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RESEARCH ARTICLE

EFFECTIVENESS OF HYDROXYUREA THERAPY IN PATIENT WITH HEMOGLOBINOPATHIES IN HEREDITARY BLOOD DISEASE CENTER AT KARBALA TEACHING HOSPITAL.

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Key words:-
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Abstract

Background:- Hydroxyurea is an antimetabolite drug increase fetal hemoglobin level and reduce the symptoms of sickle cell disease.

Aim:- To identify the effect of hydroxyurea in cases with frequent painful crisis or frequent blood transfusions of sickle cell disease and non-transfusion dependent thalassemia (NTDT) in hereditary blood disease center of Karbala teaching hospital from June 2010 till December 2015.

Method:- An eighty three cases conducted in our case control study .From which forty two cases received hydroxyurea in dose 10 -20 mg /kg/day orally and their follow up every two weeks in the first three months by taking blood samples for investigation (Hb, WBC, platelet count and renal function) with assessment of adverse effects.After that patient investigated according to their routine visit.The remaining forty one patient who refused drug therapy considered as a control group.

Result:- The frequency of the painful crisis in our case group after receiving hydroxyurea was mainly more than 13 weeks (40.5%) in P value 0.0001.

The frequency of blood transfusion of cases receiving hydroxyurea was mainly no transfusion (69%) in P value 0.025.

There was no side effect in 79% of cases received hydroxyurea.The remaining 21% of cases had mainly nonspecific side effects.

Conclusion:- In patient with hemoglobinopathies who had frequent painful crisis, Hydroxyurea therapy significantly decreases the frequency of the painful crisis,blood transfusion requirement with few adverse effects.

Introduction:-

The term sickle cell disease is generally used to describe all of the conditions associated with the phenomenon of sickling, whereas the term sickle cell anemia is generally used to describe homozygosity for hemoglobin S (i.e. HbSS).

The disorder is more severe in patients with homozygosity for HbS, of intermediate severity in hemoglobin SC disease (HbSC, combined heterozygosity for hemoglobin S and C), and generally benign in those with sickle cell

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trait (heterozygosity for HbS).(1)

Among patients with sickle cell-beta thalassemia, the disease varies with the quantity of hemoglobin A, often being quite severe in patients with sickle cell-beta (0) thalassemia and less severe in patients with sickle cell-beta (+) thalassemia. There are an estimated 54,736 babies born with HbSC disease each year worldwide.(2)

Acute painful crisis— Episodes of acute pain, previously called sickle cell crisis, are the most common type of vasoocclusive event.(1)

It is characterized as unremitting discomfort that can occur in any part of the body, but most often occurs in the chest, abdomen, or any extremities. These painful episodes are often abrupt and cause disruption of daily life activities and anguish for children and their caregivers.

The exact etiology of pain is unknown, but the pathogenesis are initiated when blood flow is disrupted in the microvasculature by sickled cells, resulting in tissue ischemia. It may be precipitated by physical stress, infection, dehydration, hypoxia, local or systemic acidosis, exposure to cold, and swimming for prolonged periods.(3)

Hydroxyurea is an antimetabolite drug shown in adults with sickle cell disease (SCD) to increase fetal hemoglobin levels and reduce the symptoms of SCD. We hypothesized that hydroxyurea therapy in children with severe (defined as ≥3 vasoocclusive events per year) SCD could improve hematologic parameters and reduce vasoocclusive events.(4)

Hydroxyurea is the only drug proven effective in reducing the frequency of painful episodes.In children with sickle cell anemia, a safety, feasibility trial of hydroxyurea demonstrated that hydroxyurea was safe and well tolerated in children over 5 years of age infant treated with hydroxyurea also experienced fewer episodes of pain, dactylitis and acute chest syndrome, and were less often hospitalized or received a blood transfusion.(3)

However, based on data from a large body of observational cohort studies and small clinical trials, the agent may be considered in the certain groups of NTDT patients that include β-thalassemia intermedia, pulmonary hypertension, alloimmunized patients, extra medullary hematopoietic pseudo tumors, leg ulcers, and patients with the following clinical morbidities.(5)

The mechanisms by which hydroxyurea produces its beneficial effects in patients with sickle cell disease are uncertain. Known pharmacological effects of hydroxyurea that may contribute to its beneficial effects include increasing hemoglobin F levels in red blood cells, decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickle cells and altering the adhesion of RBCS of endothelium.Its metabolism is 60% by liver and gastrointestinal tract. Its half-life is 2-4 hours and it excreted in urine.(6)

The typical starting dose is 15 -20 mg/kg given once daily, with an incremental dosage increase every 8 weeks of 5 mg/kg, and if no toxicities occur, up to a maximum of 35 mg/kg per dose. (3)

The safety measures should be evaluated performing complete blood counts, every 2 weeks for the first three months, then monthly,in addition to hepatic and renal function studies every 2 weeks for first three months then monthly. History and physical examination evaluating for GIT, CNS, dermatological side effects should be evaluated monthly.(5).

