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IV MAGNESIUM FOR SICKLE CELL PAIN CRISIS IN CHILDREN- A RANDOMIZED CONTROLLED STUDY.

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Abstract:
In United States there are approximately 100 000 individual suffering from sickle cell disease of which 40% are children. There are 18 000 hospitalizations and 75 000 hospitalization days annually for the children who experience sickle cell pain crises. Much of the morbidity of the disease is a result of recurrent pain crises, which often result in emergency department (ED) visits and hospitalizations and adversely affect quality of life 4-7. Despite advances in the management of other comorbidities of sickle cell disease, little has changed in the management of pain crises. Standard supportive therapy remains intravenous (IV) opioids and the judicious use of IV fluids. In acute sickle cell painful crises many several multicenter trials have been closed because of inadequate enrollment, making advancements in the field difficult. The primary factors in the initiation and prolongation of pain crises in sickle cell disease v Vasoconstriction and inflammation.
The main limitation of the study was measurement of opioid use, rather than pain scores. Although the clinical utility of pain scores is clear, the variability in pain scores throughout the day and the criticism that the timing of opioid treatments could significantly affect timed pain scores resulted in our decision to focus our secondary outcome on pain medication use.
Intravenous magnesium does not shorten LOS, lessen opioid use, or improve HRQL in children who require hospitalization for sickle cell pain crisis. Close collaboration between pediatric emergency medicine physicians and pediatric hematologists allows for the successful, efficient enrollment of large numbers of children in an acute intervention trial for children with sickle cell anemia.

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INTRODUCTION:

In United States there are approximately 100 000 individual suffering from sickle cell disease of which 40% are children. There are 18 000 hospitalizations and 75 000 hospitalization days annually for the children who experience sickle cell pain crises. Much of the morbidity of the disease is a result of recurrent pain crises, which often result in emergency department (ED) visits and hospitalizations and adversely affect quality of life 4-7. Despite advances in the management of other comorbidities of sickle cell disease, little has changed in the management of pain crises. Standard supportive therapy remains intravenous (IV) opioids and the judicious use of IV fluids. In acute sickle cell painful crises many several multicenter trials have been closed because of inadequate enrollment, making advancements in the field difficult. The primary factors in the initiation and prolongation of pain crises in sickle cell disease v Vasoconstriction and inflammation. To modify the pathophysiology of pain crises, a well-known vasodilator is Magnesium which has anti-inflammatory effect. Much work has been conducting on oral administration of magnesium to prevent the crises. An institute has conducted different studies on examining the result of magnesium on acute pain crisis. It produced inconsistent results. One study has showed very limited length of stay from a median of 5 days to a median of 3 days compared with previous hospitalizations by the same individuals. In contrast another randomized controlled trial study conducted in Canada in which there were 104 children who had average LOS more than 5 days and found no decrease in length of hospitalization. To justify these results groundwork for a large randomized trial is required to answer the question of magnesium's efficacy.

The aim of the study is to determine the effect of the adding IV magnesium to standard therapy for children hospitalized with pain crises.

MATERIALS AND METHOD:

It was a randomized controlled trail. Participants who met the inclusion criteria were recruited into the study. Age ranges from 3 to 21 years old were the set criteria. Individuals who were admitted for pain management due to sickle cell anemia were eligible. Two groups were formed magnesium group and placebo group. In placebo group there was only normal saline added to standard therapy for the treatment of pediatric sickle cell pain crisis. The genotype was reported by the parent and confirmed by either review of original electrophoresis or past hematology note. In Magnesium group IV magnesium with dose 40 mg/kg after every 8 hours of total 6 doses was administered. Whereas in placebo group there was 1mL/kg of normal saline administered. A written informed consent was obtained from the participants after explaining the purpose of the study. The primary outcome was length of stay from the time of first drug infusion until 12 hours after the last IV opioid dose or time of discharge, whichever occurred first. Secondary outcomes included opioid use, HRQL, markers of inflammation, hemolysis and endothelial activation, and adverse events. All opioid doses, whether IV or oral, were recorded and converted to IV morphine equivalents. The PedsQL generic core scales andthe PedsQL multidimensional fatigue scales, which are valid and reliable for use in patients with sickle cell disease. HRQL was also used.

