls. We interpret these data cautiously since the numbers are small, and the differences not significant. The investigators met on May 2, 2017 to discuss options for phase 2 and after a long discussion we decided to modify the protocol for phase 2. We present a modified protocol for consideration by the DSMB.

In the phase 2 trial, we propose to test two doses of sodium nitrite (45 and 60 mg) each as compared to a placebo group by adding a third arm to the study. This requires increasing the number of enrolled patients to 1500 (from original of 1000). Since we are increasing the number of patients for phase 2, this will require expansion of the study to include all of King County in order to finish enrollment within 2.5 years. The study outcomes will not change.

This study will inform the design of a phase 3 trial, since data on the safety of both doses will be determined.

It is possible that both doses will demonstrate safety, in which case we will propose that phase 3 use the higher dose of 60 mg.

If the safety data suggest harm at the 60 mg dose but not the 45 mg dose, we will propose to use the 45 mg dose for phase 3.

If safety data suggest increase benefit combined with increased harm for the 60 mg dose compared to the 45 mg dose, we will discuss potential options with the DSMB. For example we may see increased rate of re-arrest with the 60 mg dose, but a higher rate of survival to hospital admission or to discharge. In this case, an argument to use the 60 mg dose would be made.

Finally if both the 45 and 60 mg dose demonstrate an adverse safety signal then we will abandon plans for a phase 3 trial.

PHASE 2. EXAMINE THE SAFETY AND EFFICACY OF FIELD ADMINISTRATION OF SODIUM NITRITE DURING RESUSCITATION OF OUT-OF-HOSPITAL CARDIAC ARREST

The hemodynamic effects of the optimal dose of IV nitrite administered in patients with cardiac arrest are unknown. A significant negative hemodynamic effect from nitrite would decrease the proportion of patients admitted to the hospital, increase rate of re-arrest, or increase the need for vasopressor support in the field. In Seattle/King County, typically 40% of out-of-hospital cardiac arrest patients attended to by paramedics have ROSC and are admitted to the hospital. In this study, 1500 patients

with out-of-hospital cardiac arrest who are undergoing resuscitation by paramedics will be randomized to receive placebo (n=500) or 45 mg IV (n=500) or 60 mg dose (n=500) of sodium nitrite. We will have 80% power to detect an absolute increase in hospital admission rate of 8% (1-sided .05 level test for each of the two comparisons (45 mg vs placebo and 60 mg vs placebo, no adjustment for multiple comparisons), with a hospital admission rate of 40% in the placebo group and with one interim analysis and stopping only for potential futility and/or harm). We will examine the proportion of patients who survive to discharge as a secondary measure of efficacy.

Overview of Study design and definitions

In this phase 2 study, a total of 1500 patients with out-of-hospital cardiac arrest in Seattle/King County will be enrolled. This will be a randomized clinical trial and patients will receive either two different doses of IV sodium nitrite (45 mg or 60 mg) or placebo during resuscitation in the field by paramedics. The primary safety outcome will be proportion of patients surviving to hospital admission and primary efficacy outcome will be survival to discharge.

Patients will be eligible for both studies if:

1. Intravenous access/intraosseous access
2. Cardiac arrest, either VF or non-VF patients receiving ACLS by Seattle Medic One paramedics.
3. Age 18 years or older
4. Comatose

Exclusion Criteria

1. Traumatic cause of cardiac arrest
2. Prisoner, pregnancy, age less than 18 (special population/vulnerable population)
3. Known DNAR
4. Drowning as cause of arrest.

Primary Outcomes

Survival to hospital admission

Secondary Outcomes

Survival to discharge

Number of days in ICU

Survival to 24 h, survival to 48 h

Neurologic status at discharge

Re-arrest or ROSC or use of vasopressors in the field

Definitions:

Return of spontaneous circulation (ROSC): After resuscitating a patient from out-of-hospital cardiac arrest, paramedics document a pulse.

Awake: Patients who are documented to have comprehensible speech, to follow commands, or to have other specific evidence of conscious behavior. Patients who are not awake will be considered comatose. For simplicity, in this proposal, we will not distinguish between those who are comatose and those who are in a vegetative state.

Initial Rhythm will be classified as:

Asystole will be defined as background electrical activity less than 0.2 mV in amplitude with ≤10 beats per minute average rate (e.g., a 6-second strip without ventricular complexes).

VF will be defined as irregular, disorganized ventricular electrical activity of variable amplitude exceeding 0.2 mV.

VT will be defined as HR > 100 bpm with QRS duration greater than 110 msec. with evidence of AV dissociation and absence of palpable pulse.

