Date	**:**	**April 14, 2015**
Version	**:**	**5**
Test drug	**:**	**Intravenous Nitroglycerin (NTG)**
Title	**:**	**Contrast Nephropathy and Nitrates (CoNaN)**
Principal Investigator	**:**	**Gervasio A. Lamas MD**
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Co-Principal Investigator	**:**	**Paul Kurlansky MD**

Confidentiality Statement

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1.0 EXECUTIVE SUMMARY

Study Design

This is a placebo controlled study in 400 patients, testing the hypothesis that pre-treatment use of intravenous nitroglycerin will decrease the incidence of renal insufficiency after percutaneous angiography, cardiac or lower extremity

Intervention

Patients undergoing percutaneous angiography will be randomly assigned to receive intravenous nitroglycerin (5 mcg/min, titrated up to 50mcg/min for at least 1 hour, maintaining systolic blood pressure (BP) > 100 mmHg, before and 3 hours after the procedure) or a normal saline placebo in a 1:1 ratio.

Enrollment period

The patients will be enrolled during a 2 year period.

Rationale for this study

Animal models suggest that the impaired synthesis of nitric oxide is one important contributor to the pathogenesis of the vasoconstriction caused by exposure to contrast-media. Our previous, retrospective, pilot study supported the hypothesis that the administration of nitrates, particularly intravenous nitroglycerin, before PCI, may decrease the incidence of contrast induced nephropathy (CIN).

Primary Endpoint:

1- The primary endpoint will be the change in estimated glomerular filtration rate (eGFR) assessed by modification of diet for renal disease formula, after percutaneous angiography.

Secondary Endpoints:

1- CIN will be defined as an increase in serum creatinine of 25% or ≥ 0.5 mg/dl post-percutaneous angiography.
2- Safety profile of the intervention including volume overload, hypotension, headache, the need for hemodialysis, intra-aortic balloon pump, endotracheal intubation or the use of pressors.
3- Analysis and comparison to a CIN predictive score calculator (Mehran Score).

2.0 BACKGROUND

2.1 INTRODUCTION

CIN is a complication of percutaneous angiography that, when it occurs, usually begins shortly after the administration of contrast media (1-3). The incidence has been reported in the range of 0 to 50%, depending on comorbidities and risk factors (4-8). CIN usually resolves spontaneously, but it has been associated with an increased risk of morbidity, in-hospital death, and late mortality (9-10). There is no specific management for renal insufficiency after the development of CIN. Therefore, there is interest in finding preventive strategies. Available evidence supports the use of hydration, sodium bicarbonate, and reduction of contrast volume administered to patients at risk (22). Statin use for prevention of CIN is still controversial (30-32), with a recent publication showing promising results (33). A hydration system was proposed by Briguori et al. (34) that showed CIN preventive effects. Further studies are needed to support these findings. Other agents, such as N-acetylcysteine, fenoldopam, nifedipine, captopril, prostaglandins and aminophylline have been evaluated in the prevention of CIN with varying results (23-29).

Animal models suggest that the impaired synthesis of nitric oxide is one important contributor to the pathogenesis of the vasoconstriction that may lead to CIN (11-13). We plan to investigate whether the use of intravenous nitroglycerin before exposure to contrast media reverses this vasoconstriction, and therefore, prevents the development of CIN.

The present manuscript describes the background, rationale, study design, safety monitoring, and analysis plan for the proposed contrast nephropathy and nitrates trial (CoNaN).

2.2 CONTRAST-INDUCED NEPHROPATHY AND NITRIC OXIDE

The pathophysiology behind CIN is not well understood. Different mechanisms have been proposed to explain the decrease in glomerular filtration rate after exposure to contrast media. The two major theories for the development of CIN are renal vasoconstriction resulting in medullary hypoxemia, and direct cytotoxic effects of the contrast agents (14-18).

