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RESEARCH ARTICLE

THE ROLE OF HU IN THE MANAGEMENT OF VASO-OCCLUSIVE CRISES IN SICKLE CELL ANEMIA.

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Manuscript Info

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Abstract

Background: Sickle Cell Anemia (SCA) is a chronic inherited form of haemolytic anemias. The estimated prevalence of SCA trait carriers in Saudi Arabia is 4.2%. Patients manifest with frequent infections and recurrent Vaso-Occlusive Crisis (VOC). Hydroxy Urea (HU) is used to modulate the severity of SCA phenotype, and for treating painful VOCs.This study aim to explore the perceptions of SCA patients on HU, and other clinical and biomedical manifestations.

Methods: A prospective comparative study, conducted in Jeddah. Patients were classified into two groups; (10) patients in the study group on HU, and (8) others in the control group on other treatments.

Results: The study included (18) patients, (12) females and (6) males, aged between (8-36) years. While the group on HU had slightly lower Hb levels (7.95 ± 1.3 Vs 8.44 ± 1.3), the controls had lower MCV levels. Platelets, Reticulocytes and WBCs were lower for the HU group. Except for Alkaline Phosphatase (ALP), liver function indices were higher for the study group. A significant association was detected between low ALP and using HU. Six patients on HU said: "they felt better after using HU", and felt that "their need for blood transfusions decreased after using HU". Patients noticed a decrease in admissions after using HU, and the average number of admissions was (3) per patient.

Conclusion: Patients on HU experinced some improvement, some stabilty of thier hematologic parameters, and reduced hospitalization. More studies should be conducted to undesrtand the benefits and risks of HU use in SCA patients.

Introduction:-

Sickle Cell Anemia (SCA) is a chronic inherited form of haemolytic anemias. The abnormal form of Haemoglobin (i.e. HbS) polymerize Red Blood Cells (RBCs) into the deformed characteristic sickle shape, leading to functional disturbances and hemolysis. [1-3] SCA is a recognized global burden world-wide. It is particularly common in Sub-Saharan Africa, South and Central America, southeast Asia and the Mediterranean countries. [4-7] The Saudi National Premarital Screening Program estimated the prevalence of sickle cell trait carriers to be (4.2%), with (0.26%) of the screened population already suffering from sickle cell disease, [8-9] with higher rates is some regions. [10] In Saudi Arabia, SCA is more prevalent in the Eastern, Western, and Southwestern provinces.

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SCA is attributed to many serious complications such as strokes, retinopathies, priapism, splenic infarctions, renal and hepatic failures, pulmonary hypertension, and acute chest syndrome. [11-12] Patients usually manifest with chronic haemolysis, frequent infections and recurrent Vaso-Occlusive crisis (VOC). The latter is characterized by severe acute pain in the abdomen and /or extremities, and can result in organ damage as result of progressive vasculopathy and acute infarctions. [13-15]

The treatment of SCA can vary between countries according to the available resources and disease prevalence. Treatment options include rehydration and blood transfusion to correct anemia, vaccinations and prophylactic antibiotics to reduce and prevent infections, as well as pain management to reduce the burden of painful crisis and improve the functioning abilities of patients. [16-18] Hydroxy Urea (HU) is a urea analogue which inhibits DNA synthesis in the S-phase of cell cycle. [19] It is used to modulate the severity of SCA phenotype, and for the treatment of painful crisis. The benefits of HU in sickle cell disease were evaluated in a number of studies, some of which facilitate the wider use of HU, and others highlighted some of its adverse effects. [20-25]

Although the condition is widely prevalent in Saudi Arabia, research around SCA management and the use of HU remains limited. In this study, we explore the perception of SCA patients admitted with VOC on the use of HU, and any accompanying clinical or biomedical changes.

Materials and Methods:-

This prospective comparative study was conducted at King Abdulaziz University Hospital (KAUH)in Jeddah, in the western region of Saudi Arabia. Ethical approval was obtained from the Ethical and Technical Committee at KAUH, along with all other administrative approvals. We recruited patients over a one year period, starting June 2011 to May 2012, and targeted known SCA patients who were admitted to KAUH for the management of VOC. Prior to participation in this study, informed consent was obtained from adult patients, and from the guardians when children were involved.

Patient Charachteristics:-

The study's population consisted of SCA patients admitted suffering from an acute VOC. As per the diagnostic protocol followed by Department of Haematology at KAUH, patients in VOC are those experiencing an episode of acute pain in the abdomen and/or extremities, with other signs of increased or exacerbated hemolysis. In order to assess patients' condition, including disease phenotype and severity, the following investigations are requested at the time of admission; Complete Blood Count (CBC), Blood Film (BF), Haemoglobin Electrophoresis (HbE), Sickle Solubility test, Liver Function Tests (LFTs) including serum bilirubin, and Renal Function Test (RFTs) namely serum creatinine. Patients were invited to participate in the study irrespective of their age, gender, previous history or current treatment regimen. The latter is often decided by the attending hematologist after discussing treatment options with the patient.

