The Effect of Nitric Oxide on Pain From Acute Vascular Occlusion Crisis in Sickle Cell Disease: A Systematic Review

Kristina Huffaker

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The Effect of Nitric Oxide on Pain From Acute Vascular Occlusion Crisis in Sickle Cell Disease: A Systematic Review

Abstract
Background: Acute vaso-occlusive crisis is a common occurrence in patients with Sickle Cell disease. The main symptom is pain, which is currently treated with medication such as morphine. Further treatments to alleviate pain would be beneficial to patients suffering from this condition. One possible treatment is inhaled nitric oxide. To review evidence of the efficacy of nitric oxide, the GRADE tool will be used to evaluate the strength of existing study data.

Method: PubMed, NLM Gateway, Medline, and EBM Multifile were used to perform an exhaustive search of medical literature. Results were limited to studies with human subjects that were published in English in 2000 or later.

Results: Three studies were reviewed, all of which were randomized controlled trials. All had small study sizes, and studied the subjective outcome of patient-evaluated pain level. Two of the three showed positive results for reduction in pain with inhaled nitric oxide therapy, and one study showed no change in pain with inhaled nitric oxide therapy. The primary outcome of decreased pain was graded as a moderate. Other outcomes of length of hospital stay and amount of pain medication used were also graded as moderate, however the outcomes of methemoglobin levels and harm were graded as high quality outcomes.

Conclusion: It is difficult to clearly state that inhaled nitric oxide does or does not decrease pain in acute vaso-occlusive crisis in patients with Sickle Cell disease. No adverse side effects have been seen, and some patients have reported decreased pain with nitric oxide; even if not shown to be statistically significant, this could be significant to the patient in question. Therefore, the option should currently be based not only on physician preference, but also on patient preference. Larger studies need to be conducted to increase current knowledge.

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The Effect of Nitric Oxide on Pain From Acute Vascular Occlusion Crisis in Sickle Cell Disease: A Systematic Review

Kristina Huffaker

A course paper presented to the College of Health Professions in partial fulfillment of the requirements of the degree of Master of Science

Pacific University School of Physician Assistant Studies

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Biography

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Keywords: sickle cell, pain, nitric oxide
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INTRODUCTION

Background

Sickle Cell disease (SCD) is an autosomal recessive disease most often diagnosed in people of African descent (Natarajan, Townes, & Kutlar, 2010). Though not a common disease, it can be a life-threatening one. Between 70,000-100,000 people in the United States alone were affected with SCD as of 2010 (Centers for Disease Control and Prevention [CDC], 2010). Researchers have found that the average life expectancy for patients with SCD has been steadily increasing, from approximately 10 years in the 1960s, to nearly 45 years in the 1990s (United States Department of Health and Human Services, 2010).

As published in Williams Hematology by Natarjan et al. (2010), the causative problem in SCD is the sickling, or change in shape, of red blood cells (RBC) due to abnormal hemoglobin contained within them. They discuss that this abnormal hemoglobin, Hb S, amasses into polymers, causing a collection which alters the shape of the RBC. Accordingly, these crescent moon, or sickle, shaped RBCs are more prone to causing obstruction in vessels, especially in small capillaries in the body, often beginning in the extremities. This leads to low oxygen supply to tissues, ultimately resulting in tissue death. It is also believed that chronic inflammation of vasculature may be a co-existing issue (Natarajan et al., 2010).

Sickling of RBCs is a process that is initially reversible, but which, with time, becomes an irreversible process. According to Natarajan et al. (2010), there are many damaging processes that occur simultaneously in SCD which
contribute to these periods of cell aggregation and blockage, known as acute vaso-occlusive crisis (VOC), which is characterized by the patient’s perception of pain, commonly located in the chest, extremities, and lower back areas. Due to the fact that sickled cells are unable to preserve potassium in the cell, there is activation of potassium-chloride channels which result in dehydration of the patient. VOC is caused by a promotion of aggregation, another agent of which is vascular cell adhesion molecule, VCAM, which causes aggregation due to its promotion of the union of sickled cells to the endothelium (Natarajan et al. 2010). Another detrimental processes in SCD to which the book refers are chronic high amounts of white blood cells, increased proinflammatory mediators, increased tissue factors promoting coagulation, and reperfusion injury after VOC due to oxidant stress. Eventually an atherosclerotic-like change to the vasculature occurs due to these processes (Natarajan et al., 2010).

