



Comparison between Hydroxyurea alone and Hydroxyurea with Oral Magnesium for Reducing Acute Painful Crisis in Sick Cell Patients

Mohammad Ali Molavi¹, Mahmoud QasemyZadeh², Abdolmajid Nazemi^{3*}, Rakhshane Goodarzi³, Mostafa Moghtadaie³, Saeid Hosaini⁴, Kamyar Molavi²

¹ Department of Pediatric Hematology, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

² Medical university of Hormozgan, Bandar Abbas, Iran

³ Department of Pediatric, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

⁴ Epidemiologist, Nursing school, Hormozgan University of Medical Science, Iran

* Corresponding author's Email: Anazemi@yahoo.com

ABSTRACT: In the U.S, sickle cell disease is the most common genetic disease identified through the state-mandated newborn screening program. The cardinal clinical feature of sickle cell anemia is pain from vasoocclusive episode. The only measure of the intensity of pain is the patient at the peak levels of pain, the patient is often admitted in hospital. In many past articles, the efficacy of magnesium in reducing painful crisis were studied and they showed the beneficial effects of magnesium. In this article we studied the beneficial effects of adding magnesium to hydroxyurea for reducing painful crisis, reducing admission and increasing HbF and Hb level of SCA patients. **Method:** In this clinical trial study, population consists of sickle cell anemia or disease by age between 2 months to 18 years old who were referred to Bandar Abbas Pediatric Hospital. The subjects were classified in two groups, group A-patients were treated with hydroxyurea and group B-patients who treated with hydroxyurea and magnesium. CBC, diff, Hb, electrophoresis, liver and kidney markers were checked and after 4 weeks and 6 months later, the patients or parents were asked for pain crisis episodes, admission, admission periods and Hb level and Hb electrophoresis were checked. **Statistics:** were elaborated with the Spss16 software and analyzed with chi-square test. **Results:** In group B the mean of pain attacks after 6 months were (0.88-1.5) and P-value was 0.46. In group B after 6 months, the mean of electrophoresis was (22.5+11.5) and in group A was (17+8.8) and P-value was less than 0.05 that meant the increase of HbF in group B were significant but in other category weren't any difference between two groups. **Conclusion:** this study indicated that adding magnesium to hydroxyurea in sickle cell anemia patients reduced the episodes of painful crisis within 6 months later and increased the HbF level in electrophoresis within 6 months later but hasn't any significant difference between two in other variables.

Key words: Sickle Cell Anemia, Pain Crisis, Hydroxyurea, Magnesium

INTRODUCTION

As we know, in U.S, sickle cell disease (SCD) is the most common genetic disease which identified what ought the state-mandated newborn screening program. Mostly of these patients will be catch functional asplenia before 5 years old because of abnormal immunologic function. Bacterial sepsis is one of the most important mortality factors in SCD patient. The cardinal clinical feature of sickle-cell anemia (SCD) is pain from vasoocclusive episode. Pain looks like continuous discomfort what usually involve chest, abdomen and distal of extremities. Painful crisis is a suddenly attack; it can be disconcert patients and their parents. The only measure of intensity of pain is the patient.

Predisposing factor of pain is infection, local or general acidosis, physical stress, dehydration, hypoxia, cold weather.

Lucrative treatment will be needed a patients and parents education about sign and symptom of painful crisis and how to manage it. Painful crisis has a variable treatment such as, acetaminophen, NSAIDs in early stage, short acting opioid, long acting opioid or at the peak levels of the pain, the patient is often admitted in the hospital and treated by IV morphin. Hydroxyurea is a bone marrow suppression drug and it can be decrease episodes of painful crisis and also increase level of HbF and Hb. usually hydroxyurea reduce 50% of painful crisis

episode, it can be decrease 50% of acute chest syndrome attack and transfusion in adults, too.

As a theory, hydroxyurea has been potent to make leukemia and unknown side effect. Hydroxyurea is an effective treatment of sickle cell anemia alone, so it's important to study about effect of other drugs on SCA treatment. The effect of nicosan, sinapaeque, clotrimazol, magnesium had been studied. In one study, it shown that magnesium had a modulatory effect in k-ca channel and decreased dehydration in cells and reduced pain crisis in SCA patient (Brugnara et al., 1996). Full magnesium regime in SCA rats, increased mg, k in erythrocyte and reduced transmission k and cl and decreased painful crisis with this mechanism (De Franceschi et al., 1996). Add oral magnesium supplement to SCA patients regime reduced painful crisis in patients (De Franceschi et al., 1997). In another study, magnesium was used as a treatment of SCA patient and it shown that magnesium could be reduce painful crisis in 4-6 weeks (De Franceschi et al., 2000). Combination of hydroxyurea and magnesium could be reduce painful crisis (Winfred et al., 2005; Winfred et al., 2009). Magnesium sulfate had a positive effect on slave painful crisis in SCA patients (Friedman 2008). In many many past articles, the efficacy of magnesium in reducing painful crisis were studied and they showed the beneficial effects of magnesium, in this article we decided to study the beneficial effects of adding magnesium to hydroxyurea ad reducing painful crisis, reducing admission and increasing HbF and Hb level of SCA patients.