Eighteen patients were recruited, and all were known to carry the Hb (SS) phenotype. According to the treatment used patients were classified into two groups; a study group and a control group. The study group included (10) patients, all were on an escalating dose of HU starting at 10 mg/kg/dose, and up to 35 mg/kg/dose. The remaining (8) patients were enrolled in the control group, and were prescribed other treatments.

Data collection:-

In order to use the most appropriate tool, a literature search was undertaken in the search of relevant questionnaires. We've considered studies focusing on: (a) the prevalence of HU use in a country or region; (b) the indications, age group, dosing and regimen, route of drug administration, maximum tolerated dose, minimum effective dose and (c) monitoring for efficacy and side effects. We compared these tools against each other, and to our study's objectives. We developed a questionnaire that was tested and validated prior to data collection. The questionnaire was designed to collect the following information: date of birth, nationality, number of VOCs, hospital admissions and blood transfusions, and for those on HU, their perceptions on their appreciated health, their compliance, and any side effects (including: drowsiness, nausea, vomiting and diarrhea, constipation, mucositis, anorexia, stomatitis, bone marrow toxicity and/or infections.

Management protocol:-

Patients in the study group were prescribed HU, while the control group where on different medications including paracetamol , bruffin and folic acid as well. Prior to commencing treatment, patients were oriented on the adverse

effects of HU and its monitoring protocol. All female patients within reproductive age were advised against pregnancy, and were strongly advised to use suitable contraceptives during the trial period. All male subjects were counselled regarding the effects of HU on spermatogenesis, and when feasible sperm cryopreservation was recommended before commencing the HU treatment. All patients received the recommended vaccines, including Haemophilus Influenza, Neisseria meningitis, Hepatitis B and influenza, and were on penicillin prophylaxis.

For the study group: all (10) patients were started initially on an oral, daily, (10) mg/kg dose of HU. This dose was increased at a rate of (5) mg/kg/week, as long as the hematologic indices remained within acceptable range, and given that the patient showed no evidence of adverse effects. The maximum dose of HU reached per patient was between (25) to (35) mg/kg/day. All patients remained on HU for six to nine months, and was only discontinued when adverse events were reported, the latter included symptoms such as hair loss, gastrointestinal upset and rash, or disturbance of their blood indices; Hb drop to (6) g/dl, platelet count <80,000 or a neutrophil count <2,500.
Regarding monitoring, patients' hematological profile including Hb, Fetal Hemoglobin (HbF), MCV levels, neutrophil and platelet counts were measured every two weeks in the first month, and then once per month until the end of the study period. Moreover, features of organ damage were monitored by assessing several parameters, including but not limited to: LFTs (liver damage); creatinine levels (chronic renal failure); pitted red cells (spleen damage); transfer factor (chronic sickle lung disease); intelligence quotient (IQ) and changes in neuro-psychometric tests (neurological damage), Priapism, leg ulcers and any other appreciated toxicity or adverse effects.

Statistical analysis:-
Data were analyzed using a standard IBM Statistical Package for Social Sciences (SPSS) version 19.0; SPSS, Inc., Chicago S. Descriptive analysis was used to summarize patient characteristics in frequencies and percentages for categorical variables, while continuous variables were presented by means and standard deviations (SD). The student *t-test* was used to compare statistical differences between the two group. A p value below (P<0.05) was considered statically significant.

Results:-

The study included (18) diagnosed SCA patients, (12) females and (6) males. Their ages ranged between (8 – 36) years, and with a mean age of (29) years. Patients were randomly assigned into two groups, a study group including (10) patients, and the remaining (8) were enrolled in the control group. The following parameters were measured and compared for the two groups:

Hematological Profile:-
Regarding their hematological profile, those on HU reported slightly lower Hb levels when compared to the controls (7.95 ± 1.3 Vs 8.44 ± 1.3), yet they had higher MCV levels (88.25 ± 14.3 Vs 78.78 ± 12.77). **(Table 1)** Platelets, Reticulocytes and WBCs were all lower for the study group. A significate difference was detected between the two groups, suggesting an association between being on HU and having lower hematological indices. (P<0.001) **(Table 1)**

Measures of organ damage:-
Except for Alkaline Phosphatase (ALP) levels, all other liver function indices, including total protein, albumin, serum bilirubin and other enzymes' levels, were found higher for the study group. **(Table 2)** When tested, no significant difference was detected. However, a significant association was found between low ALP and using HU. Serum creatinine levels were (41.79 ± 11.37) for SCA patients on HU, and (35.75 ± 9.37) in the SCA patients not taking HU. Elevated serum creatinine levels was strongly associated with the use of HU. (P<0.001). **(Table 2)**
All other monitored parameters showed no differences between the two groups.