Hydroxyurea should be temporarily discontinued and dose adjusted if the absolute neutrophil count falls below 2000/µL or platelets below 80000/µL.(3)

Its side effect includes nausea, vomiting,constipation, diarrhea, mucositis, acute pulmonary reactions, genetic mutation, myelosuppression, secondary leukemia, hyperuricemia and renal failure, dermatological changes (hyperpigmentation)(6),azoospermia ,fertility side effect.(7)

It is contraindicated in cases of severe anemia, bone marrow depression(WBC less than 2500/mm3,plateletsare less than 100000/mm3, pregnancy and lactation. (6)

It can be used in pregnancy only in life-threatening emergencies when no safer drug available. It excreted in breast milk. And should not used in patients with hepatic and renal failure. (5)

It is important to monitor for signs of hydroxyurea toxicity.(8)

Patients and Method:-

An eighty three cases conducted in our case control study were known cases of non-transfusion dependent thalassemia and sickle cell anemia who were treated in a hereditary blood disease center in Karbala teaching hospital for children for blood transfusion and treatment of severe frequent crisis.

The study was done from June 2010 till December 2015, from which; 43 cases were male and 40 were female. The cases included in our study had frequentpainful crisis (three to four attacks per year) or frequent blood transfusion. From these 83 patients, 42 received hydroxyurea in a dose 10 – 20 mg/kg/day as 500mg capsule taken orally after meal. 18 0f them diagnosed as sickle cell anemia,16 patients diagnosed as a sickle thalassemia syndrome and 8 had thalassemia intermedia.The remaining 41 patients who refused drug therapy considered as control and they were as the following: 24 were sickle cell anemia, 13 had sickle thalassemia syndrome and 4 patients had thalassemia intermedia .

Patients on hydroxyurea followed up every 2 weeks in the first 3 months by taking a blood sample (3 ml for each patient) investigated for HB,WBC total and differentials, platelet count (this was measured by Syemex XT -2000 i) and renal function test (measured by Cobas Integra 400 plus). After the first three months of treatment, the patients investigated according to their routine visit, or when they were seeking for medical advices.

From whole study only 5 patients stopped treatment as a result of appearance of side effect of drugs as the following:

- Sickle cell anemic patient stopped treatment because dropping of WBC count to reach 2×10^9/L after 2weeks of starting treatment.
- Sickle thalassemic patient stopped treatment due to complaining from severe vomiting and abdominal pain after 10 days of starting treatment.
- Sickle thalasemic patient stopped treatment due to the appearance of ecchymotic spots as a result of dropping platelet count to reach 25×10^9/Lafter 3 weeks of starting treatment.
- Patient with thalassemia intermedia stopped treatment due to azoospermia after 6 months of treatment.
- Sickle thalassemic patient stopped treatment because of appearance of azosthenia after 14 months of treatment.

Result:-

Forty two(25 male and 17 female) cases were received hydroxyurea.From which 18 sickle cell anemia, 16 sickle thalassemia,8 thalassemia intermedia.Their mean ages were 24.3 years (9-50).The control group were 18 male,23 female.From which 24 sickle cell anemia,13 sickle thalassemia and fourcases were thalassemia intermediaas shown in table 1.

Table.1:-Descriptive analysis of cases and controls according to diagnosis and gender.

	Cases		Control	
	Number	% of total	Number	% of total
Sickle cell	18	22	24	29
Sickle-thalassemia	16	19	13	16
Thalassemia intermedia	8	9	4	5
Male	25	30	18	22
Female	17	20	23	28
Total	42	50.6	41	49.4

The painful crisis in case group before receiving hydroxyurea were mainly 8-12weeks (38.1%) and in control group 4-7 weeks (61%).

After receiving hydroxyurea painful crisis were mainly > 13 weeks (40.5%) in P value 0.0001 as shown in figure 1 and 2.

