Nitrous Oxide for the Treatment of Complex Regional Pain Syndrome: A Prospective Randomized Controlled Pilot Study

Version 1.0 Dated: December 20, 2018
Version 2.0 Dated: March 5, 2019
Version 3.0 Dated: March 23, 2019
Version 4.0 Dated: March 28, 2019
Version 5.0 Dated: July 8, 2019
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Version 2.0 - February 26, 2019 Amendment 1

Page 7 – changed from the control group will receive 100% oxide to control group will receive 50% oxide

Version 3.0 – March 23, 2019 Amendment 1

Page 7 – Active Control: The control group that receives 50% oxygen will also receive 2mg midazolam by intravenous injection. The study group that receives nitrous oxide will receive 2ml normal saline by intravenous injection as a placebo.

Version 4.0 – April 28, 2019 Amendment 1

Pages 7 – Initial Recruitment: the recruitment process was edited to incorporate use of the recruitment letter.
Page 9 – schema was edited to reflect this change as well.

Version 5.0 – July 8, 2019 Amendment 1

Page 7 – Treatment Phase: Active Control. After discussion with our research team, we decided to give all patients (control and study group) a 2mg dose of intravenous midazolam, to infuse over 5 minutes, at the start of each breathing treatment session. We believe this will greatly reduce participants' ability to determine which arm of the study they are in.

Version 6.0 – October 18, 2019 Amendment 1

Page 9 – Allocation will be stratified by use of spinal cord stimulator.

Version 7.0 – October 18, 2019 Amendment 1

Page 6 – We will include Patients ages 18-70

Page 8 – added approximately

Background and Significance

Medical Background and Pharmacologic Basis

Complex Regional Pain Syndrome (CRPS), formerly known as reflex sympathetic dystrophy, is a debilitating neuropathic chronic pain condition that most commonly develops as a sequela of traumatic injury to an extremity. The condition is characterized by severe pain (including hypersensitivity and allodynia), swelling, decreased range of motion, as well as skin and bone changes. The incidence is approximately 6 per 100,000 person-years, and the condition can have a profound impact on quality of life.[1] The annual healthcare cost is high, and was reported to be €5700 per year in the Netherlands in 1998.[2] There is little addition data regarding current healthcare costs, but many patients with CRPS do not work, worsening the disease's socioeconomic impact.[3]

The approach to treatment is often multimodal, including various classes of pain medications, physical therapy, nerve blocks, peripheral and central neural stimulation, and intrathecal drug therapy.[4] Patients who are refractory to many treatment modalities may be candidates for subanesthetic ketamine infusions, typically administered for several sessions over days.[5] At our institution, patients who undergo ketamine infusions receive sub-anesthetic infusions for four hours each day over a period of five days. Ketamine is a well-known *N*-methyl-D-aspartate (NMDA) receptor antagonist, and this pharmacologic mechanism is believed to underpin its efficacy in this setting. NMDA agonism is believed to contribute to hypersensitivity within the central nervous system and play a fundamental role in the pathophysiology of CRPS.[6,7] Furthermore, ketamine is known to provide an analgesic effect long after the drug has been eliminated.[8] Ketamine appears to be effective in the treatment of CRPS, but only one double-blind placebo-controlled study examining ketamine therapy for this condition has been published.[9] Ketamine infusion may provide more than 30% pain reduction in 58% of CRPS patients during the 1-3 month follow up period according to a recent meta-analysis.[55]

Unfortunately, ketamine infusions are costly, require intravenous access, and necessitate continued patient monitoring. Ketamine has a well-known side effect profile. For patients undergoing outpatient ketamine infusions for CRPS, these side effects specifically include feelings of inebriation, nausea, psychotomimetic effects, headaches, hypertension, and elevated liver enzymes as the most common problems.[10] Other potential side effects include agitation, confusion, arrythmias, vomiting, anaphylaxis, and even respiratory depression at high doses. Though perhaps beneficial for certain patients, ketamine is not an ideal medication for easy outpatient administration.

In addition to ketamine, there are only a handful of other commonly used NMDA receptor antagonists used in clinical practice, one of which is nitrous oxide. Nitrous oxide gas is a low potency inhalation anesthetic used frequently for both general anesthesia as well as sedation for less invasive office-based medical procedures. Though commonly used in operating rooms around the world, its role as an analgesic agent in chronic pain had scarcely been studied. The side effect profile is minimal to negligible, patient monitoring requirements are far less, ventilation and oxygenation are not affected, and it is rapidly eliminated via the lungs, making nitrous oxide a much easier drug to administer in the outpatient setting.

