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Treatment of Vaso-Occlusive Pain Related to Sickle Cell Disease in Pediatric Patients: A Systematic Review

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Sickle cell disease (SCD) is a rare inherited disorder that affects the shape of erythrocytes. SCD is estimated to affect 70,000 - 100,000 Americans and is seen predominately in African-Americans. In SCD, the body produces sickle-shaped red blood cells, which have shorter lifespans than normal red blood cells and can lead to anemia. The abnormal shape causes them to become lodged in blood vessels, causing pain and organ damage. Symptoms generally begin by three years of age and complications of sickle cell disease include vaso-occlusive crises, acute chest syndrome, and others. A vaso-occlusive crisis is an episode of pain, described as sharp, intense, and throbbing, most commonly occurring in the lower back, leg, hip, abdomen, or chest. It typically begins at night and lasts 3-14 days. It is the most common reason for hospitalization in patients with SCD. Episodes increase in frequency throughout childhood. No cure for SCD is widely available; treatment is symptomatic and supportive. No evidence based guidelines for the treatment of pain during vaso-occlusive crises in pediatric patients with SCD are published.

**INTRODUCTION**

The purpose of this literature review was to evaluate the safety and efficacy data of selected trials, provide a summary of evidence-based treatments, and identify specific areas where more studies are needed in the treatment of vaso-occlusive crises in pediatric patients.

**METHODOLGY**

Studies were included in the review if they were randomized controlled trials. Trials must include participants 18 years and younger with sickle cell disease. The intervention must be an FDA approved medication (not necessarily approved for SCD). One of the outcomes measured in the trial must be reduction in pain score; no standard pain score exists so different scores will be included (Wong-Baker FACES Pain Rating Scale, Visual Analog Scale, etc. See Figure 1 and Figure 2). Secondary outcomes include serious adverse events. Studies were evaluated for rigor using the JADAD score, and were included if the score was ≥ 3.

**RESULTS**

Of the six studies analyzed, two showed statistically significant difference in the decrease in pain scores in children with vaso-occlusive crises. The Fein trial showed a significant reduction in pain scores after 15 minutes, while the administration of intranasal fentanyl. The difference was seen at 20 minutes after administration, but not 10 or 30 minutes. The Morris trial showed a significant difference in pain scores at discharge in patients in the arginine arm. The other studies did not show statistical significance, however the small sample size of the trials only has the power to detect large changes in outcomes. Another consideration is the difference between clinical significance and statistical significance. While the trials may not have had a statistical difference in pain scores, the differences may have been enough to show clinical improvements in patients. No serious adverse effects were seen in any of the trials.

A strength of this study is limited inclusion criteria to allow for as many trials to be included as possible. The literature search was comprehensive and complete. Weaknesses include the small sample sizes in trials, differences in pain scales used, and differences in the time periods in which pain was measured during the crisis. Each trial measured pain scores at different points throughout treatment, and it is difficult to compare and generalize the different results. Limited published trials exist that are controlled clinical trials with strong design.

**CONCLUSIONS**

Based on the results of the literature review, intranasal fentanyl and L-arginine have some evidence for use in pediatric patients with vaso-occlusive crises. More evidence is needed; however both may be safe, reasonable options in uncontrolled pain as an adjunct to standard therapy.

Trials are needed with larger sample sizes to detect a smaller change in outcomes. It would be beneficial if trials used a standard pain scale, easing the comparison between trials. Studies in this population are difficult because of the subjective nature of endpoints, such as pain and length of stay. Length of stay may be influenced by many non-treatment related factors (e.g., discharge paperwork), although it was included in many of the reviewed trials as an outcome. Future reviews may evaluate the efficacy of medication for vaso-occlusive crises based on different outcome measures. The ethical concerns of studying medications in children, the lack of incentives for studying rare diseases, and the subjectivity of pain make studying the management of vaso-occlusive crises in pediatric patients very difficult, however this review provides information regarding safe and effective, evidence-based treatments for pediatric patients with vaso-occlusive pain.

**REFERENCES**