“Nitrous Oxide for Analgesia in Sickle Cell Vaso-occlusive Crisis”

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Study Purpose and Rationale:

Sickle cell disease (SCD) is an autosomal recessive disorder that produces abnormal hemoglobin and deformed red blood cells. Vaso-occlusive crisis (VOC) is a complication of SCD in which the abnormal red blood cells occlude small blood vessels, causing episodes of severe, unremitting pain. VOC is the most common cause of acute morbidity in SCD, and the number-one reason for hospitalization.(1) The current treatment of VOC consists primarily of opioids and non-steroidal anti-inflammatory medications (NSAID).(2) However, this current approach is inadequate in decreasing the rate of hospitalization for VOC, lengths of stay, and subsequent morbidity. In addition, the repeated and chronic administration of opioids can lead to both short and long term adverse effects, including constipation, hypotension, respiratory depression, seizures, opioid induced hyperalgesia, opioid tolerance, and chronic pain irrespective of VOC episodes.(2-4) Nitrous oxide (N2O) is commonly used for VOC in France despite the absence of randomized trials to determine its efficacy or safety. N2O is a gas that produces analgesia, anxiolysis, and amnesia by NMDA receptor antagonism and release of endogenous opioid peptides (EOP).(5-7) A recent survey of 85 French pediatric emergency departments (PED) reported that almost half of them used N2O for analgesia when morphine was insufficient.(8) N2O administered for 20 minutes has also been shown to provide analgesia lasting up to 3 hours in inpatient children with VOC refractory to morphine infusions.(9) In addition to providing acute relief from pain and serving as a potentially opioid-sparing modality, N2O may also be able to provide long-term benefit due to its antagonism of NMDA receptors, as N2O has been shown to alleviate opioid-induced hyperalgesia and neuropathic pain in other populations. (10,13-15) The purpose of this pilot study is to describe the analgesic effect that N2O has on patients with SCD who have a VOC in the emergency department. The investigators have the following specific aims:

1. To determine whether N2O produces a clinically significant decrease in pain in patients with SCD who have a VOC that does not improve after initial standard treatment.

2. To determine the duration of analgesia produced by N2O in the aforementioned population.

Study Design:

We will conduct a single center pilot study in the pediatric emergency department (PED) of an urban, tertiary care children's hospital. The study is an interdivisional study between pediatric emergency medicine (Dr. Tsze) and pediatric hematology (Dr. Ender).

Patient demographics for each patient will be documented, and a baseline neurological exam performed by the attending pediatric emergency medicine physician responsible for their care during that PED visit An 8-week follow up physical examination will be performed if vitamin B12 levels obtained during the PED visit are low (see STUDY PROCEDURES: Follow-up Procedures). Vitamin B12 levels are being done solely for the conduct of this research. Our primary outcome will be the change in pain score from just prior administration to immediately following the discontinuation of N2O. The pain score will be measured using a numeric rating scale (NRS) of 0 (no pain) to 10 (worst pain), which is a valid and responsive scale for measuring pain in children older than 8 years of age. Our secondary outcomes will include:

1) the duration of analgesia resulting from N2O, which will be defined as the time elapsed from the discontinuation of N2O to the time at which the pain score becomes > or = 7/10 (for those whose score decreased below 7), the patient receives additional analgesia, is discharged home, or is admitted to hospital. This time will be measured in minutes. Additional secondary outcomes will include,

2) complaints or physical findings suggestive of peripheral neuropathies (which may present as numbness, tingling, pain, or loss of feeling in fingers or toes; or weakness or difficulty moving the arms or legs) at the 8 week follow-up, as well as,

3) the presence of macrocytic anemia at 8 weeks time in patients who had low vitamin B12 levels at the time of enrolment.

STUDY PROCEDURES

A) The following procedure is STANDARD care: Patients with SCD who present to the ED with VOC and a pain score of > or = 7/10 (i.e. severe pain) will receive IV fluids, NSAIDs, and IV morphine or hydromorphone. Blood work will be drawn and includes CBC, reticulocytes, and type and screen. After administration of the analgesics, the patient's pain will be reassessed after 15 minutes. If pain is still > or = 7/10, the patient will receive a "rescue" dose of IV morphine or hydromorphone. The patient's pain will be reassessed every 15 minutes and IV morphine or hydromorphone will be repeated until the pain score is < 7/10, at which point the patient's pain is reassessed (usually at least once every hour – there is no standardized interval) and the patient is transitioned to an oral analgesic at the attending physician's discretion, in conjunction with the hematology service.