Recent literature regarding nitrous oxide primarily focuses on its use peri-operatively as an analgesic agent with the potential to reduce opioid use and the development of chronic pain in surgical patients.[11,12,13] Nitrous oxide has also been shown to inhibit opioid-induced hyperalgesia in humans in the setting of acute surgical pain.[14] With respect to chronic pain, animal studies have demonstrated the efficacy of nitrous oxide in alleviating pain hypersensitivity in rats with neuropathic pain. The efficacy was not only dose dependent but persistent as well (at least 3 weeks with 50% nitrous oxide).[15] Another neuropathic pain rat model study showed that a single nitrous oxide exposure caused a reduction in pain hypersensitivity of the injured extremity, abolished pain hypersensitivity of the contralateral extremity, and prevented thermal allodynia completely. These effects were persistent for more than 1 month.[16] We have successfully administered nitrous oxide to chronic pain patients in an outpatient setting.[17]

CRPS can be a truly debilitating disease with the potential to significantly compromise quality of life. Treatment of refractory CRPS patients can be both costly and unsuccessful, and better treatment modalities are needed for this complex disease. Based on the abovementioned preclinical reports and the essential role of the NMDA receptor in the pathophysiology of CRPS, we believe that nitrous oxide will provide clinically meaningful pain reduction and functional improvement in patients suffering from CRPS.

Clinical Research of CRPS and Selecting Outcomes

Subjective Data - Patient Reported Outcomes:

Until recently, there was no proposed standardized set of outcome measures for clinical studies of CRPS. CRPS studies have previously employed a diverse range of questionnaire outcome measures, making aggregation and comparison of data difficult. In 2017, McCabe *et. al.* published a proposed core measurement set to help researchers standardize their approach to CRPS clinical research outcomes.[18] This core measurement set, “Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies” (COMPACT), provides recommendations for studying CRPS based on eight domains: patient characteristics (demographics), pain, disease severity, participation of physical function, emotional and psychological function, catastrophizing, self-efficacy, and patient's global impression of change.

The measurement set proposed in COMPACT is a compilation of pre-existing items frequently used for Patient-Reported Outcomes Measurement (PROM). More specifically, COMPACT recommends the

PROMIS-29 Profile (version 2) survey. PROMIS-29 v2 comes from the Patient-Reported Outcomes Measurement Information System (PROMIS), which is a National Institute of Health funded system.

PROMIS-29 v2 includes a 0 through 10 pain scale, which will be used for our primary outcome. Because PROMIS-29 v2 also encompasses three of the eight domains listed above (pain, participation and physical function, emotional and psychological function), we selected PROMIS-29 v2 scores as one of our secondary outcomes.

Objective Data

We will collect daily opioid consumption data by having patients record and report their daily opioid use before and after treatment. Oral and transdermal opioids will be converted to standardized morphine equivalents and adjusted for bioavailability.

Objectives and Hypotheses

Primary Aim: To evaluate the efficacy of intermittent nitrous oxide exposure in reducing pain in CRPS.

Primary Hypothesis: Nitrous oxide exposure in CRPS patients will decrease pain scores compared to patients who do not receive nitrous oxide over the follow-up time period (1 week and 1 month after the last inhalation treatment).

Secondary Aim 1: To more broadly evaluate the efficacy of intermittent nitrous oxide exposure as a treatment modality for CRPS.

Primary Hypothesis 1: Nitrous oxide exposure in CRPS patients will improve (increase) PROMIS-29 v2 survey scores when compared with survey scores of patients who do not receive nitrous oxide over the follow-up time period (1 week and 1 month after the last inhalation treatment).

Secondary Aim 2: To evaluate patients' overall perception of disease improvement.

Secondary Hypothesis 2: Nitrous oxide exposure in patients with CRPS will improve (reduce) patients' Global Impression of Change scores (PGIC scale) when compared with patients who do not receive nitrous oxide over the follow-up time period (1 week and 1 month after the last inhalation treatment).

Exploratory Aim 1: To evaluate the effect of nitrous oxide exposure on opioid consumption in patients with CRPS.

Exploratory Hypothesis 1: Nitrous oxide exposure in patients with CRPS will reduce average daily opioid use (converted in mg IV morphine equivalents) when compared with patients who do not receive nitrous oxide over the follow-up time period (1 week and 1 month after the last inhalation treatment).

Exploratory Aim 2: To evaluate the effects of nitrous oxide on neuropathic pain symptoms in patients with CRPS.

Exploratory Hypothesis 2: Nitrous oxide exposure in patients with CRPS will improve (decrease) scores for the 6 neuropathic pain items in the short-form McGill Pain Questionnaire 2 when compared with patients who do not receive nitrous oxide over the follow-up time period (1 week and 1 month after the last inhalation treatment).

Methods

This study is a prospective randomized controlled pilot trial.