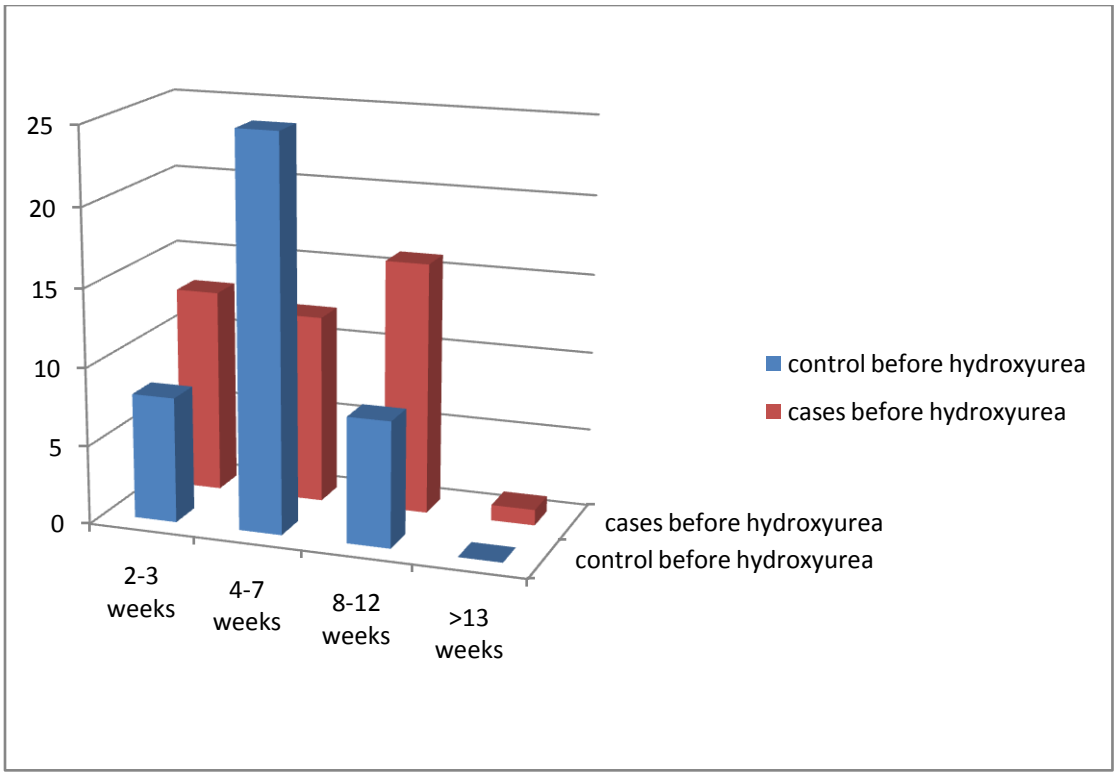

Figure 1:- Frequency of crisis in cases and control groups before hydroxyurea.