B) The following procedure is for RESEARCH purposes: Patients with SCD will be identified by a research assistant or study investigator if they have VOC and a pain score of > or = 7/10. If the patient has not already been consented (see informed consent), the primary physician providing care for the patient in the ED will be approached and asked to approach the patient and family to see if they would be interested in participating in the study. If they say yes, then a study investigator will approach the family to obtain informed consent. The reason why the family is approached at this point in time is so that the N2O treatment can be immediately initiated if the initial standard treatment is not effective, and so that there is no delay in care in providing analgesia when they have severe pain.

   The patient will still receive the standard care of IV fluids, NSAIDs, and IV morphine or hydromorphone. In addition to the standard blood work, a vitamin B12 level will be drawn for study purposes. An additional 1 mL of blood (less than a quarter of a teaspoon) will be required. The pain score will be reassessed 15 minutes after the initial is still > or = 7/10, we will administer N2O at a concentration of 50% for 20 minutes. N2O is approved for use in the pediatric emergency department as per NYP Policy S100, and all standard procedures for administration and monitoring as per this policy will be followed.

   Five minutes after discontinuation of the N2O, the patient's pain score will be assessed. If the pain score is still > or = 7/10, the patient will receive a "rescue" dose of IV morphine or hydromorphone, similar to the procedure in standard care, and will continue to be treated as per standard care.

   If the patient's pain is < 7/10, the patient will have their pain reassessed by a study investigator every 15 minutes for the first hour, and then every 30 minutes after the first hour is completed OR whenever the patient volunteers or requests a pain assessment. Pain assessments will continue until the patient is discharged home. This frequency of pain assessment is the same, if not more frequent, than what occurs in standard care. The primary attending, in conjunction with the hematology service, will determine the transition to an oral analgesic and when to discharge the patient home.

C) The following follow-up procedure is for RESEARCH purposes: Within 48 hours of the ED visit, a study investigator will review the laboratory results drawn at the time of enrollment. If the vitamin B12 level is

normal, then a study investigator or research coordinator will conduct a follow-up telephone call at week 8 to assess for any neurological symptoms. If the vitamin B12 level is low, the study investigators will notify the patient's attending hematologist within 24 hours and a follow up appointment will be scheduled at 8 weeks post enrollment at an outpatient clinic (hematology clinic or CTSA outpatient resource [if approved]). During this visit, one of the study investigators will conduct a physical examination and obtain laboratory tests (CBC and differential, vitamin B12) to evaluate for any potential long term side effects of receiving N2O (e.g. peripheral neuropathies, megaloblastic anemia).(7,17) Of note, the chances of these adverse events are low; they do not present acutely (onset is typically between 1 to 8 weeks); they are completely reversible with vitamin B12 supplementation; and have only been reported in the context of severe vitamin B12 deficiency and prolonged and repeated N2O administration.(7,17,18) Sickle cell patients are not expected to have vitamin B12 deficiency that would predispose them to these adverse events.(19) In discussion with our hematologists at NYP, it is their experience that our population of patients with SCD are at low risk of being deficient in vitamin B12.

Statistical Procedures:

Sample size: Twelve patients will be analyzed for this pilot study. This sample size was selected as there is minimal increase in precision expected around the mean and variance in the pain score change with additional patients enrolled. (16) To meet this analysis sample size, we anticipate that we may enroll up to 24 patients with severe VOC. This is because we expect that 50% of patients who are consented will ultimately not fulfill all inclusion criteria (i.e. their pain may be adequately managed with initial standard treatment, and may not require additional parenteral analgesia). The experience at our institution is that approximately 53% of patients with SCD who present to the PED with a VOC requiring parenteral analgesia as initial standard treatment require additional parenteral analgesics. We will not wait until patients have demonstrated a need for additional analgesia to begin the consent process, as this would delay the administration of analgesia in a patient with severe pain.

Statistical Plan: To assess the primary outcome, the mean difference and standard deviation in pain score before and immediately after N2O administration will be calculated for the NRS. Assessment of the secondary outcomes will be performed as follows:

1) the duration of analgesia will be determined by calculating the mean time and standard deviation (minutes) after discontinuation of N2O administration until the time at which the pain score becomes > or = 7/10, the patient receives additional parenteral analgesia, is discharged home, or is admitted to hospital. The pain scores for each patient will also be plotted on a chart to illustrate the change in pain over time (y-axis = pain score, x-axis = time).