Study Population

Patients ages 18-70 with a diagnosis of CRPS (type I and type II) who are seen at Cleveland Clinic's Pain Management clinic will be considered for invitation to participate.

Inclusion criteria:

1. Patients must be diagnosed with CRPS based on the revised International Association for the Study of Pain criteria.
2. Duration of disease must be at least 6 months.
3. Written informed consent.

Exclusion criteria:

1. Patients who had no subjective benefit from ketamine infusions, as determined by interview during the recruitment process.
2. Patients taking more than 60mg of morphine equivalents or more daily for an alternative chronic pain condition.
3. Patients with both coronary artery disease (as determined by cardiac catheterization) and a functional status of less than 4 metabolic equivalents. The limited functional status must be secondary to cardiopulmonary symptoms (angina, dyspnea on exertion). Patients with coronary artery disease and a limited functional status (<4 METS) secondary to chronic pain can be included.
4. Patients with congestive heart failure of any etiology that are NYHA Class III or IV
5. Patients with moderate or severe pulmonary hypertension as determined by echocardiogram or right heart catheterization.
6. Patients with intraocular surgery within the past 14 days

7. Patients with worker's compensation claims and active litigation.
8. Patients who have been diagnosed with COPD.
9. Patients who use home oxygen therapy for any condition.
10. Diagnosis of Alcohol Use Disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
11. Illicit drug use within the past three months (not including marijuana).
12. Pregnant patients or patients with upcoming planned pregnancy.

Initial Recruitment

A list of patients who are seen at CCF Pain Management clinic with a diagnosis of CRPS (type I and type II) will be screened by manual chart review for eligibility. Patients who appear to meet the inclusion/exclusion criteria will be mailed the recruitment letter.

Patients who call back to express interest in participating will be provided with the informed consent document (by mail or E-mail, whichever the patient prefers). Patients may either take time to consider the informed consent form and call back at another time, or they can schedule an appointment with CCF Pain Management clinic at main campus.

When the patient comes for this scheduled clinic appointment, they will meet with the research coordinators afterwards and complete the informed consent process, provided that they still meet all inclusion/exclusion criteria. Patients will then be scheduled for their three breathing sessions, and they will also be given their first 7-day opioid use log.

Treatment Phase

Patients will present for the first scheduled treatment and they will fill out the PROMIS-29 v2 survey and the SF-MPQ-2 (6 neuropathic pain items). They will also turn in their opioid use log. They will receive a phone call 1 week before the first session to remind them to start filling out the opioid use log.

Vital signs will be obtained. Patients with significantly abnormal vital signs or vital signs that are significantly deviated from baseline will be referred to appropriate medical care.

Patients will then be randomized via a web-based randomization system Redcap with stratification by spinal cord stimulator status to either the nitrous oxide study group or the 50% oxygen control group. The nitrous oxide group will receive 50% nitrous oxide mixed with 50% oxygen, and the control group will receive 50% oxygen (oxygen plus air mixture).

Active Control: Because patients may be able to tell if they are receiving nitrous oxide, patient blinding may be compromised. Therefore, we plan to utilize an active control. The study group that receives nitrous oxide and the control group that receives 50% oxygen will BOTH receive 2 mg of intravenous midazolam, a short-acting mild sedative that will simulate the effects of nitrous oxide. This baseline

sedation given to all patients will significantly reduce the likelihood that patients will be able to tell which arm of the study they are in.

Intravenous access will be obtained by research staff or a registered nurse in a non-affected extremity. Patients will receive the midazolam injection immediately upon starting each breathing treatment session, and the 2mg dose will infuse over a duration of five minutes. IVs will be removed at the conclusion of each breathing treatment.

Both groups will undergo inhalation therapy for a duration of 2 hours via an FDA-approved mask breathing circuit. Vital signs (blood pressure, respiratory rate, heart rate) will be monitored every 30 minutes. Pulse oximetry monitoring will be continuous. Patients will be monitored for side effects including nausea, vomiting, desaturation, sedation, respiratory depression, and dizziness. Patients and other involved providers will be blinded to the treatment type. Research investigators administering the treatments will not be blinded.

At the conclusion of inhalation therapy, the gas will be turned off and patients will breathe room air. All patients will be monitored for an additional 30 minutes. This recovery time is more than sufficient to ensure nitrous oxide is completely eliminated in those patients who receive it. Patients will be monitored and asked about side effects.

Patients will receive a total of three treatments (6 total exposure hours) over one week with 2 or 3 days between each session. Possible treatment schedules: Monday-Wednesday-Friday, Wednesday-Friday-Monday, or Friday-Monday-Wednesday. After the conclusion of the third treatment, patients will be followed with phone calls as detailed in the Measurement section below.

Measurements

Demographic data will be collected and recorded: age, sex, duration of disease, extremity/extremities affected.