METHODS AND MATERIALS

This clinical trial study was done in the Bandarabbas Pediatric Hematology Clinic in March 2009 to March 2010. The study was conducted on children with

sickle cell anemia aged 2 months to 18 years old who admitted or referred to Bandar Abbas Pediatric Hospital. Diagnosis of anemia was done by specialty hematology pediatric through electrophoresis and cell blood count. We had 50 patients who were classified in two groups. Group A-patients were treated with hydroxyurea 15-20mg/kg/day and group B-patients were treated with hydroxyurea 15-20mg/kg/day and magnesium carbonate 150mg/day. At the start of study CBC, diff, Hb electrophoresis, na, k, BUN, Cr, ALT, AST, Alkp, Retic were checked and after 4 weeks and 6 months later, the patients or parents were asked for pain crisis episodes, admission, admission periods and Hb level and Hb electrophoresis were checked. Patient's records were reviewed and Statistics were elaborated with the Spss16 software and analyzed with chi-square test.

RESULTS

The average age of children in group A was 4.9 with standard deviation 3.4 and the average age of children in group B was 6.5 with standard deviation 3.6. The comparison of average of admission in hospital in two groups is shown in table 1 during 4 weeks and 6 months. The comparison of average of admission duration between two groups during 4 weeks and 6 months is shown on table 2. Table 3 is showing the comparison of average of painful crisis between two groups during 4 weeks and 6 months.

The comparison of average of Hb electrophoresis (HbF) between two groups during 4 weeks is shown in table 4. Table 5 is showing the comparison of the average of Hb between two groups during 4 weeks and 6 months. The data in these tables showed that there was significant correlation between magnesium and decrease painful crisis after 6 months and increase HbF after 6 months but in other weren't any significant difference between 2 groups.

Table 1. Comparison of average of hospital admission between two groups

Group	Frequency	Average	t	P-value
A during 4 weeks	50%	0.12+-0.33	---	0.691
B during 4 weeks	50%	0.16+-0.37	0.4	0.691
A during 6 months	50%	0.4+-0.5	1.2	0.234
B during 6 months	50%	0.24+-0.43	1.2	0.234

Table 2. The comparison of mean of admission duration between two groups

Group	Frequency	Average	t	P-value
A during 4 weeks	50%	0.2+-0.57	-0.8	0.376
B during 4 weeks	50%	0.4+-0.95	-0.8	0.376
A during 6 months	50%	0.88+-10.2	12	0.208
B during 6 months	50%	0.48+-0.91	12	0.208

Table 3. The comparison of average of painful crisis between two groups

Group	Frequency	Average	t	P-value
A during 4 weeks	50%	0.2+-0.5	0	1
B during 4 weeks	50%	0.2+-0.64	0	1
A during 6 months	50%	17.5+-8.8	-1.9	0.033
B during 6 months	50%	22.05+-11.5	-1.9	0.033

Table 4. The comparison of average of Hb electrophoresis (HbF) between two groups

Group	Frequency	Average	t	P-value
A during 4 weeks	50%	1.8+-1.7	2	0.046
B during 4 weeks	50%	0.88+-1.5	2	0.046
A during 6 months	50%	14+-8	-0.9	0.373
B during 6 months	50%	13.3+-5	-0.9	0.373

Table 5. The comparison of average of Hb between two groups

Group	Frequency	Average	t	P-value
A during 4 weeks	50%	1087+-1.7	1.2	0.217
B during 4 weeks	50%	10.2+-1.5	1.2	0.217
A during 6 months	50%	10.88+-1.96	0.39	0.697
B during 6 months	50%	10.6+-1.55	0.39	0.697

DISCUSSION

Hydroxyurea is a bone marrow suppression drug and it can decrease episodes of painful crisis and also increase level of HbF and Hb. As a theory, hydroxyurea has been potent to make leukemia and unknown side effect. Hydroxyurea is an effective treatment of sickle cell anemia alone, so it's important to study about effect of other drugs on SCA treatment. Magnesium is one of the rare elements on body and it hasn't any side effect, yet, it's too important to study about that. In De Franceschi et al. (1996), full magnesium regime in SCA mouse, increased mg, k in erythrocyte and reduced transmission k and cl and decreased painful crisis with this mechanism. In another De Franceschi et al. (1997), magnesium was used as a treatment of SCA patient and it shown that magnesium could be reduce painful crisis in 4-6 weeks. Our study shows that the average of hospital admission in group B during 6 months is 0.24+-0.43 but in group A is 0.4+-0.5 which hasn't significant difference between two groups. The mean of painful crisis after 6 months in group B was 0.88+-1.5 and P-value was 0.46 and the mean of HbF electrophoresis was 22.05 +-11.5 in group B. This study indicated that adding magnesium to hydroxyurea in SCA patients reduced the episodes of painful crisis within 6 months later and increased the HbF level in electrophoresis within 6 months later but hasn't any significant difference between two groups for other variables.

REFERENCES

- Brugnara C. (1996) inhibition of K transport by divalent cations in sickle cell erythrocytes. *Blood* 1987;70:1810
- De Franceschi, et al. (1996). Modulation of erythrocytes KCL co transport by dietary magnesium intake in SAD mouse. *Blood*:88:2738
- De Franceschi, et al. (1997). Oral magnesium supplements reduce erythrocyte dehydration in patient with SCD. *Blood*:100:1847.
- De Franceschi, et al. (2000). Oral magnesium pidolate: effects of long term administration in patients with SCD. *BJH*:108:284.

- Winfred C, Wang MD. (2009). Evaluating the safety and effectiveness of hydroxyurea and magnesium to treat dell disease. FDA, VSA.
- Winfred C, Wang MD. (2005). Use hydroxyurea and magnesium-pidolate for treatment of SCD, clinical trial gov FDA, USA.
- Friedman Jeremy. (2008). Magnesium for sickle cell acute crisis in childhood. Clinical trial.