Devrim et al, performed a randomized animal model trial, exposing rat kidneys to contrast media and measuring nitric oxide (NO) levels after exposure. They suggested that non-ionic low osmolar contrast medium administration leads to accelerated oxidant reactions and decreased NO level in rat kidney tissues. (13)

In another animal model completed by Brezis et al. they exposed anesthetized rats to the inhibitor of NO formation, L-NG-monomethylarginine (LNMMA). While increasing blood pressure and reducing renal blood flow they measured a decline in oxygen tension. These responses were promptly reversed by L-arginine, a NO donor, which bypasses the LNMMA blockade. They concluded that vasodilatation by nitroglycerin may participate in the balance of

renal medullary oxygenation and play an important role in the prevention of medullary hypoxic injury. (19)

Agmon et al, produced a simple model of radiocontrast induced nephropathy. Rats were pretreated with indomethacin (prostaglandin blocker) and N omega-nitro-L-arginine methyl ester (L-NAME, to inhibit nitric oxide synthesis) and then exposed to a contrast agent. Acute renal failure consistently developed, with a decline in creatinine clearance. Pretreatment with L-NAME or indomethacin reduced basal medullary blood flow. It was concluded that prostanoids and nitric oxide have an important protective role in the renal response to radiocontrast material, and reduced synthesis of these vasoactive substances in renal/vascular diseases may predispose patients to radiocontrast nephropathy. (11)

The mechanism by which N-acetylcysteine and other antioxidants have been proposed to confer renal protection in some animal models and human trials is through stimulation of nitric oxide synthase (NOS) to increase the endothelial production of NO. (17)

Nitroglycerin exerts its effects by bypassing the NOS mechanism and forming nitric oxide. In smooth muscle, nitric oxide activates guanylate cyclase which increases guanosine 3'5' monophosphate (cGMP) leading to dephosphorylation of myosin light chains and smooth muscle relaxation. It produces a vasodilating effect on the peripheral veins and arteries, with more prominent effects on veins than arteries. (20)

In the study of Efrati et al, the administration N-acetylcysteine was associated with maintenance of higher urinary NO levels after exposure to contrast media in comparison to the placebo group, were it was associated with a decrease of NO urinary levels after exposure to the toxin. They explained that "contrast media agents can cause a direct tubular injury, leading to the generation of oxygen free radicals, which in turn react with nitric oxide to produce peroxynitrite. Peroxynitrite is a potent oxidant that further decreases nitric oxide bioavailability and results in more tissue injury. Patients with chronic renal failure, diabetes mellitus, and heart failure have impaired nitric oxide activity, which could account for their susceptibility to develop contrast media nephrotoxicity". (17)

We recently completed a small retrospective study at our institution (exhibit A). We sought to investigate whether the use of nitrates before PCI reduces the incidence of CIN. We evaluated patients that were admitted to the hospital after PCI and had repeat serum creatinine measured. We measured the effects of pre-procedure nitrate use on post-PCI renal function in patients who received nitrates within 24 hours before the procedure and compared it with that of those who did not receive nitrates. Multivariable logistic regression analysis demonstrated that the use of nitrates correlated with a decrease incidence of CIN. Intravenous nitroglycerin infusion was associated with a lower risk of CIN compared with other means of administering nitrates. We concluded that the study supported the hypothesis that the administration of pre-PCI nitrates, particularly intravenous nitroglycerin, may decrease nephrotoxicity caused by contrast-media. But prospective, randomized-controlled trials are warranted to support or refute this hypothesis.

The mechanistic hypothesis of the CoNaN trial is that by pre-treating with intravenous nitroglycerin and exposing the renal vasculature to nitric oxide donor (NO), the damage caused by renal vasoconstriction and hypoxia due to radiographic contrast agent will be ameliorated, thus reducing the incidence of CIN.