Patients will have two follow-up phone call appointments at approximately 1 week and at approximately 1 month after the final inhalation treatment session. Patients will be instructed (and reminded) to record their daily opioid use during the week preceding each phone call appointment. During each phone call appointment, patients will:

1. Complete the PROMIS-29 v2 survey questionnaire (including the 0-10 pain scale)
2. Complete the Patient's global impression of change survey measured with PGIC, which is a seven point scale ranging from 1 – "very much improved" to 7 – "very much worse."
3. Complete the 6 neuropathic items of short form McGill pain questionnaire 2 (SF-MPQ-2); each item ranging from 0 (no pain) to 10 (worse pain).
4. Report their daily opioid use over the past seven days; average daily opioid use in mg IV morphine equivalents will be calculated for statistical analysis.

The REDcap (Research Electronic Data Capture) database, which is a Cleveland Clinic internal database system, will be used to collect and store all the study information, including screening log, randomization, demographics, the outcomes, and the follow-up call logs.

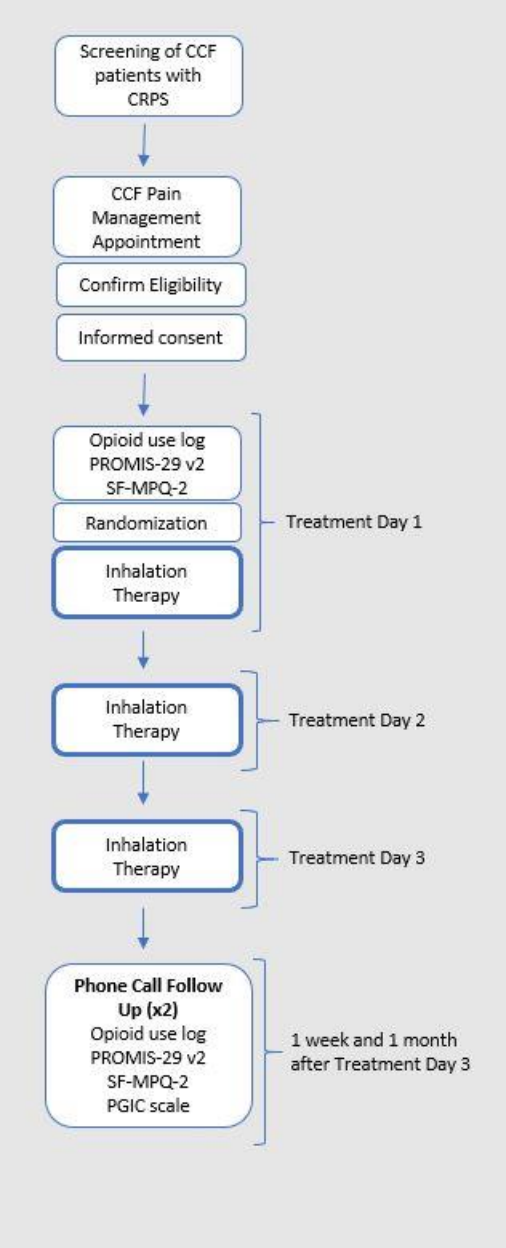
Blinding

The initial set of pre-treatment data for each patient (PROMIS-29 v2, SF-MPQ-2, opioid use log) will be collected prior to randomization on Treatment Day 1. Only research fellows/staff who are directly administering inhalation therapy will know which treatment the patient is receiving. For the duration of the study, patients will be blinded and will not know which treatment they are receiving. Alternate research fellows/staff who call patients for follow up data collection (PROMIS-29 v2, SF-MPQ-2, PGIC score, opioid use log) over the phone will be blinded to which treatment patients received.

Randomization

Patients who have met inclusion/exclusion criteria and are enrolled in the study will be randomized on Treatment Day 1 using the Redcap randomization module immediately before receiving the first inhalation therapy. Allocation will be stratified by those who have a spinal cord stimulator implanted and those who do not.

See schema below.



PGIC – Patient's Global Impression of Change
SF-MPQ-2 – short form McGill pain questionnaire 2 (the 6 neuropathic pain items)
Opioid use log – patients will report their recorded daily opioid use over the previous seven days, which will be averaged

Assessment of Resources

Patients' contact information will be stored securely in a log so that investigators will be able to contact participants with instructions and reminders to ensure consistent follow up and participation. A screening log will be maintained in REDcap. All screened candidates will be documented for inclusion and also reasons for exclusions from the study. Research fellows and staff in the Department of Outcomes

Research (Anesthesiology Institute) will be primarily responsible for recruiting participants, obtaining informed consent, administering surveys, administering the inhalation treatments, providing patients with instructions, and ensuring consistent follow up.