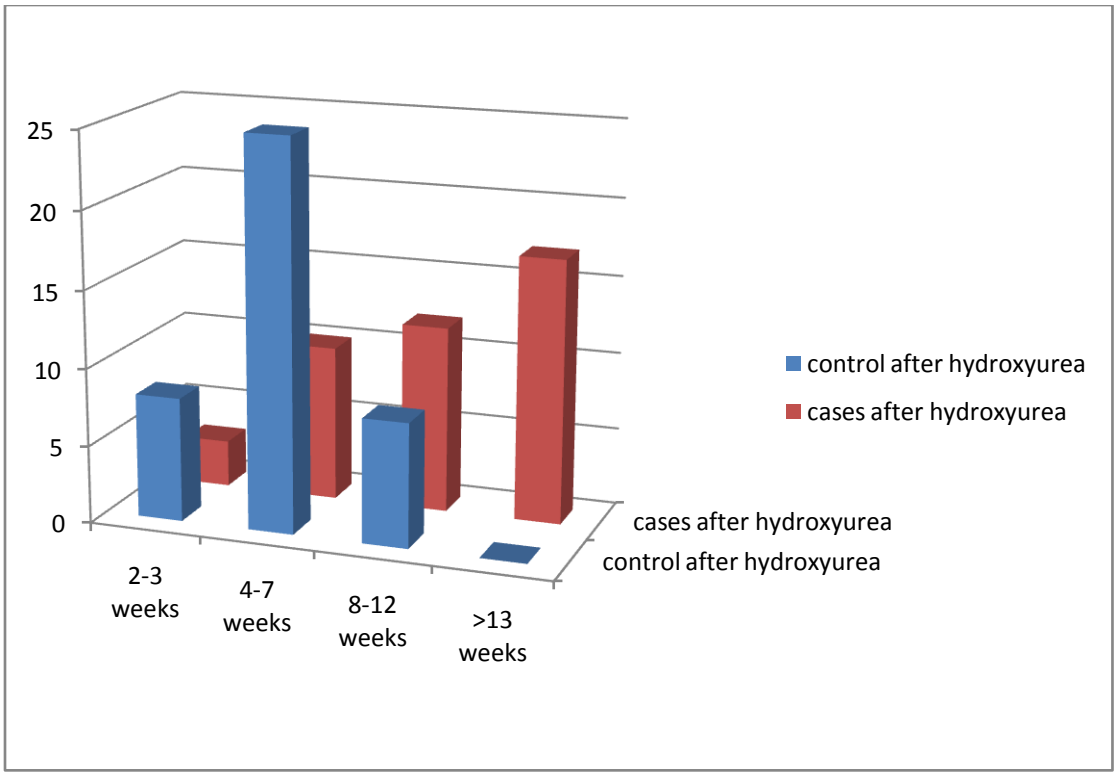

Figure 2:- Frequency of crisis in cases and control groups after hydroxyureaP value 0.0001

The blood transfusion in case group before receiving hydroxyurea were mainly > 13 weeks (33.3%) while in the control group were mainly no transfusion which were 15 (36.6%) in P value 0.145 .

After receiving hydroxyurea were mainly no transfusion which was 29 (69%) in P value 0.025 as shown in figure 3 and 4.

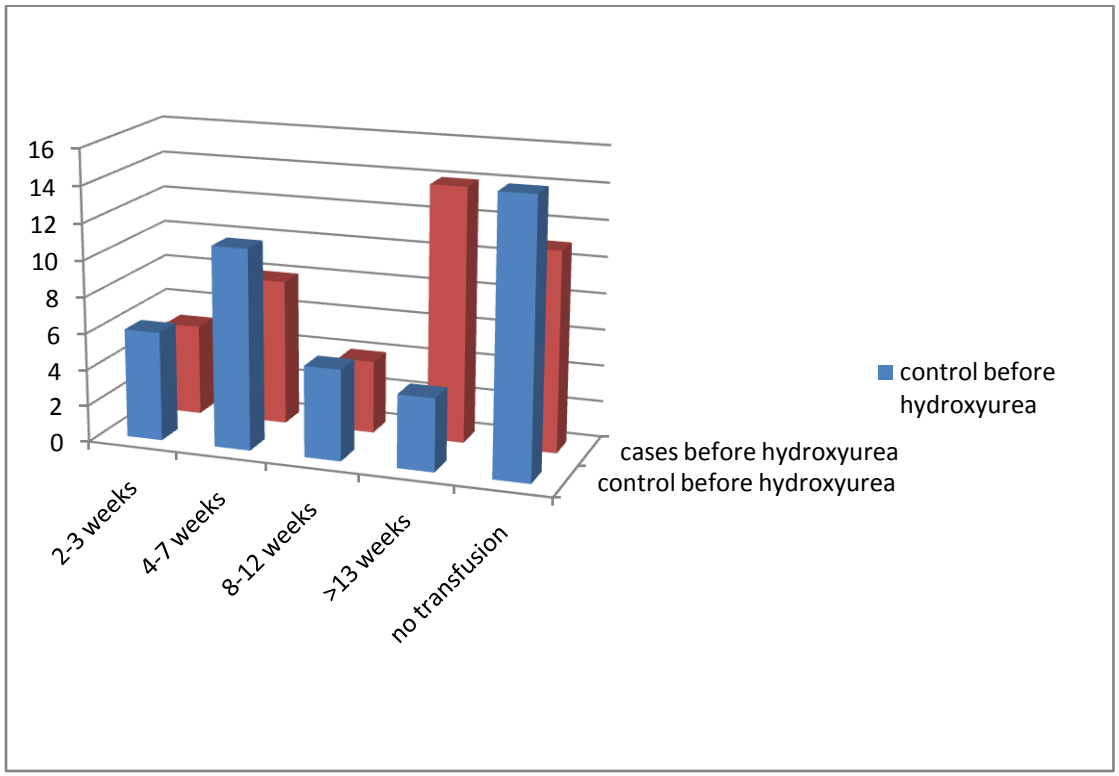

Figure 3:- Frequency of blood transfusions of cases and control groups before hydroxyurea P value 0.14