2.3 NITROGLICERYN TO PREVENT CONTRAST INDUCED NEPHROPATHY

Experimental animal studies provide evidence that NO plays a role in CIN. The clinical information on the use of intravenous nitroglycerin to prevent CIN is limited to one retrospective study. Our hypothesis that pre-PCI exposure to intravenous nitroglycerin could prevent CIN has a favorable theoretical basis. The reality of our premise is still uncertain.

Our proposal for a randomized clinical trial will answer a simple clinical question. It will help to demonstrate a correlation or not, between experimental results obtained in animal models and human subjects. It will also contribute to clarify the role of NO donors in the renal vasculature.

3.0 INVESTIGATORS AND FACILITIES

3.1 STUDY LOCATION

The CoNaN trial will be performed at Mount Sinai Medical Center in Miami Beach, Florida. The Departments involved in the developing of the trial include: the Columbia University Division of Cardiology, the Division of Nephrology and the Department of Medicine.

3.2 STUDY MANAGEMENT

The trial will be coordinated by the CoNan Trial research teams that consist of the principal and co-principal investigators, sub-investigators, and a study coordinator. The study coordinator will evaluate eligibility; obtain consent, schedule subject's follow-up visits, data collection and maintenance of study documentation. Handling of investigational products will be the responsibility of an onsite pharmacist as well as the assistant investigators.

3.2.1 SUB-INVESTIGATORS

Vertilio Cornielle MD, Sabas I. Gomez MD, Orlando Santana MD, Robert Goldzer MD, Javier Reyna MD, Carlos Podesta MD, Hany Elmahdy MD, Omar Issa MD.

3.2.2 STATISTICIAN

Statistical consultation will be provided by Helen Parise PhD, Chief Statistician for the Cardiovascular Research Foundation.

3.2.3 INDEPENDENT DATA AND SAFETY MONITORING COMMITTE

The DSMB will be composed of experts not associated with the trial. The Chair and members are: Esteban Escolar MD (Chair), Juan Carlos Brenes MD and Ayman Layka MD (Nephrologist). They will review unblinded data, and obtain statistical consultation as needed.

The first data monitoring will occur once 100 patients have been enrolled. After the first visit has been completed, monitoring visits frequency will be every 12 months, depending on enrollment

4.0 CONAN TRIAL DESIGN

The Contrast Nephropathy and Nitrates trial (CoNaN) is a single center, randomized, 1 x 1 factorial clinical trial designed to test the effects of intravenous nitroglycerin infusion in renal function given prior to angiography.

Specific aims for this trial include:

- To determine whether the intravenous nitrates have any effect on the glomerular filtration rate (GFR) after the exposure to contrast media.
- To determine if intravenous nitroglycerin will decrease the incidence of CIN.

4.1 PRIMARY ENDPOINT

The primary endpoint for this trial will be to determine the change in glomerular filtration rate after exposure to contrast media. We will compare the change in GFR before and after percutaneous angiography of the group that received intravenous nitroglycerin with the change in GFR before and after percutaneous angiography of the group that did not receive intravenous nitroglycerin.

4.1.1 GLOMERULAR FILTRATION RATE

We will estimate the GFR using the modification of diet in renal disease (MDRD) formula:

$GFR = 175 \times SerumCr^{-1.154} * age^{-0.203} * 1.212$ (if patient is African American) * 0.742 (if female)

4.2 SECONDARY ENDPOINTS

Major secondary endpoints will include:

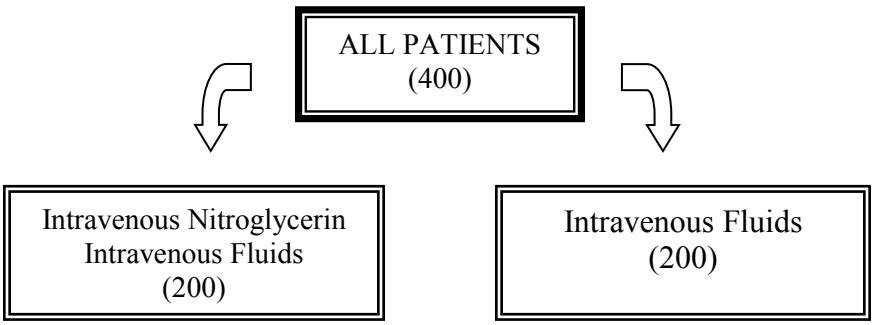
1- Incidence of CIN, defined as an increase in baseline serum creatinine of 25% or ≥ 0.5 mg/dl 48 to 72 hours post-percutaneous angiography
2- Safety profile of the interventions including volume overload, hypotension, headache, medication interaction, the need for hemodialysis, intra-aortic balloon pump, endotracheal intubation or the use of vasopressors.
3- Analysis and comparison to a CIN predictive score calculator (Mehran Score).

4.2.1 MEHRAN SCORE

According to a validated score proposed by Mehran et al. patients with a score equal or greater than 6, has a 14% chances or more of developing CIN (21). We will use this value to recruit patients with a high probability of developing CIN. The score will be calculated using the following variables: hypotension (5 points for BP <80/60mmHg), intra-aortic balloon pump use before during or after the procedure (5 points), congestive heart failure (5 points for New york Heart Association Class II-III, history of pulmonary edema or an ejection fraction <40%) age > 75 years (4 points), anemia (3 points for hematocrit <39% for men and <35% for women), diabetes mellitus (3 points), serum creatinine > 1.5 (4 points), GFR <60 (2 points for 41-60; 4 points for 21-40 and 6 points for <20) and contrast volume used (1 for each 100 cc).

4.3 SAMPLE AND METHODOLOGY

We will enroll 400 patients with a Mehran score of 6 or more that have a pre-procedural creatinine measured. Following baseline assessments, patients will be randomly assigned to receive intravenous infusion nitroglycerine plus intravenous normal saline or normal saline only.



5.0 RESEARCH DESIGN AND METHODS

5.1 SAMPLE SIZE

NOT A CASE CONTROL STUDY. This is a randomized, placebo-controlled clinical trial with a 1:1 randomization of active therapy to placebo. Prior data from our retrospective study indicate that the failure rate among controls is 0.3. If the true relative risk of failure for experimental subjects relative to controls is 0.5, we will need to study 161 experimental subjects and 161 control subjects to be able to reject the null hypothesis that this relative risk equals 1 with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05.

5.2 STUDY POPULATION

5.2.1 PATIENT RECRUITMENT

The recruitment strategies for CoNaN trial are targeted to specific groups in order to meet study goals with respect to patient enrollment and demographics. Meeting these goals, which results in a study population that reflects the typical patient population with the disease/health characteristics of interest, is necessary for making informed conclusions based on data collected during the study.

CoNaN trial will randomize 400 patients with a Mehran score ≥ 6 in a 1 x 1 trial of intravenous nitroglycerin versus intravenous saline only. All patients must complete informed consent process prior to being randomized into the trial.

Patients will be recruited primarily from 2 different sites. (1) Mount Sinai Emergency department, once they are evaluated by cardiology and scheduled for a non-emergent catheterization. (2) Directly from the Mount Sinai Medical Center catheterization Laboratory.

5.2.2 INCLUSION CRITERIA

All of the following inclusion criteria must be present for the patient to be enrolled in the trial.

1- Patient must be scheduled for percutaneous angiography, defined as diagnostic cardiac catheterization, or lower extremity or aortic iodinated contrast angiography.
2- Patients must have a Mehran score of at least 6 before the procedure.
3- Patients must have baseline creatinine and hemoblogin drawn before the procedure.
4- Signed informed consent.