Additional Study Procedures

1. Drug Handling Instructions
    a. Nitrous oxide for the study will be stored at room temperature in appropriately labeled E-cylinder tanks. Empty tanks can be refilled and reused. Remaining nitrous oxide at the conclusion of the study can be returned.
    b. Midazolam is a controlled medication and only non-blinded research staff administering this medication will have access to it.

Data Analysis

Standard descriptive statistics will be used to compare the randomized groups on baseline variables. Any imbalanced covariables will be adjusted for, in both primary and secondary analyses. Balance between groups will be assessed using absolute standardized difference (ASD), defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation. Groups were defined as imbalanced on baseline variables if ASD > $1.96 \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$, where n_1 and n_2 correspond to the number of patients in each treatment group. [Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat. Med. 2009;28(25):3083-3107. doi:10.1002/sim.3697]. Our primary analysis will be intent-to-treat.

Primary analysis

First, the randomized groups will be compared on the pain scores profiles (NRS scores ranging from 0 to 10) over follow-ups (1 week and 1 month) using multivariable linear mixed effects model (i.e. random slope and intercept model if a linear time trend of NRS appeared appropriate) with adjustment for baseline pain level as a covariate. The assumptions of normality for the outcome NRS pain score and no interaction between the treatment group and baseline pain score on the outcome will be assessed. If either assumption is not met, then the baseline covariate would need to be categorized, or another method (i.e. analyze the change from baseline or percent change from baseline) would be used, as appropriate. The model based Wald test would be used for formal assessment at 0.05 significance level. If the significant difference between two study groups in pain scores profiles is observed, then the two separate testing for each follow-up time point (1 week and 1 month) will be performed using two separate multivariable linear regression models with same adjustment for baseline pain level and possibly for interaction between the treatment group and baseline score. This testing will be done at the overall 0.05 significance level and will be adjusted for multiple testing via Bonferroni correction (0.05/2 follow-up tests=0.025). The interaction between the treatment assignment and spinal cord stimulation implant

status on the primary outcome will be assessed (P-value < 0.10 will be considered as significant for interaction).

Secondary analysis

To compare the randomized groups on the PROMIS-29 v2 survey scores over 1 week and 1 month post treatment, the multivariable linear mixed effects model will be employed with adjustment for the baseline score. Transformations of the data will be made as needed to meet model assumptions. The model based Wald test would be used for formal assessment at 0.025 significance level (Bonferroni correction for two secondary outcomes: 0.05/2=0.025). If the significant difference between two study groups in PROMIS score profiles is observed, then the two separate testing for each follow-up time points (1 week and 1 month) will be performed in the same manner as the primary analysis. The Bonferroni correction for multiple testing (0.025/2=0.0125) will be employed.

In the same manner, first, the PGIC score profiles will be compared overall over follow-up time using multivariable linear mixed effects model; if significance is observed, PGIC scores will be compared separately at 1 week and 1 month follow-up with significance criteria of 0.0125.

The interaction between the treatment assignment and spinal cord stimulation implant status on two secondary outcomes will be assessed (P-value < 0.10 will be considered as significant for interaction).

Exploratory analysis

For exploratory analysis we report by study groups the appropriate summaries of daily opioid use (median [interquartile range]) and 6 neuropathic pain items in the SF-MPQ-2 (mean and standard deviations).

SAS 9.4 software (SAS Institute, Cary, NC) will be used for all analyses and graphics.

Sample size consideration

This study is a pilot trial, which aim to collect initial information on nitrous oxide effect on pain reduction and functional improvement in patients suffering from CRPS. Given an average annual number of the CRPS (type I and type II) patients at Cleveland Clinic's Pain Management and limited amount of resources we plan for about 40 study patients total to limit this study within 2 years.

The sample size is based on being able to detect the clinically important differences of 2 units or more in the mean numeric rating scale (NRS: between 0-10) of the nitrous oxide and placebo groups using analysis of covariance on the outcomes at 1 week follow-up. Using an SD estimate of 2 units for NRS (based on experience and literature) with standard type I and type II error rates (alpha = 0.025 due to Bonferroni correction for multiple testing, ß = 0.20), a 21 patients per group are needed (total sample size of 42 patients)

We also plan for one interim analyses at 50% of the planned enrollment, therefore, interim adjusted sample size is N=22 patients per group, or N=44 total. We will use the gamma spending function with parameters -4 and -1 for alpha (efficacy) and beta (futility), respectively. If the alternative hypothesis is true there will be a cumulative probability of 37% and 100% of crossing either an efficacy or futility boundary at the 1st and final analyses, respectively. Table 1 and Figure 1 below contains boundary Information. Planned first interim analyses will be performed upon accrual of 22 patients. **Therefore, planned number of patients for the analysis is N=22 patients per group, or N=44 total.**