Pulseless electrical activity (PEA) will be defined as electrical activity with R-waves of any width at an average rate of >10 beats per minute (e.g., organized ventricular electrical activity with R waves of any width that occur more than once over a 6-second period). The rate of PEA will be recorded as well. A paced rhythm will be considered to be PEA.

Study Recruitment

All patients with out of hospital cardiac arrest who are attended to by Seattle/King County paramedics will be eligible for the study, including both VF and non-VF patients. Paramedics will resuscitate patients according to standard protocols. For this study, cardiac arrest is defined by:
a. No detectable pulse or blood pressure.
b. Being unconscious.
Both criteria are established by paramedics. The proposed study area will be the city of Seattle and surrounding King County and in an average year, Medic One paramedics start resuscitation in ~1000 patients

The target population for randomization will be the 1000 treated cardiac arrest patients (per year) and thus we expect to enroll about 85% of the treated cardiac arrest patients (n=850/year) will meet eligibility requirements and be enrolled into the study. King County EMS providers have enrolled a similar proportion of eligible patients in the ongoing Resuscitation Outcomes Consortium (ROC) drug trial[1]. We are allowing for enrollment to occur over 2.5 years.

Phase 2 (n=1500) Randomized clinical trial

This will be a randomized, placebo control study to determine safety and efficacy of sodium nitrite during resuscitation.

Randomization

Patients will be randomized to the 45 mg or 60 mg or placebo group on a 1:1:1 basis. Each paramedic unit will carry a study kit, which will be labeled with a study number. Each kit will contain a sterile sodium nitrite syringe or identical appearing placebo syringe (normal saline). The paramedic will place the content of the syringe into the IV line over 1-2 min. Once a study kit has been opened, the patient will be considered randomized, even if the paramedic is unable to administer the study drug.

Before enrollment commences, the study statistician will randomize each study kit number, to either nitrite 45, nitrite 60 mg, or placebo by masked allocation using permuted blocks of concealed size. This list will be given to the investigational pharmacy team at Harborview Medical Center and the numbered kits will be assembled with the properly assigned placebo or nitrite. Besides the study number all kits will look exactly the same. Once the paramedics have used the kit, a new kit will be placed into the paramedic unit. Only the investigational pharmacy staff and (Drs. May and Maynard, study statisticians) will know whether nitrite or placebo was administered. All other study staff (paramedics, nurses, investigators) will be blinded. There will be no facility for emergency unblinding. There are two clinical reasons for this decision. Firstly, knowledge of treatment assignment would not impact any care decisions being taken if an adverse event occurred. Secondly, there is no antidote to the study medication.

Intervention:
Treatment group: Randomized patients will receive 45 mg or 60 mg IV nitrite or placebo. Patients will receive the dose as soon as possible after CPR or defibrillation (if necessary), IV access is established and after first round of ACLS drugs have been delivered.

Preparation of nitrite doses:

We will contract with Exela Pharma Sciences LLC to provide sterile syringes containing identically-appearing 45 mg, 60 mg IV sodium nitrite or placebo.

Control group:

The contents of the identical-appearing placebo syringe will be given

Subsequent Care:

After receiving the IV nitrite or normal saline, all patients will receive standard of care following cardiac arrest by the paramedics.

Notification of enrollment and notification of family members as requirement for waiver of consent study:
Since paramedics will enroll and randomize patients without subject (or family consent) we have instituted a protocol by which study personnel are notified that a patient has been enrolled. Besides tracking the number of patients that have been screened and enrolled, up to date information is needed so that study

personnel can discuss and inform patient family members that the patient has been enrolled into a clinical trial.

After a patient has been randomized the paramedic will leave a message with the study nurse, which will include the patient's name, study number and hospital name. As soon as is feasible, the study nurse will contact the patient or more likely the legal next-of-kin to explain the study and seek consent for continued participation. In that the consent would be obtained after the study intervention, the consent would be for permission to review medical records.

Initial critical care management of the post-cardiac arrest patient has a large influence on neurologic recovery and survival. Even though sodium nitrite is delivered in the field and its pharmacologic protective effects are expected to last only a few hours, the effects of hospital care (e.g. use of hypothermia, withdrawal of care) will affect outcomes. Even though this is a randomized trial and hospital treatment effects are expected to be divided evenly between the treatment and intervention group, we will collect hospital data, which are relevant to outcome. The study nurses will be responsible for abstracting the medical records, which will include the incident report and copy of the medical records.