2) The presence of signs or symptoms suggestive of peripheral neuropathies will be documented, and the proportion calculated.

3) The presence of macrocytic anemia, if patients who have a low initial vitamin B12 level (see STUDY PROCEDURES: Follow-up Procedures) will also be documented and the proportion calculated.

Potential Risks:

There is limited data on the risks associated with N2O in patients with SCD. There are reports of long term side effects such as peripheral neuropathies and megaloblastic anemia).(7,17) The chances of these adverse events are low and have only been reported in case reports. They do not present acutely (onset is typically between 1 to 8 weeks), are completely reversible with vitamin B12 supplementation, and have only been

reported in the context of prolonged, continuous N2O administration (i.e. over 24 hours continuously), in the context of severe vitamin B12 deficiency, and prolonged and repeated N2O administration (e.g. 2 to 3 exposures a week for 6 weeks, and up to 3 hours each exposure). (7,17 18) Sickle cell patients are not expected to have vitamin B12 deficiency that would predispose them to these adverse events.(19) In discussion with our hematologists, it is also their experience that our population of patients with SCD is at low risk of being deficient in vitamin B12.

The risks associated with N2O in the general population are minimal (20,21). In a prospective sur vey of 35,828 administrations of 50% N2O, there was an incidence of 4.4% adverse events. The most frequent adverse events were nausea and/or vomiting (2%) and agitation or euphoria (1.8%). There was a 0.08% incidence of serious adverse events, including oxygen desaturation and cardiac arrest. However, both of these episodes were linked to inappropriate use of the administrative device and insufficient surveillance.(22) The rate of major adverse events when administering N2O concurrently with opioids is low. In one study of 7511 cases, there was no difference in the rate of major adverse events when 50% N2O was given with an opioid compared with when 50% N2O was given alone (0.33%).(23) In a separate report of 35,828 cases of 50% N2O administration, the overall rate of major adverse events when 50% nitrous administered alone was 0.08%, with the rate of major adverse events associated with any concomitant sedative administration (i.e. not exclusively opioids) being 0.03%.(22)

Potential Benefits:

The patient may experience pain relief of greater degree and duration than that achieved by receiving opioids. The patient may also receive more frequent assessment of their pain compared to the usual practice in the PED. The patient may benefit by avoiding short-term opioid-related side effects resulting from multiple doses of opioids acutely, such as hypotension, respiratory depression, or seizures. The patient may also benefit by attenuating, avoiding, or even improving long-term ad verse events related to chronic opioid use, such as opioid-induced hyperalgesia, opioid tolerance, and chronic pain irrespective of VOC.

Alternatives:

The patient and parent may choose not to participate in the study.

Data and Safety Monitoring:

Pediatric emergency medicine attendings and fellows will implement the N2O intervention. These physicians will have all been trained and certified as per NYP policy to administer N2O in the PED. On an ongoing basis, each enrolled patient will be reviewed by the investigators to monitor adherence to study protocol, assess data quality, and to collect and review any acute adverse events and other subject safety matters. The study team as a whole will meet at the start of the study, and then every 6 months during patient enrollment. A Data and Safety Monitoring Board (DSMB) will be instituted, and will evaluate adherence to the protocol every 6 months, and will report any protocol violations to the IRB. In addition, a safety report will be provided to the DSMB after 3 (three) patients complete participation. The DSMB will consist of two pediatric subspecialists who are not involved with the study and have no vested interest in the study (TBD). Adverse Event Reporting: An adverse event is any untoward medical occurrence experienced by a subject. For each patient, the study investigators will evaluate adverse events from commencement until completion of the study. These adverse events will include, but are not limited to: nausea, vomiting, agitation, oxygen desaturation, apnea, respiratory distress, cardiac arrest, hypotension, megaloblastic anemia, and peripheral neuropathies. All unanticipated problems (including adverse e vents that meet the criteria of an unanticipated problem) will be reported to the IRB promptly, but not later than one week following the occurrence of the unanticipated problem or the PI’s acquiring knowledge of the unanticipated problem, and at the time of continuing review.

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