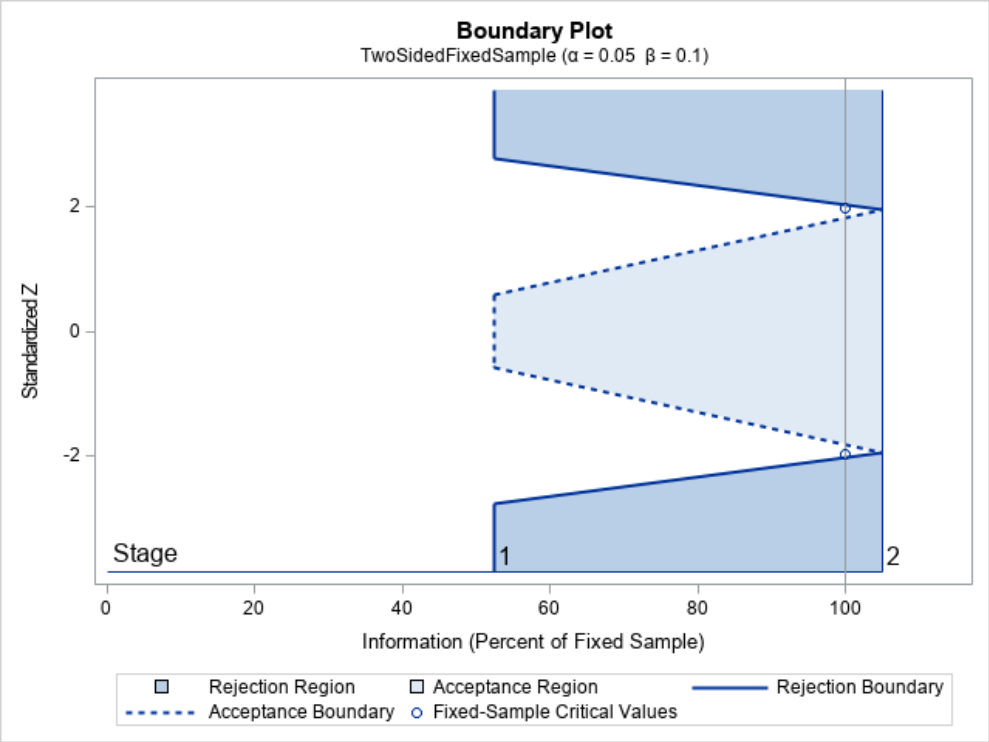
Also, assuming the drop-out rate of about 20% (due to withdraw and other unexpected events) we plan to enroll 27 patients in each group, total of 54 patients. If drop-out rate is less or more than expected the number of enrolled patients will change to reach N=44 patients needed for the analysis. In addition, we plan for 2 pilot patients (1 per group) in the beginning of the study. **Therefore, we anticipate enrolling 28 patients in each group, total of N=56 patients.**

Table 1. Boundary Information for interim analysis (2 analyses = 2 stages: 50% interim and final):

Boundary Information (Standardized Z Scale)

Stage	Information level	Alternative		Boundary Values			
		Reference		Lower		Upper	
	Proportion	Lower	Upper	Alpha	Beta	Beta	Alpha
1	0.5	-2.349	2.349	-2.750	-0.591	0.591	2.750
2	1.0	-3.322	3.322	-1.946	-1.946	1.946	1.946

Figure 1 Boundary Information



Study Limitations

Potential limitations:

1. Patients may be able to discern whether they are receiving nitrous oxide or 50% oxygen plus midazolam. This may impact survey results.
2. As CRPS severity and treatment response is quite variable, our study results may not apply to all patients with CRPS.
3. Despite using validated surveys/questionnaires, much of the data collected will be subjective.

Ethical Considerations

1. Informed Consent
    a. Patients who satisfy inclusion and exclusion criteria and agree to participate in the study will undergo the informed consent process immediately after their regular, non-research-study pain management clinic appointment.
    b. The research study will be explained in detail to each patient, and, if patients are still willing to participate, they will sign the informed consent associated with this study.

c. Patients will be informed that their decision to participate in this study is entirely voluntary and will not influence their regular medical care in any way. Choosing not to participate in the study will also not affect their care in any way.
d. Investigators listed in this protocol will be involved in explaining the research study and, briefly, its scientific basis. Investigators will also explain the schedule and follow up timeline, the potential benefits, the possibility of side effects, and the fact that patients will be randomized to either the study group or the control group when they present for treatment. Patients will be informed that they will be blinded to the treatment they receive. Further, patients will be informed that participants randomized to the control group are not expected have any benefit from the treatment sessions.
e. The patient will be required to verbalize their understanding of the research study and its intended purpose.
f. Patients will be informed of their right to opt out of study participation at any time.