The cause of acute VOC is unknown. However, multiple theories have been postulated. Steinberg (2011) discusses these methods, the first of which is that inflammation leads to leukocytes joined to endothelium, causing an obstruction in flow and promotion of sickling. Activation of macrophages is a second theory. This would cause platelet and endothelial cell activation, causing coagulation of cells. As mentioned before, dehydration is suggested as a cause of RBC adhering to the walls of vessels due to elevated thrombospondin or vonWillebrands factor. Chaos theory is a ubiquitous theory, suggesting that cell sickling and aggregation are random occurrences, with no apparent trigger (Steinberg, 2011). Proposed chronic inflammation of vasculature may, in turn,
alter normal nitric oxide levels, affecting cell aggregation. It has also been shown that there is decreased production and availability of nitric oxide (NO) due to hemolysis (Natarajan et al., 2010).

Acute VOC is dangerous to the patient because it may lead to the more serious side effects of acute chest syndrome or death. The more pain a patient has during this time is directly correlated to the increased risk of death (Field & DeBaun, 2010).

Current treatment for acute VOC is simply control of pain, since this is the primary symptom. Field and DeBaun (2010) illuminate this process, which is achieved using pain medication, typically morphine administered every 2-3 hours with dosing for breakthrough pain. They state that fluids are also administered to combat dehydration. Once admitted, the patients are typically put on patient-controlled analgesia (PCA) with pain medication constantly administered at a baseline level. Possible adjuvant therapies that may be included in the treatment plan include non-steroidal anti-inflammatories (NSAIDS) or glucocorticoids, also for pain control as well for as anti-inflammatory effect (Field & DeBaun, 2010).

Nitric oxide is proposed to alleviate acute crisis pain in a variety of ways. It has the natural affects of vasodilation on smooth muscle vasculature, anti-inflammatory effects, and also inhibits platelet aggregation, all of which are contributing factors in SCD (Natarajan et al., 2010). With lower levels of NO, there is increased inflammation and decreased vasodilation, which are promoting factors in cell aggregation. It is the cell aggregation, resulting in blockage of blood flow, which causes pain in these patients and can lead to potentially fatal
events. Low levels of NO are shown to be related to increased pain levels experienced by patients during acute VOC (Morris, Kuypers, Larkin, Vichinsky, & Styles, 2000). Pain levels correspond to increased risk for death and, since levels of NO correspond with pain levels, it is reasonable to conclude that levels of NO during this period may correspond to risk of death. A previous study completed by Head et al. (1997) showed that low supplemental levels of NO increase the affinity of oxygen for sickle cells, without toxic levels of methemoglobin, which is noxious when produced in high concentration. This suggests a possible therapeutic effect on deoxygenated cells, as is seen in Sickle Cell acute VOC. Improved resolution of sickling is thought to lead to an reduced level of pain in these patients.

Purpose of the Study

The purpose of this study is to perform a systematic review of the literature on the effect of nitric oxide on pain control for patients experiencing acute vaso-occlusive crisis in sickle cell disease. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group will be used to evaluate the evidence.

METHOD

An exhaustive literature search was conducted using PubMed, NLM Gateway, Medline, and EBM Multifile. Medline and EBM Multifile were accessed through the Pacific University Library system. The following keywords were
searched individually and in combination: “sickle cell”, “pain”, and “nitric oxide”. The search was limited to human subjects and the English language. The initial results included 156 articles. Articles older than 2000 were excluded, which limited the number of available articles to 146. Book entries, drug information databases, current clinical trial notes, and hazardous substance database entries were excluded. Of the resulting 109 studies, only randomized controlled trials were included, and of those, only studies investigating the effect of inhaled nitric oxide (NO) in acute sickle cell crisis pain were reviewed. Asthma and NO exhalation studies were excluded. This resulted in three studies which were included in the final analysis.

Inclusion Criteria

Inclusion criteria included randomized controlled trials conducted since 2000, involving participants over 10 years old. Only studies directly investigating the effects of inhaled NO on pain in acute sickle cell crisis were reviewed.

Exclusion Criteria

Excluded were clinical trial notes, hazardous substance database entries, book entries, drug information databases, books, and duplicate studies. Excluded were any combination therapies except those including traditional pain management, as well as studies focusing on acute chest syndrome seen in Sickle Cell disease.

