**Introduction**

Sickle Cell Disease (SCD) is an autosomal recessive disease most often diagnosed in people of African descent (Natarajan, Townes, & Kutlar, 2010). Between 70,000-100,000 people in the United States alone were affected by SCD in 2010 (Centers for Disease Control and Prevention [CDC], 2010).

The causative problem in Sickle Cell Disease (SCD) is the sickling, or change in shape, of red blood cells (RBC) due to abnormal hemoglobin contained within them. 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. This leads to low oxygen supply to tissues, ultimately resulting in tissue death. This blockage is what causes acute vaso-occlusive crisis (VOC), normally noted by pain.

Nitric oxide (NO) causes vasodilation and anti-inflammatory effects. Since it is inflammation and decreased vasodilation that are thought to be causative agents in VOC, NO is contemplated as a potential therapeutic. However, levels of NO are shown to correlate to increased pain levels. Current treatments are medications such as morphine.

**Purpose**

The purpose of this study was 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 ten years 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 control trials were included, and of those, only studies investigating the effect of inhaled nitric oxide (NO) in acute sickle cell disease pain, not asthma or NO exhalation, were included. The studies investigating effect of inhaled nitric oxide in acute sickle cell crisis pain, not asthma or NO exhalation, were included in the final analysis.

**Results**

Gladwin, et al. (2011) performed a randomized controlled trial (RCT) entitled Nitric Oxide for Inhalation in the Acute Treatment of Sickle Cell Pain Crisis. This study enrolled 150 patients and randomized them to groups of either nitrogen with oxygen or NO with oxygen. They found that time to VOC resolution was not altered by use of NO (p=0.87), and neither were the outcomes of pain score, amount of opioid needed, length of hospital stay, and number returning in 30 days (p values between 0.08 and 0.90). No harm or toxicity was seen.

Weiner, et al. (2003) conducted an RCT entitled Preliminary Assessment of Inhaled Nitric Oxide for Acute Vaso-Occlusive Crisis in Pediatric Patients with Sickle Cell Disease. They enrolled pediatric patients randomized into groups of 10 receiving either oxygen alone or NO mixed with oxygen. They found that there were decreased pain scores and lower amounts of pain medication used (p=0.37 and 0.15). These were not statistically significant results but may suggest a clinical difference. No harm or toxicity was seen.

Head, et al. (2010) conducted an RCT entitled Beneficial Effects of Nitric Oxide Breathing in Adult Patients with Sickle Cell Crisis. This study enrolled adult patients and randomized them into groups of 9 receiving either oxygen alone or NO mixed with oxygen. Their results showed decreased pain scores in the treatment group (p=0.0376). They also reported decreased amount of pain medication used, although this was not statistically significant (p=0.26). No harm or toxicity was seen.

**Discussion**

The Weiner, et al. (2003) study was one of two to suggest a positive effect of inhaled NO. Limitations included study size, the subjective endpoint of pain, and possible hydroxyurea use. One major limitation noted for this study is the fact that, despite having positive outcomes, they had a p value 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.

The Head et al. (2010) study was nearly a duplicate of Weiner et al’s, with the major change being the enrollment of adults only. The limits of this study are, therefore, similar to the first. One other 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 seen as unimportant.

The Gladwin et al. (2011) study was the largest by far. The authors admit that their results include wide confidence intervals, which may call the significance of their negative results into question.

In order to assess the quality of these studies, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used. The first and main outcome was the measurement of changes in pain, and was started as a high grade but downgraded to moderate due to lack of consistency. The second outcome measured was the amount of pain medication used, and was also started at a grade of high and later downgraded to moderate due to lack of consistency. The third outcome measured was length of hospital stay, and only two of the studies evaluated this outcome. This outcome was similar to the first two in that it was started at a grade of high and downgraded to moderate due to lack of consistency. The level of methemoglobin in the blood was a fourth outcome measured as a potential toxicity, as well as the outcome of harm in general which included blood pressure, oxygen saturation, and other laboratory levels. These started and ended at a grade of high.

As two of the primary outcomes were measured as moderate and one (harm and methemoglobin levels together) 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.

**Conclusion**

An overall grade of moderate tells us that there would be a great benefit from further studies in this area (Goyal 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. At present, larger studies need to be conducted as randomized controlled trials to further the available knowledge in this possible treatment.

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**