2. Risks and Side Effects
    a. The potential for side effects using a gas mixture of 50% nitrous oxide with 50% oxygen is extremely low. This gas mixture has been shown not to predispose to desaturation, nausea, or vomiting.[19]
    b. A known side effect of nitrous oxide is peripheral neuropathy. This effect is attributed to nitrous oxide causing irreversible inhibition of methionine synthase, an important enzyme in DNA synthesis that is vitamin B12 (cobalamin) dependent. Prolonged exposure to anesthetic concentration of nitrous oxide may lead to bone marrow depression and/or peripheral neuropathy.[20] Clinically, this effect has primarily been reported as case reports of peripheral neuropathy in the setting of individual patients who habitually and chronically abused nitrous oxide for its euphoric effect. These patients had heavy use of nitrous oxide for extended periods of time. Furthermore, the peripheral neuropathy that develops is reversible with discontinuation of nitrous oxide.[21,22,23] Therefore, with only a brief duration of exposure as outlined in this protocol, it is exceedingly unlikely that patients participating in the study would develop this complication.
    c. Adverse events
        i. Serious adverse events from the administration of nitrous oxide, oxygen, or both is exceedingly unlikely. Patients who develop concerning symptoms such as chest pain, respiratory distress, or severe headache will have their inhalation therapy stopped and they will be referred to the Emergency Department for immediate evaluation.
        ii. Serious adverse events from the administration of 2mg midazolam is exceedingly unlikely. Patients will be continuously monitored via intermittent vital signs and continuous pulse oximetry.
        iii. Patients will not be compensated for care related to adverse events.

3. Benefits to Subjects
    a. Patients with CRPS who are randomized to receive nitrous oxide may experience a reduction in pain, a reduction in pre-existing disability, and/or a reduction in the amount of opioids they use on a daily basis.

b. Demonstrating benefit from nitrous oxide exposure will further the scientific and medical communities' understanding of neuropathic pain management. Demonstrated benefit may also lead to an additional treatment option for CRPS.

4. Cost to Subjects
    a. Cost to participants includes the cost of travelling to appointments and treatment sessions.
5. Compensation to Subjects
    a. None.
6. Provisions for vulnerable subjects
    a. There will be no vulnerable subjects in this study.
7. Subject Privacy and Data Confidentiality
    a. Privacy of Participants
        i. Subject participation in this study will not be disclosed to anyone other than their regular pain physician
        ii. Participants will be able to discuss their participation with a research investigator in a private setting (office or exam room)
        iii. Participants may be visible to other patients, research staff, and any additional clinical staff while they are undergoing inhalation treatment in the designated treatment area.
    b. Confidentiality of Data
        i. Upon entering into the study and completing the informed consent process, patients will be assigned an identifier number that does not contain any protected health information. The identifiers will be linked with patient's names in a separate spreadsheet that will be accessed only for the purpose of patient identification.
        ii. Only the research investigators who are enrolling patients (including informed consent), administering treatments, scheduling patients for appointments/treatment, collecting survey and other subjective data, or collecting blood samples will have access to this spreadsheet that links patient names with identifiers.
        iii. Both the patient name/identifier spreadsheet and the main data collection spreadsheet will be stored securely on Cleveland Clinic servers.
        iv. Data of any kind will not be allowed off campus. Non-electronic data (i.e. any printed data) must be appropriately destroyed when no longer needed.
        v. All investigators will have access to the de-identified main data collection spreadsheet.
    c. Plans for Record Retention and disposal
        i. The completed de-identified data will be retained indefinitely on a Cleveland Clinic secure server in the event that re-analysis or additional analysis of the data is ever desired.
        ii. The patient name/identifier spreadsheet will be deleted upon completion of all study procedures and statistical analyses.

Plans for Dissemination of Findings

The data and relevant statistical analysis will be prepared as a manuscript for publication in a peer-reviewed journal. Prior to completion of the finished manuscript, this research study may be presented as an abstract at a relevant regional or national medical conference.