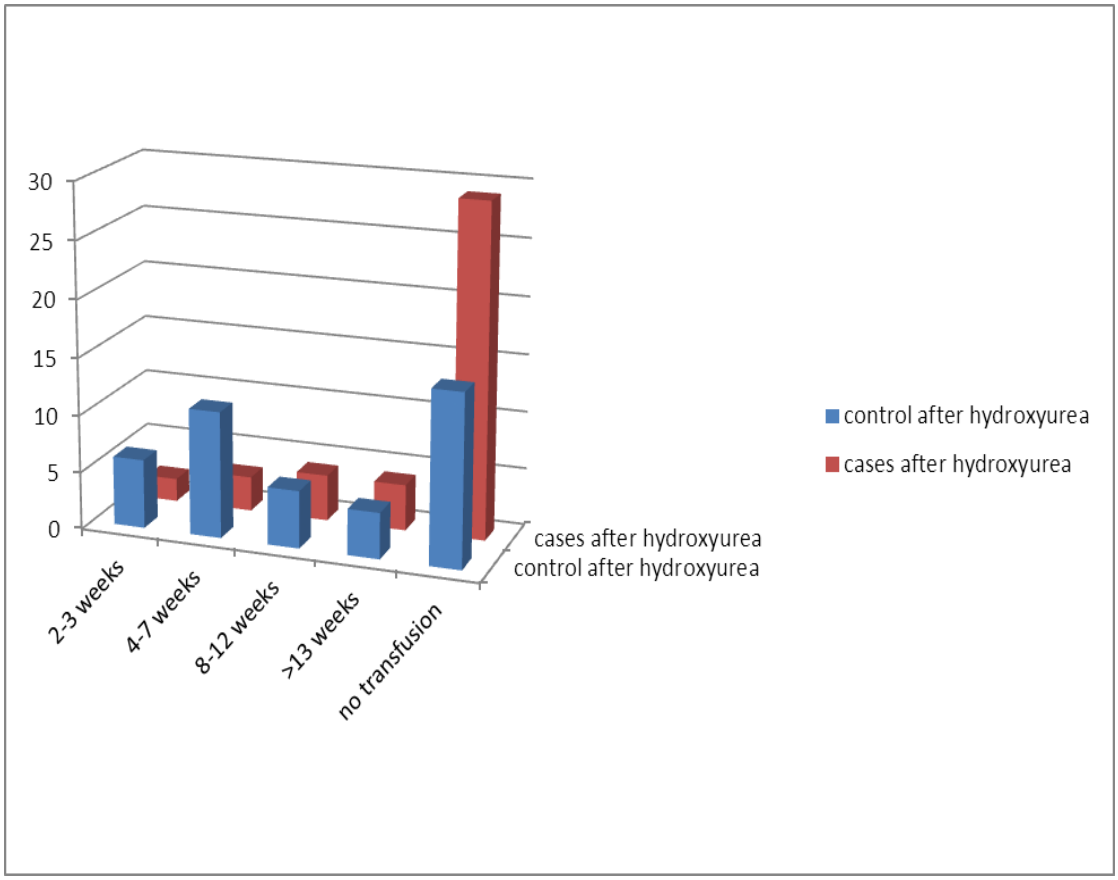

Figure 4:- Frequency of blood transfusions of cases and control groups after hydroxyurea. P value 0.025

Mainly There were no side effects of hydroxyurea in case group (79%),others had nonspecific side effects (nausea ,vomiting or fatigue) in 13% ,the remaining side effects (agranulocytosis, thrombocytopenia, azosthenia and azospermia) were 2% for each one.as shown in figure 5.