RESULTS
Nitric Oxide for Inhalation in the Acute Treatment of Sickle Cell Pain Crisis: A Randomized Control Trial

Gladwin, et al. (2011) performed a randomized controlled trial conducted at 11 different medical centers in the United States. The authors selected 150 eligible patients 10 years and older with sickle cell disease in acute vaso-occlusive crisis, and divided them into two groups, each with 75 patients. The authors note that two of the 11 sites tended to enroll patients with lower pain scores, who later trended to have shorter hospital stays. All patients were assigned to groups by randomization, and both patients and staff involved were blinded to treatment group. The placebo group received a study gas which was 100% nitrogen gas, delivered with air and oxygen to achieve a 24% fraction of inspired oxygen (FIO2). The treatment group received 800 ppm nitric oxide mixed with nitrogen, air, and oxygen, to supply a similar FIO2 as the placebo group. Treatment was administered for a total of 8 hours. Both groups received traditional pain management by administration of morphine and fluids.

Outcomes measured included primarily time to conclusion of VOC, and secondarily length of hospital stay, pain scale, total amount of opioid pain medication given, rate of acute chest syndrome (ACS) or pneumonia, proportion of discharges within 24 hours, number of patients returning to ER within 30 days, and changes in nitrate and methemoglobin levels. Safety was monitored throughout, including measuring methemoglobin levels, blood pressure, sepsis, and pulse oxygenation (above 85% being normal). The pain scale was measured by means of the visual analog scale using numbers from 0 to 10, 0 being no pain
and 10 being worst pain ever experienced, along a 10cm horizontal line for patients to subjectively measure their own pain level at baseline and again after 2, 4, 6, and 8 hours.

Levels of significance for p values and intention to treat were results less than 0.05. The authors found that time to VOC resolution was not altered by the use of inhaled NO, as the p value was 0.87 (95% confidence interval (CI) was 46.0-91.0). They also concluded that of the secondary outcomes, length of hospital stay, pain score, amount of opioid medication, occurrence of ACS, proportion discharged in 24 hours, and number returning within 30 days was neither positively nor negatively affected by the use of inhaled NO, with p values ranging between 0.08 and 0.90 (confidence intervals were 2.0 to 6.0, 5.3 to 6.8, 1.4 to 6.1, 4.7 to 19.9, 2.2 to 14.9, and 5.7 to 21.8, respectively). Of the secondary outcomes measured, only plasma nitrate levels and methemoglobin levels were significantly higher in the inhaled NO group over the placebo group (p values of 0.03 and <0.001, respectively). However, neither level exceeded the upper limits of the normal range. No deaths occurred during this study, and no toxicity was seen. The authors of this study concluded that there is no benefit or harm to using inhaled NO in patients with acute vaso-occlusive crisis due to Sickle Cell disease.

Preliminary Assessment of Inhaled Nitric Oxide for Acute Vaso-Occlusive Crisis in Pediatric Patients with Sickle Cell Disease
Weiner, et al. (2003) conducted a randomized controlled trial at an urban hospital in the United States that specializes in children’s care. The authors selected 20 patients aged 10-21 years presenting with acute vaso-occlusive crisis from sickle cell disease. These patients were split into two groups using randomization, with 10 patients in each group. There were no dissimilarities between groups. Patients and staff were both blinded to treatment group.

The 10 patients in the placebo group received 21% inspired oxygen by face mask, combined with morphine for traditional pain management. The 10 patients in the treatment group received 80 ppm inhaled NO mixed with oxygen for a concentration of 21% oxygen. They also received traditional pain management by morphine administration. Inhaled treatment, either oxygen or NO, was continued for 4 hours in each group.

Outcomes measured were primarily the change in pain score at 4 hours, and secondarily the amount of pain medication needed and length of hospital stay. Safety was assessed in both groups for blood pressure (systolic of 80 mm Hg being the low end of normal), laboratory studies for methemoglobin (no more than an increase of 5% from baseline allowed), and oxygen saturation (90% being the low end of normal). There were no deaths in this study, and no toxicity seen. The only medications allowed were morphine, diphenhydramine and ondasetron.