References

1. Bussa M, Guttilla D, Lucia M, Mascaro A, Rinaldi S. Complex regional pain syndrome type I : a comprehensive review. *Acta Anaesthesiol Scand*. 2015:685-697. doi:10.1111/aas.12489
2. Goebel A. Complex regional pain syndrome in adults. *Rheumatology*. 2011;50:1739-1750. doi:10.1093/rheumatology/ker202
3. Sandroni P, Benrud-larson LM, Mcclelland RL, Low PA. Complex regional pain syndrome type I : incidence and prevalence in Olmsted county, a population-based study. *Pain*. 2003;103(1-2):199-207. doi:10.1016/S0
4. Gierthmühlen J, Binder A, Baron R. Mechanism-based treatment in complex regional pain syndromes. *Nat Publ Gr*. 2014;10(9):518-528. doi:10.1038/nrneurol.2014.140
5. Zhao J, Wang Y, Wang D. The Effect of Ketamine Infusion in the Treatment of Complex Regional Pain Syndrome : a Systemic Review and Meta-analysis. *Curr Pain Headache Rep*. 2018;22(2):12.
6. Bennett GJ. Update on the Neurophysiology of Pain Transmission and Modulation : Focus on the. *J Pain Symptom Manage*. 2000;19(1):2-6.
7. Petrenko AB, Yamakura T, Sakimura K, Baba H. Defining the role of NMDA receptors in anesthesia : Are we there yet ? *Eur J Pharmacol*. 2014;723:29-37. doi:10.1016/j.ejphar.2013.11.039
8. Rabben T, Skjelbred PER, Øye I. Prolonged Analgesic Effect of Ketamine, an N -Methyl- D -Aspartate Receptor Inhibitor, in Patients with Chronic Pain. *J Pharmacol Exp Ther*. 1999;289(2):1060-1066.
9. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome : A double-blind placebo controlled study. *Pain*. 2009;147(1-3):107-115. doi:10.1016/j.pain.2009.08.015
10. Azari P, Lindsay DR, Briones D, Clarke C, Buchheit T, Pyati S. Efficacy and Safety of Ketamine in Patients with Complex Regional Pain Syndrome A Systematic Review. *CNS Drugs*. 2012;26(3):215-228.
11. Richebe P. Nitrous Oxide Revisited: Evidence for Potent Antihyperalgesic Properties. *Anesthesiology*. 2005;(4):845-854.
12. Chan MT V, Wan ACM, Gin T, Leslie K, Myles PS. Chronic postsurgical pain after nitrous oxide

anesthesia. *Pain*. 2011;152(11):2514-2520. doi:10.1016/j.pain.2011.07.015

13. Roth J. Chronic Pain and the Opioid Epidemic: Are We Ignoring the Potential Benefits of Nitrous Oxide? *Anesth Analg*. 2018;126(4):1423-1424. doi:10.1213/ANE.0000000000002710

14. Elgueta F, Fierro C, Bugedo D, Faba G, In R. Nitrous oxide (N2O) reduces postoperative opioid-induced hyperalgesia after remifentanil – propofol anaesthesia in humans. *Br J Anaesth*. 2011;107(September):959-965. doi:10.1093/bja/aer323

15. Boujema M Ben, Laboureyras E, Pype J, et al. Nitrous oxide persistently alleviates pain hypersensitivity in neuropathic rats : A dose-dependent effect. *Pain Res Manag*. 2015;20(6):309-315.

16. Bessiere, B, Laboureyras, E, Chateauraynaud, J, Laulin, J.P., and Simonnet G. A Single Nitrous Oxide (N2O) Exposure Leads to Persistent Alleviation of Neuropathic Pain in Rats. *J Pain*. 2010;11(1):13-23. doi:10.1016/j.jpain.2009.05.003

17. Turan A, Sarwar S, Atim A, et al. Nitrous Oxide for the Treatment of Chronic Low Back Pain. *Anesth Analg*. 2015;121(5):1350-1359. doi:10.1213/ANE.0000000000000951

18. Grieve S, Perez RSGM, Birklein F, et al. Recommendations for a first Core Outcome Measurement set for complex regional PAin syndrome Clinical sTudies (COMPACT). *Pain*. 2017;158(6).

19. Peyton PJ, Ph D, Wu CY. Nitrous Oxide – related Postoperative Nausea and Vomiting Depends on Duration of Exposure. *Anesthesiology*. 2017;(5):1137-1145.

20. Hadzic, Admir, Glab, Krzysztof, Sanborn, Kevin, Thys D. Severe Neurologic Deficit after Nitrous Oxide Anesthesia. *Anesthesiology*. 1995;83:863-866.

21. Richardson PG. Peripheral neuropathy following nitrous oxide abuse. *Emerg Med Australas*. 2010;22:88-90. doi:10.1111/j.1742-6723.2009.01262.x

22. Cheng HM, Park JH, Hernstadt D. Subacute combined degeneration of the spinal cord following recreational nitrous oxide use. *BMJ Case Rep*. 2013:2012-2014. doi:10.1136/bcr-2012-008509

23. Hsu, C, Chen, Y, Lung V, His, S, Lo, H, Shyu H. Myelopathy and polyneuropathy caused by nitrous oxide toxicity: a case report. *Am J Emerg Med*. 2012;30(6):3-6. doi:10.1016/j.ajem.2011.05.001