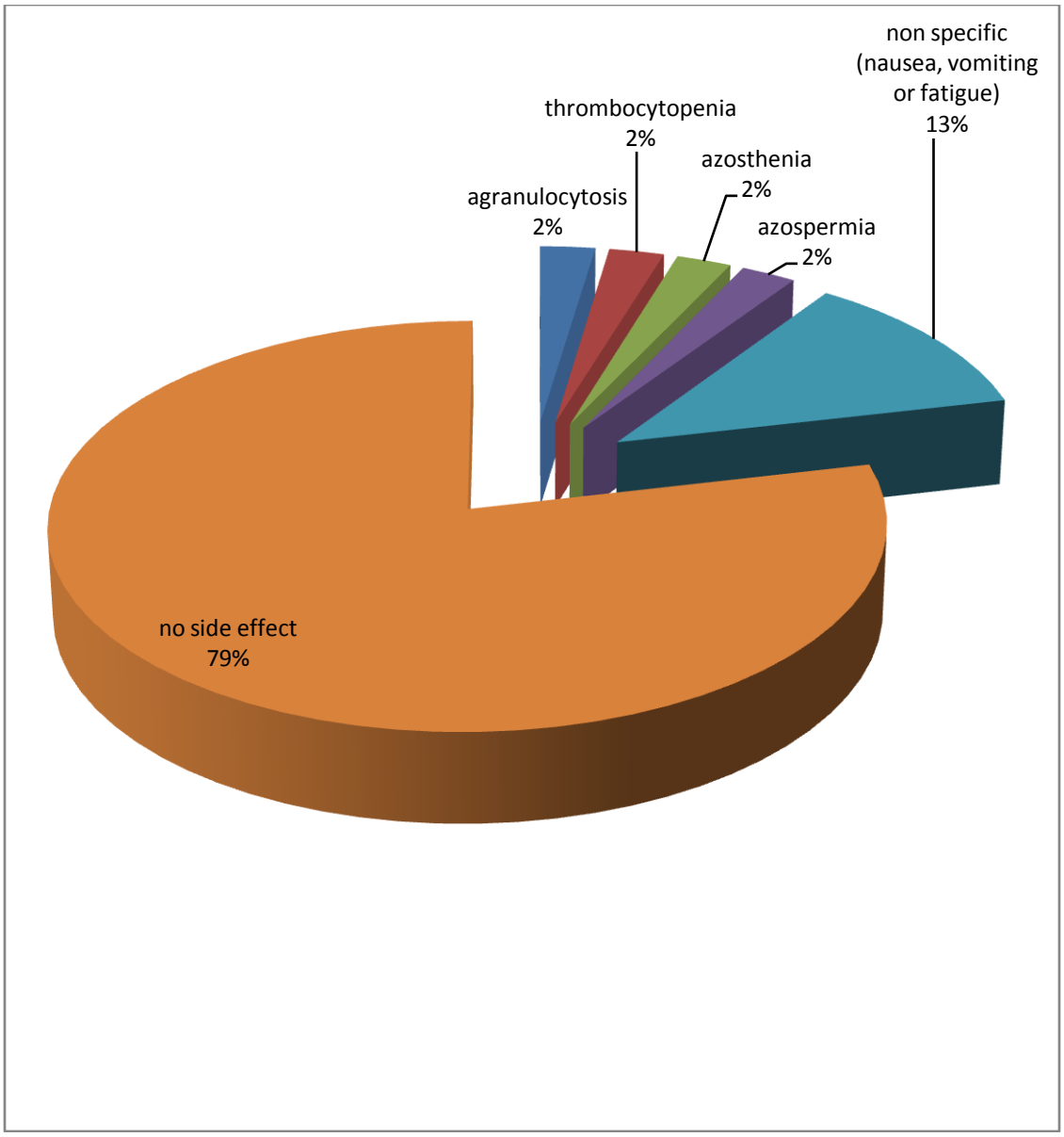

Figure 5:-Percentage of side effects after hydroxyurea therapy.

Discussion:-

The significant decrease in painful crisis syndrome and frequency of blood transfusion in case group in our research goes with that research of JAIN DL (2012)(9) in Indian children with sickle cell disease that show there were significant decrease in no. of vasoocclusive crisis, transfusion requirement, hospitalization with hydroxyurea compared with placebo despite high baseline HbF.

The study of Wang WC in amulticenter randomized controlled trial 2011 show that there were decrease in pain and dactylitis as well as a moderate decrease in acute chest syndrome, hospitalization rate and transfusion(10).

Other studies that went with our result were Sharef SW(2013) (11), Rigano P (2013)(12), Gilmore A (2011) (13), Nzouakou R(2011) (14), Voskandou E (2010) (15), Italia k (2009) (16), Charache S 1995) (17).

Recommendation:-

1. We recommend the use of hydroxyurea in the treatment of patients with sickle cell disease and non-transfusion dependent thalassemia.
2. We recommend further studies in using hydroxyurea in young children with hemoglobinopathies .
3. We recommend further study to confirm that hydroxyurea treatment may cause malignancy.
4. We recommend further study for evaluation of azoospermia and azosthenia whether reversible or not after stopping hydroxyurea therapy.

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