A p value of 0.05 or less was considered significant in this study. The authors concluded that there were decreased pain scores in the group using inhaled NO at 4 hours. The pain score was measured using the visual analog
system by means of the visual analog scale using numbers from 0 to 10, 0 being no pain and 10 being worst pain ever experienced, along a 10cm horizontal line for patients to subjectively measure their own pain level. A non-statistically-significant decrease of pain of $p=0.37$ was measured using the pain scale. At the 3 hour point the $p$ value was 0.05, which was not statistically significant. They do note, however, that the results at this point in the study were trending in the direction of statistical significance. They also found that the treatment group used less pain medication over a 24 hour period than did the placebo group. This $p$ value of 0.15 was not statistically significant. There was also a trend toward shorter hospital stays in the inhaled NO group ($p=0.19$). No significant episodes of hypotension, decreases of oxygen saturation, harmful levels of NO, or high levels of methemoglobin were seen. The authors of this study concluded, that since the patients in the treatment group receiving NO used less pain medication, this may suggest a clinical significance for the use of inhaled NO. They suggest that inhaled NO may “offer promise” for decreasing pain in acute VOC caused by sickle cell disease, and encourage further studies to continue to examine these results.

Beneficial Effects of Nitric Oxide Breathing in Adult Patients with Sickle Cell Crisis

Head, et al. (2010) conducted a randomized controlled trial consisting of 18 adult patients divided into two groups using randomization, with 9 patients per group. Both staff and participants were blinded. The treatment group received 80
ppm of inhaled NO mixed with oxygen for a resulting 21% oxygen concentration. The placebo group received 21% inspired oxygen. Inspiratory treatment was given for 4 hours in each group. Both groups also received traditional pain treatment using morphine combined with diphenhydramine if necessary. There was no discussion on if placebo and treatment groups were matched.

Outcomes measured in the study were primarily reduction of pain scores, and secondarily total amount of morphine needed, and monitoring for toxicities. Safety was measured through blood pressure and oxygen saturation monitoring, laboratory samples to test for methemoglobin, as well as concentration of nitrogen dioxide.

The authors report a significant decrease in pain scores in the group receiving inhaled NO, as shown on the visual analog scale (p value was 0.0376 at 3 hours, statistical significance designated to be <0.05). These decreased pain levels were maintained even after therapy was discontinued. The placebo group had no such effect. The result of their measured secondary outcome was that the treatment group required slightly lower amounts of narcotic pain medication, however the results were not statistically significant (p= 0.26). Since the amount of pain medication used between groups was similar in that there was no statistical difference, the authors conclude that the groups used “equivalent” amounts. They believe this may be due to narcotic tolerance which is sometimes seen in sickle cell disease patients. They also noted that levels of nitrogen dioxide and methemoglobin, though increased in the treatment group, were not high enough to reach statistical significance (p of 0.09 and 0.74, respectively).
The authors thus conclude that inhaled NO shows significant decrease in pain in Sickle Cell patients during acute vaso-occlusive crisis.
DISCUSSION

Patients with Sickle Cell disease experience painful acute vaso-occlusive crisis multiple times throughout their lifetime, and currently there is no effective treatment to resolve such crises, only palliative treatment using morphine and similar medications. Therefore, the promise of additional effective treatments for alleviating pain or resolving the crisis itself would be a welcome addition to current treatment plans. There have currently been three studies done to evaluate the effectiveness of inhaled nitric oxide in the resolution of pain from acute VOC in sickle cell disease. Two of these studies show a positive effect or trend towards a positive effect from inhaled NO, and the other, slightly larger study, shows no effect whatsoever. The results of these studies need to be examined closely to interpret the value of their findings, as two of the three studies did not show statistically significant effects and therefore draw conclusions that still seem to be in the realm of hypothesis.

The first study, by Weiner, et al. (2003), was one of the two studies to suggest a positive effect of inhaled NO. The study was not without its limitations, however. Their sample size, at just 20 patients, was very meager. They also used the subjective endpoint of patient-assessed pain measurement using a visual analog scale. However, an objective assessment of pain without confounders would be difficult if not impossible to obtain. One major limitation noted for this study is the fact that, despite having positive outcomes, their statistical significance was a p of 0.05 at best, with a p of 0.05 being statistically significant. Thus, none of their outcomes were statistically significant, though
there was a trend heading towards statistical significance seen especially in the third hour of the study. There is also the problem that their study tested use of inhaled NO for only four hours, when acute VOC typically lasts much longer than that. This study only enrolled the pediatric population, which would be a limitation when applying the results to the adult population. Another possible confounder is that the concurrent use of hydroxyurea was not made clear, and some patients may have been on this medication which has been shown to have diminutive effects on acute VOC. The “findings” in this study could be viewed with some skepticism based on the fact that the results do not strongly point one way or another. Thus when the authors anticipate what may be seen in future studies they seem to be extending their findings beyond what was proven, and focus instead on the trends seen in the data.