Data Collection:

Documentation of Treatment This will be assessed as treatment assignment; treatment received; time points used to monitor the time-dependent nature of the intervention including call to 911, onset of arrest for EMS-witnessed arrest, sustained restoration of spontaneous circulation (ROSC), and initiation of study treatment.

Data will be collated from three sources: a list of study numbers and treatment assignments; a review of the patients' medical records related to the arrest including the paramedics report and the hospital records. The unique study number will be assigned to the patient at the time of randomization and will be used to link information from these three sources. Care providers, patients and families will be kept blinded to treatment assignment. The first data collection form will cover information routinely recorded on the paramedic form in patients with cardiac arrest. From the paramedic form will come information on location of arrest, initial rhythm, whether arrest was witnessed, presence of reactive pupils and of spontaneous respiratory efforts before ROSC, response times, treatments, complications such as recurrent arrests, and outcome. From the hospital records will come information on: a) processes of care; b) safety data; c) comorbidities; and d) outcome. We have attached in the appendix the data abstraction sheets we used for our prehospital hypothermia study. We are planning to submit these forms for IRB approval to utilize for the phase 2 nitrite study.

Monitoring for Outcomes Study staff will review subject's clinical record daily to monitor for outcomes and potential adverse events as well as to monitor use of concomitant treatments.

Primary Outcomes-definitions

Survival to admission: assessed as being admitted to the hospital intensive care unit.

Nitrite therapy is generally well-tolerated, but several side effects will be monitored. We anticipate that the most serious side-effect will be related to a potential decrease in blood pressure. Since the half-life of nitrite is less than 60 minutes, most of the acute effects will be within the first few hours after arrest and a significant deleterious hemodynamic effect will result in reduced survival to hospital admission.

Secondary and Exploratory Outcomes-definitions

Survival to discharge: assessed as alive when discharged from the acute care facility to home, nursing facility or rehabilitation. Patients transferred to another acute care facility (e.g., to undergo implantable defibrillator placement) will be considered still hospitalized.

Withdrawal of Care assessed as the reduction of support (i.e. reducing vasopressors, lab draws or medications) or withdrawal of support (i.e. extubation, stopping drips/meds, changing to comfort care only).

Survival to 24, 48, 72 h from arrest assessed as alive 72 h after the index call to 911 (or time of EMS-witnessed arrest). Withdrawal of care before 72 h is not recommended but is common,[2] and attenuates the benefit of any intervention intended to treat and reduce early cardiogenic shock after resuscitation from OHCA.

Awake assessed as documented to have comprehensible speech, to follow commands, or to have other specific evidence of conscious behavior. Patients who are not awake will be considered comatose. For simplicity, we will not distinguish between those who are comatose and those who are in a vegetative state.

Neurologic Status at Discharge assessed as modified Rankin Score (MRS) at discharge. This can be determined via review of the clinical record.[3,4] It uses a seven-point scale, from zero (i.e. no symptoms) to six (i.e. dead).[5] Patients who die before discharge will be assigned an MRS of 6. MRS is well validated in patients with OHCA. [6-9]

Safety Outcomes

The number and nature of any serious adverse events in each arm will be recorded. Safety parameters, however, will be collected up to hospital discharge. A comparison will be made between the control and nitrite groups. Other safety effects will be related to potential hemodynamic effects and include:

ROSC

Re-arrest or use of pressors in the field by paramedics**.** Re-arrest is defined as loss of pulse. These data are routinely recorded by paramedics and collected. Vasopressors are (Dopamine, Phenylephrine, Vasopressin, or Epinepherine)

Blood pressure and heart rate at ED arrival**.** These will be obtained from review of medical records.

Hypotension assessed as systolic BP <80 mmHg during any 6 h period within 24 h of the index arrest not due to a correctable cause, and treated with vasopressors or placement of a mechanical cardiac assist device (i.e. intra-aortic balloon pump, or percutaneous or transthoracic ventricular assist device). Such cardiogenic shock correlates with survival after resuscitation from cardiac arrest.

Unexpected Adverse Events (UAE***)*** These will be defined as any serious unexpected adverse effect on health or safety or any unexpected life-threatening problem caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigation plan or application, or any other unexpected serious problem associated with a device that relates to the rights, safety or welfare of subjects. Death or neurological impairment will not be considered an adverse event in this study, as it is an expected part of the natural history of the illness for a large proportion of the population.

Covariates

Key covariates of interest include:

Initial rhythm- (i) VF, versus (ii) PEA, versus (iii) asystole, versus (iv) unknown.