5.2.3 EXCLUSION CRITERIA

None of the following exclusion criteria must be present for the patient to be enrolled in the trial

1- Patients on renal replacement therapy before randomization, will be excluded.
2- Being exposed to any types of nitrates 48 hours prior to randomization,
3- History of allergic reaction to any of the components of intravenous nitroglycerin.
4- Exposure to contrast media 4 days prior randomization.
5- Planned revascularization in the next 24 to 48 hours of the first PCI procedure.
6- The patient is hypotensive (<90/60mmHg) at the time of randomization.
7- Patients exposed to phosphodiesterase inhibitors 48 hours prior to randomization

5.2.4 SCREENING AND BASELINE EVALUATION

Potentially eligible patients will undergo an initial evaluation in which eligibility will be confirmed and the trial protocol explained in detail. All willing and eligible patients providing informed consent will have baseline data obtained including relevant history and use of all conventional and alternative therapies. Baseline laboratory tests will be performed and information on quality of life will be obtained.

The following variables will be obtained for all patients included in the trial: age, gender, weight, height, body mass index, blood pressure, left ventricular ejection fraction, hypertension, diabetes mellitus, peripheral vascular disease, medication use (angiotensin converting enzyme inhibitors, calcium channel blockers, beta blockers, statins, ascorbic acid, acetylcysteine, angiotensin receptor blockers, diuretics, aspirin), PCI (number of vessels) smoking status, amount of contrast, type of contrast, amount of hydration, serum hemoglobin, serum sodium, serum potassium, baseline creatinine and post procedure creatinine, glomerular filtration rate.

5.2.5 RANDOMIZATION

After inclusion and exclusion criteria verification, coordinator will complete the randomization screen, in the system. The patients will be randomly assigned to one of the two treatment arms. The coordinator will order the treatment in the patient's chart and start the pre-stocked infusion. The infusions will consist in intravenous nitroglycerin in addition to Intravenous Saline or Intravenous saline.

We will randomize using a computer generated pre-set list. The computer program will randomly assign a letter (A or B) to each individual case up to 400 cases. The trial coordinator and the pharmacist will be the only un-blinded persons that will have access to the randomization list. In case that for safety reasons an investigator must know if the patient is receiving the experimental therapy or not, a copy of the randomization list will be held at the coordinator's office.

5.3 STUDY ALGORYTHM

To achieve our primary and secondary end-points we will (1) screen patients in the catheterization lab and/or emergency department of Mount Sinai Medical Center. (2) After inclusion and exclusion criteria's are verified, informed consent will be signed by the patient. (3) a case report form will be completed. (4) The research staff will order a treatment protocol to be administered. (5) Laboratory studies will be performed if needed. (6) The patients will receive an intravenous infusion of nitroglycerin and/or saline for at least 1 hour. (7) Coronary angiography will be performed and another screening for exclusion criteria will be done by the coordinator and assistant investigators. (8) Variables such as volume of contrast and number of vessels stented will be obtained. (9) Patients will go to recovery area and another infusion will be started for another 3 hours. (10) 48 hours later patient will be contacted to come to the hospital for another set of laboratory studies or patients that stayed in the hospital will be contacted and all the information needed will be completed.

5.4 TREATMENT REGIMENS

Continuous intravenous infusion of nitroglycerin 5 mcg/min will be started and titrated every 3-5 minutes for a maximum of 100 mcg/minute if tolerated by blood pressure (>100/60mmHg), at least 1 hour before and 3 hours after the procedure. The nitroglycerin for infusion comes in a pre-mixed 250 ml bottle, with a concentration of 200 mcg/ml.

Intravenous sodium chloride 0.9%, will be administered at 1ml/kg/hr at least 1 hours before the procedure and at least 3 hours after for both treatment arms. If the ejection fraction is known to be less than 40% or patient have signs and symptoms of volume overload, a 0.5 ml/kg/hr regimen will be utilized. If the patient is in acute congestive heart failure, no intravenous fluids will be given.

5.4.1 NITROGLYCERIN PHARMACOLOGY

Nitroglycerin is a vasodilator and antianginal agent, that can be administer intravenously, orally, intra-anal, as a topical agent, as a patch, sublingual and as a translingual spray. In our study it will be administered via intravenous infusion as previously specified by the protocol.