The second study, by Head et al. (2010), was completed in order to assess the same subjective endpoint of pain in VOC as the first study, with the difference being that their goal was to assess this outcome in the adult only population. The study was nearly a duplicate of the first, with the major change being the enrollment of adults only. The limits of this study are, therefore, similar to the first. Their test also included only four hours of inhaled NO, and the concurrent usage of hydroxyurea was not made clear. Their sample size of 18 patients was even smaller than that of the first study. The authors failed to make clear their inclusion and exclusion criteria in their study report, thus making it somewhat difficult to compare the study group and placebo group, as well as
comparing all patients included to the general population. This could allow room for confounders.

Head et al. (2010) also failed to mention whether there were any significant differences between the placebo and treatment groups. Another limitation of this study is the fact that the authors decided to measure outcomes at 3 hours instead of at 4 hours, which was done in the pediatric study. This is notable due to the fact that the pediatric study saw their most significant results at the 3 hour mark. Therefore, these authors may have altered their time of treatment in the hopes of seeing the greatest outcome. One last mentionable limitation is the fact that the authors found slightly less use of narcotic pain medication in the NO treatment group, but since this result was not found to be statistically significant, the results were written off as unimportant. They conclude that the “mean narcotic use was equivalent” between groups (Head et al., 2010). Therefore they assume that this postulation could be caused by narcotic pain medication tolerance in patients with Sickle Cell, which seems to be quite an extrapolation from the measured data.

The third and last study, by Gladwin et al. (2011), was the largest by far, with 150 participants. The subjective endpoint of patient-assessed pain was also a limitation in this study, as in the other two. The authors admit that their results include wide confidence intervals. Confidence intervals measure the precision of their information, and wide confidence intervals imply that the precision of the information was lacking. This may call the significance of their negative results into question, especially in light of the fact that this is the only study which
reported no improvement with inhaled NO. One possible confounder that the authors noted was the fact that two of the 11 sites conducting the study consistently enrolled patients with lower pain levels, and resultantly had shorter hospital stays.

In order to assess the quality of these studies, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, developed by the GRADE Working Group, was used. The GRADE tool evaluates outcomes to place each one into one of four different levels of strength. These are high, medium, low, and very low. By GRADE’s definitions, a high quality study shows that the current evidence is strong and “further research is very unlikely to change our confidence in the estimate of effect” (Guyatt et al., 2008, p.926). A moderate quality study would recommend further studies saying that “further research is likely to have an important impact” on current recommendations on the topic (Guyatt et al., 2008, p.926). A low quality study means that “further research is very likely to have an important impact” as this would be extremely likely to change current recommendations (Guyatt et al., 2008, p.926). Finally, a very low quality study results shows that “any estimate of effect is very uncertain” (Guyatt et al., 2008, p.926). It was discovered that the three studies mentioned previously had multiple evaluated outcomes in common. These outcomes were changes in pain, amount of traditional pain medication needed, methemoglobin levels, and harm. Two of the studies also measured length of hospital stay as an outcome.
The first and main outcome was the measurement of changes in pain. Since all three studies that evaluated this outcome were randomized controlled trials (RCTs), the level of evidence started at high. This was downgraded, however, due to the fact that only two of the three studies were in agreement as to the results, which lowered the consistency of the results. Precision in one study could be questioned due to the wide confidence intervals, but as this was the study which conflicted with the others, the grade was not further downgraded. The other factors which may downgrade the evidence are study quality, directness, and publication bias, but for this outcome these levels were not affected. Therefore, the ending level of strength for this outcome was moderate.

The second outcome measured was the amount of pain medication used. This could potentially be an objective way to measure the patient’s change in pain without asking the patient to subjectively measure it themselves. All three studies measured this outcome, and similar results were seen to that of the change in pain outcome. All were RCTs and thus this level of evidence was started at high. This outcome was also downgraded to moderate due to lack of consistency because one study showed a decrease amount of pain medication necessary, and the other showed no change. It is interesting to note that one of the studies which originally showed a decrease in pain with inhaled NO showed that the amount of pain medication necessary between groups was similar. These authors speculate that this could be due to narcotic tolerance, thus requiring more morphine for lower levels of pain (Head, et al. 2010). This would make the amount of pain medication needed look similar between groups,
Despite one group having decreased pain, although their conclusions in this area were far from definitive.