Observational status of arrest: (i) witnessed by EMS, versus (ii) witnessed by bystanders, versus (iii) unwitnessed.

Bystander CPR status: (i) performed, versus (ii) not performed, versus (iii) unknown.

Response time interval from call to arrival at scene by EMS, among witnessed cardiac arrests: (i) < 10 minutes, versus (ii) ≥ 10 minutes;[10]

Gender: (i) male versus (ii) female.

Time from cardiac arrest to awakening, death, or hospital discharge alive will be determined by review of hospital records. The place to which the patient is discharged and if it differs from where they lived before the cardiac arrest will be abstracted: home, rehabilitation, or some other supervised care setting. The degree of medical support and the timing of changes will be coded: full support; do not attempt resuscitation; and limitation or withdrawal of artificial life-sustaining treatments as indicated by "comfort care".

Analyses for Phase 2 study

Baseline Factors and Covariates:

Recorded will be demographics, response times (call receipt to arrival at patient side, etc.), witnessed status, bystander CPR, location of arrest (public vs. private location), resuscitation therapies (drugs, shocks, advanced airway), presence of reactive pupils or spontaneous respirations, and first recorded ECG rhythm (VF or non-VF).

Also recorded will be major procedures after the index arrest (in-hospital cooling, coronary catheterization, percutaneous coronary intervention, other), withdrawal of care (DNAR status), restoration of spontaneous circulation, and potential adverse events

Analyses

1. Primary outcome:

Statistical analyses for the phase 2 pilot study will be on an intention-to-treat basis. A one-sided test for proportions will be used to test the primary hypotheses separately for two comparisons: 45 mg versus placebo and 60 mg versus placebo. The primary hypotheses that will be tested (stated under the alternative): (1.1) The administration of 45 mg IV of sodium nitrite during resuscitation will increase the proportion of patients who survive until hospital admission.

(1.2) The administration of 60 mg IV of sodium nitrite during resuscitation will increase the proportion of patients who survive until hospital admission.

a) Primary outcome (survival to hospital admission)

1.1 H_o: The rate of survival to admission (π) is the same or worse in the 45 mg group vs the placebo arm or

H_A lower in the 45 mg group compared to the placebo group. H_0: $\pi_{Placebo} \geq \pi_{45mg}$. H_A: $\pi_{Placebo} < \pi_{l45mg}$

1.2 H_o: The rate of survival to admission (π) is the same or worse in the 60 mg group vs the placebo arm or
H_A lower in the 60 mg group compared to the placebo group: H_0: $\pi_{Placebo} \geq \pi_{60mg}$. H_A: $\pi_{Placebo} < \pi_{l60mg}$

b) In secondary analyses we will adjust for the following predictors in generalized estimating equation models for binary outcomes to increase the efficiency: age, witnessed status, initial rhythm (VF vs non-VF), location (public vs. private), bystander CPR, response time (time from 911 call to arrival at the scene).

In the event that a patient is enrolled twice in the trial, all data pertaining to the second enrollment will be excluded from the analysis.

2. Secondary outcomes and exploratory analyses

Survival to hospital discharge, the number of ICU-free days in the first 28 days, survival at 24, 48 h, and neurologic status at time of discharge will be assessed and were chosen as additional markers of efficacy of sodium nitrite in improving outcomes.

The MRS at discharge will be used as a binary measure using the cut-points ≤ 3 vs. > 3 and as a continuous measure. Analyses of MRS will employ the similar techniques as for the primary outcome. No adjustment for multiple comparisons will be made since the secondary outcomes will be used to corroborate the conclusions from the primary outcome and not to draw final conclusions.

3. Safety Analysis

The incidence of adverse events will be recorded for all patients in the safety population and presented by treatment arm (60 mg / 45 mg / placebo) to the DSMB for their review during the conduct of the study, as well as summarized and compared across treatment arms in the final report of study results. Assessment of the statistical significance of differences in the incidence of safety endpoints plays a lesser role, due to the need to be cautious in the introduction of new treatments in a human population. Hence, emphasis is placed on the presentation of results, with statistical tests provided for guidance on the precision of estimates as indicated. Specific measures that may reflect the safety of nitrite include:

1. Delay of Treatment. The process of initiating nitrite (or placebo) could delay treatment and/or potentially cause harm in patients other than those for whom the intervention is beneficial. The distribution of time from EMS arrival on scene to patient arrival at hospital will be described using mean, standard deviation, minimum, 25th, 50th, and 75th percentiles, and maximum. These data will be compared to historical data to determine whether this study affected treatment times. When indicated, statistical tests comparing the distribution of times will be affected using the t test, which allows for unequal variances.