RESULTS:

Total 206 children recruited in the study

All children who received at least one dose of study drug are included in the analyses. Baseline characteristics were similar between the 2 groups with respect to age, sex, genotype, weight, history of acute chest syndrome or asthma, previous hospitalizations within the past 3 years, days of pain before arrival, and treatment before study drug initiation (Table 1).

Characteristic	Magnesium N= 104	Placebo N=102
Sickle cell anemia type, n (%)	91	95
HgbSS	6	5
HgbSb	13.2	14.3
Age, mean (SD)		
3-11 yrs	43	39
12-21	58	61
Patient history, n (%)		
Treated with hydroxyurea within 3 month	64	60
History of acute chest syndrome	73	77
History of asthma	49	55

Approximately 60% of children had used hydroxyurea within 3 months. The median time from first ED opioid to first study drug infusion was 7.4 hours, which was similar between the 2 groups. The median length of stay in the magnesium group was 56.0 hours whereas in placebo group there was 46.0 hours. It was same in both groups. There was no statistical difference of length of stay in both groups. Post-hospital subgroup analysis was conducted to determine whether magnesium had an effect on length of stay if the child admitted earlier in course of pain crisis. Though it revealed there was no difference in placebo versus magnesium group. When examining HRQL data in the linear mixed-effects model, there were no differences found between treatment groups in changes in markers of inflammation, hemolysis, and endothelial activation were similar between the magnesium and placebo groups. Safety analysis revealed no differences in the development of acute chest syndrome or hypotension between the groups; however, warmth on infusion was higher in the magnesium group. No significant differential treatment effect was found across subgroups.

DISCUSSION:

The current study has demonstrated that addition of IV magnesium in the general standard therapy of sickle cell disease pain crisis had not reduced the LOS, minimized the use of opioid or improved HRQL. Oral magnesium had been used to prevent the pain crisis with some initial success but later that medication was not well tolerated. In fact earlier literature favors the IV use of magnesium but current study had shown no effect in treating sickle cell pain crisis. In other pediatric emergency conditions such as asthma, IV magnesium has shown safe effective in such conditions.

In sickle cell disease there is impaired vascular function. Moreover in magnesium deficiency there is increased levels of the inflammatory cytokines interleukin 6 and tumor necrosis factor and increased expression of endothelial vascular cell adhesion molecule however this mechanism of inflammation could alter by IV magnesium. A larger study is needed to evaluate whether IV magnesium efficacy is reliable in patients with sickle cell anemia pain crisis or not. The current study has only determined

The current study has only evaluated IV magnesium but not the efficacy of orally administered magnesium therefore the results are not generalized to which have been studied in the prevention of painful crises, not the treatment of acute painful crises. Moreover opioids were used to measure the control over pain during hospitalization. Opioid medication use is a proxy for overall pain level, as the need for more pain medication is correlated with increased pain ratings by patients.

The main limitation of the study was measurement of opioid use, rather than pain scores. Although the clinical utility of pain scores is clear, the variability in pain scores throughout the day and the criticism that the timing of opioid treatments could significantly affect timed pain scores resulted in our decision to focus our secondary outcome on pain medication use. Our study was also limited by the fact that more children in the magnesium group correctly identified their randomization group. However, the most of the children in each group were either incorrect or not sure when asked about their treatment group, and it seems unlikely that child knowledge of treatment group would have decreased the likelihood of magnesium being efficacious. In conclusion, intravenous magnesium does not shorten LOS, lessen opioid use, or improve HRQL in children who require hospitalization for sickle cell pain crisis. Close collaboration between pediatric emergency medicine physicians and pediatric hematologists allows for the successful, efficient enrollment of large numbers of children in an acute intervention trial for children with sickle cell anemia.

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