The third outcome measured was length of hospital stay, and only two of the studies evaluated this outcome. However, since they were both RCTs, the level of evidence started at high. These two studies differed in their results, with one showing a shorter hospital stay in patients treated with inhaled NO, and the other showing no difference in length of stay compared to the placebo group. It is interesting that in the study which showed no statistically shorter hospital stays, 2 of their 11 sites had enrolled patients with lower pain scores and consequently shorter hospital stays. Due to this conflicting data, the evidence had to be downgraded, ending with a quality level of moderate.

The level of methemoglobin in the blood was a fourth outcome measured, because high levels of methemoglobin, a byproduct of NO, may become dangerous to the patient. If high levels were seen, then the safety of the treatment would be called into question. Elevated levels were expected due to the nature of the treatment; accordingly all three studies measured these levels repeatedly throughout the course of treatment, and detected no problems. As RCTs, the evidence started at high grade. All three studies showed similar results of increased levels of methemoglobin in the inhaled NO group. However, the levels of methemoglobin across all three studies never rose above the normal limits, and so this outcome was not downgraded. The final grade for this outcome was a high grade.
The final outcome measured was harm in general. All three studies measured this outcome, which included checking blood pressure, oxygen saturation, levels of nitrates and levels of nitrites. None of the studies showed any toxicity or harm to the patients. There was no issue with study quality, consistency, directness, precision, or publication, thus, the evidence was started at a grade of high and was not downgraded.

Since two of the outcomes were graded as high evidence, and three were graded as moderate, a decision had to be reached as to how to grade the body of evidence as a whole. As the primary outcomes of change in pain, amount of pain medication needed, and harm were the most important and pertinent, those outcomes carried the most weight in the decision. Length of hospital stay is an important factor when evaluating this potential new treatment, but was not the focus or intent of the studies. The methemoglobin and harm outcomes were weighed together as one, as these are both outcomes which, if positive, would negatively affect the study. As two of the primary outcomes were measured as moderate and one (harm and methemoglobin levels) as high, as well as the fact that three out of five outcomes measured as moderate evidence, the overall grade for the evidence was considered to be moderate.

An overall grade of moderate tells us that there would be a great benefit from further studies in this area (Guyatt et al., 2008). At this point, it is difficult to clearly state that inhaled NO does or does not decrease pain in acute VOC in patients with sickle cell disease. Three well conducted studies have been performed to investigate the data, all of which have their limitations, and one of
which has results which conflict with the other two. At present, larger studies need to be conducted as randomized controlled trials to further the available knowledge in this possible treatment. All of the current studies show that toxicity and harm are not concerning factors, and thus allow hope that inhaled NO could be a safe treatment if finally proven effective.

For now, it is suggested that clinicians consider the use of inhaled NO in sickle cell patients experiencing acute VOC, keeping in mind that the current data is conflicting as to efficacy. No adverse side effects from inhaled NO have been seen, and some patients have reported decreased pain from treatment; even if not shown to be statistically significant, this could be important to the patient in question. Given the recurrent nature of this condition, a patient may discover that this particular treatment is effective for him or her and may prefer to use it. Therefore, the option should currently be based not only on physician preference, but also on patient preference. To put it simply, it could be beneficial to a patient, and it certainly will not harm them.
REFERENCES


## APPENDIX A

### Table 1: GRADE Table

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>Overall GRADE of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitric Oxide with morphine vs. traditional pain management with morphine alone</td>
<td>Change in pain</td>
<td>2 RCT 1 RCT</td>
<td>Decreased pain, No change in pain</td>
<td>High</td>
<td>0 -1 0 0 0 0 0 0</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>Amount of pain medication needed</td>
<td>1 RCT 2 RCT</td>
<td>Decreased, No change in amount</td>
<td>High</td>
<td>0 -1 0 0 0 0 0 0</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>Length hospital stay</td>
<td>1 RCT 1 RCT</td>
<td>Decreased, No change</td>
<td>High</td>
<td>0 -1 0 0 0 0 0 0</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Methemoglobin in levels</td>
<td>3 RCT</td>
<td>Within normal range</td>
<td>High</td>
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<td>High</td>
</tr>
<tr>
<td></td>
<td>Harm</td>
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<td>No harm found</td>
<td>High</td>
<td>0 0 0 0 0 0 0 0</td>
<td>High</td>
</tr>
</tbody>
</table>