2. Complications of Treatment The incidence of any Unexpected adverse death/events UADE will be reported by treatment arm and compared as indicated using Pearson's chi squared or unconditional exact test statistic (if expected numbers for any cells are small) and trend test across placebo, 45 mg and 60 mg.

3. Serious Adverse Events The incidence of each serious adverse event, along with other major adverse medical or surgical outcomes identified during review of hospital records, will be tabulated by treatment arm and compared when indicated using Pearson's chi squared or unconditional exact test (if expected numbers for any cells are small) and trend test across placebo, 45 mg and 60 mg groups). In order to

facilitate the identification of differences in rates of such events that might be due to greater survival to hospital admission and/or hospital discharge on one of the treatment arms, the incidence of any of the above specific events and/or death (either pre-hospital or during hospitalization) will be reported using all patients randomized to the arm as the donominator. While the study is ongoing, these data will only be available to the unblinded statisticians and the DSMB.

Sample Size and Monitoring plan for Phase 2.

There are no preliminary human data available for this study. This study will provide such data. In a rodent model of cardiac arrest in which sodium nitrite is administered at the time of resuscitation, the intervention resulted in a 25% absolute increase in survival (50% to 75%)[11], however, this effect size is probably overly optimistic.

Regarding the primary hypotheses: This study will have 80% power to detect an absolute increase in hospital admission rate of 8.0% (1-sided 0.05 level test, with a hospital admission rate of 40% in the placebo group) for each of the treatment arms (45 mg or 60 mg) when compared to placebo (without adjustment for multiple comparisons). We believe that not adjusting for multiple comparisons is justifiable for this early phase exploratory study, because the major Type I error is to discontinue any further investigation of a new treatment. Figure 1 provides sensitivity analyses to the power calculations by providing power estimates for a range of effect sizes and three rates of survival to hospital admission (30%, 40% and 50%) (applicable to each of the two primary comparisons). The study will be monitored by the DSMB at least four times, after about one quarter, about half and about three quarters of patients are enrolled and at the end of the study. Because of the size of the study, a single interim formal analysis will be performed (in addition to the final analysis). Of note, the DSMB can recommend stopping of the trial if there are concerns apparent at any of the reviews even if no formal interim analysis is scheduled. A one-sided boundary was chosen such that the study will only stop for futility and/or harm if the maximum likelihood estimate of the differences in proportions of survival to hospital admission is -0.001 or less (i.e. a slightly lower proportion of patients in the treatment arm survives to hospital admission than in the control arm after 500 patients have been enrolled). At the interim analysis no consideration will be made regarding stopping the study early for superiority.

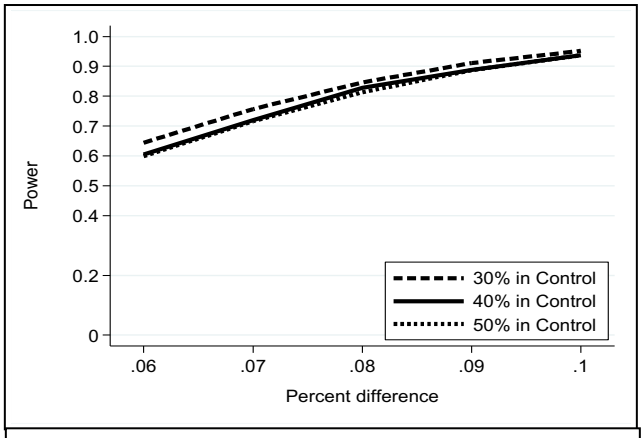

Figure 1: Power for a study with 30%, 40% or 50% survival to hospital admission for effect sizes ranging from 6% to 10%.

Regarding the secondary hypothesis of survival to hospital discharge: The study will have more than 80% power to detect an absolute increase in survival to hospital discharge or 6.7% (1-sided 0.05 level test) in each of the two treatment groups with a survival to hospital discharge rate of 20% in the placebo group. Power estimates were obtained using SeqTrial (S-Plus).

Potential outcomes after safety analysis: (stopping rules)

That we see a significant adverse safety signal for the higher 60 mg dose but not the 45 mg dose. In this case we will abandon the 60 mg dose and continue enrolling with two arms (placebo and 45 mg). This decision will be based on scientific rather than statistical considerations.

We see significant adverse safety signal for both the 60 and 45 mg dose. In this case will stop the study. Again, this decision will be based on scientific rather than statistical considerations.

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