5.4.1.1 NITROGLYCERIN HUMAN TOXICITY

Nitroglycerin serious adverse reactions include severe hypotension, nitrates tolerance, bradycardia, anaphylactoid reactions, and methemoglobinemia. Other common reactions include headaches, lightheadedness, dizziness, flushing, orthostatic hypotension, reflex tachycardia, edema, burning oral sensation (sublingual use) and tingling oral sensation (sublingual use).

5.4.1.2 SEVERE HYPOTENSION

The most common adverse effect of Nitroglycerin is hypotension. Nitroglycerin forms free radical nitric oxide. In smooth muscle, nitric oxide activates guanylate cyclase which increases guanosine 3'5' monophosphate (cGMP) leading to dephosphorylation of myosin light chains and smooth muscle relaxation. This produces a vasodilator effect on the peripheral veins and arteries with more prominent effects on the veins, decrease preload (left ventricular end-diastolic pressure); may modestly reduce afterload. This can lead to severe hypotension and paradoxical bradycardia and increased angina pectoris can accompany hypotension.

5.4.1.3 METHEMOGLOBINEMIA

Methemoglobinemia is an uncommon side effect of nitroglycerin use. Methemoglobin is an oxidized form of hemoglobin that has a decreased affinity for oxygen, resulting in an increased affinity of oxygen to other heme sites and overall reduced ability to release oxygen to tissues. The oxygen-hemoglobin dissociation curve is therefore shifted to the left when it's present. When methemoglobin concentration is elevated in red blood cells, tissue hypoxia can occur. The protective enzyme systems normally present in red blood cells maintain methemoglobin levels at less than one percent of the total hemoglobin in healthy people. Exposure to exogenous oxidizing drugs and their metabolites such is nitrates may accelerate the rate of formation of methemoglobin up to one-thousand fold, overwhelming the protective enzyme systems and acutely increasing methemoglobin levels.

5.4.1.4 NITROGLYCERIN DRUG TO DRUG INTERACTIONS

Nitroglycerin is relatively save medication. Some medications can cause severe or fatal adverse reactions. Interaction risk stratification is done following the following classification:

A - No known interaction
B - No action needed
C - Monitor therapy
D - Consider therapy modification
X - Avoid combination

- Alfuzosin: May enhance the hypotensive effect of Nitroglycerin. *Risk C: Monitor therapy*
- Alteplase: Nitroglycerin may decrease the serum concentration of Alteplase. *Risk C: Monitor therapy*

- Ergot Derivatives: May diminish the vasodilatory effect of Nitroglycerin. This is of particular concern in patients being treated for angina. Nitroglycerin may increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*
- Heparin: Nitroglycerin may diminish the anticoagulant effect of Heparin. Nitroglycerin may decrease the serum concentration of Heparin. *Risk C: Monitor therapy*
- Hypotensive Agents: May enhance the adverse/toxic effect of other Hypotensive Agents. *Risk C: Monitor therapy*
- Phosphodiesterase 5 Inhibitors: May enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*
- Prilocaine: Methemoglobinemia Associated Agents may enhance the adverse/toxic effect of Prilocaine. Combinations of these agents may increase the likelihood of significant methemoglobinemia. Management: Monitor patients for signs of methemoglobinemia (e.g., hypoxia, cyanosis) when prilocaine is used in combination with other agents associated with development of methemoglobinemia. Avoid lidocaine/prilocaine in infants receiving such agents. *Risk C: Monitor therapy*
- Rosiglitazone: Vasodilators (Organic Nitrates) may enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*
- Ethanol: Avoid ethanol (may increase the hypotensive effects of nitroglycerin). Monitor.
- Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola; licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may cause hypotension).

6.0 THE USE OF NITRATES FOR THE PREVENTION OF CIN

See retrospective study attached - Exhibit A

7.0 BUDGET

See Budget proposal attached- Exhibit B

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