Self-assessment of HU use:-
We investigated in depth patients' perceptions on HU, and asked the study group to self-assess their management. Regarding compliance, Patients were asked to describe their use of HU, exactly as prescribed by their attending hematologist. We asked them to choose between "seldom", "sometimes" and a "regular" use. A majority of (6) patients (60%) reported regular use, while (2) described their use to be "sometimes" and the last (2) as "seldom". In order to assess the effects of HU, Patients were also asked to describe how they felt after using HU. Again 6 (60%) of patients who took HU said that: "they did feel better after using HU", while the other (4) patients (40%) said "they did not". **(Figure 1.A)** This was again reflected when patients were asked to estimate their need for blood transfusions while using UH. They chose between "much less need", "less need", "the same need" or "the need for

more transfusions", and (60%) of patients expressed that their need for blood transfusions has improved, and became less after using HU. **(Figure 1.B)**

We recorded the number of admissions for major care of each patient during the last six months. All patients acknowledged to notice a decrease in the number of admissions, specifically in the number of VOC they had experienced while being on HU. In fact, out of the total patients in the study group, (4) were never admitted during the study period. The remaining (6) were admitted for different reasons, with an average of (3) admissions/patient. Only few patients reported scattered side effects including minimal bleeding, hair loss, and gastrointestinal symptoms.

Discussion:-

This prospective study aimed to assess the usefulness of HU in the management of SCA patients, along with patients' perceptions on HU. One limitation that should be acknowledged is the few number of patients recruited during the short study period. As HU is widely known among our community as an anti-cancerous agent, used solely by cancer patients, many patients refused to join this study. Moreover, within the recruited group some patients were noncompliant to HU dose, after appreciating some unwanted side effects, and this might have affected their perceptions on HU.

Comparing the two groups above, most patients on HU admitted to feel better after using it, yet some of their hematological indices were slightly lower than the controls. Although Hb levels were lower in the group using HU, their MCV levels were higher, all the remaining parameters were decreased and the latter was found associated with the HU treatment. These results correspond to reports from other international groups, one example is a clinical trial in Belgium among pediatric SCA patients. [26] In the latter study, those on HU also had higher MCV levels and lower reticulocytes and WBCs counts. [26] Similar results were also reported from the HUSOFT trail among infants, in order to explore HU toxicity. [23] Unlike our group, infants on HU showed increased levels of Hb, Fetal hemoglobin, but again being on HU was found associated with decreased reticulocytes, WBCs, and platelets counts. [23]

Regarding measures of organ damage, elevated serum creatinine was associated with the use of HU in our sample, yet the effects of HU on renal function remains controversial as reported by other studies.[24] On the other hand, proteins levels and liver enzymes were found slightly higher in the study group, but we did not find any significant difference between the two groups, and accordingly we could not attribute these changes to HU. Despite the latter, decreased ALP levels were found associated with the use of HU, and since several globally working guidelines recognize ALP as the prime marker to increase during sickle cell crises, [27] it is rational to assume that ALP decreased levels in our study group can indicate a decrease in VOCs experienced by these patinets.

The latter was further augmented when we questioned patients about their admissions for major care. Four patients were never admitted during the study period, and the rest had an average number of (3) admissions per patient, the latter was considered an improvement by the patients themselves. These matched findings of other studies. The number of admissions was significantly reduced in patients using HU in the Belgian study, [26] the "BABY HUG" trail, [24,28] and in a nine-year follow up study. In fact, the latter concluded that their patients on HU were of less morbidity and mortality because of elevated HbF levels and less frequent VOCs. [29] Clinical improvements associated with HU were also related to the decreased need for blood transfusions. Most patients described their need for blood transfusions to be "less", and although blood transfusion remains superior to the use of HU in SCA management, more local studies must be conducted to weigh HU use in the management of SCA patients against the other measures.

Despite the self-appreciated improvements among our study group, adverse events were still reported during this relatively short study period, and this highlighted the importance of monitoring patients while on HU. There is a limited number of studies which focused specifically on HU use in Saudi Arabia, studying both its benefits and risks. There is also an apparent abscane of updated local guidelines governing the use of this drug among SCA patients. More context-based, age-disggraeated studies are needed to asnwer semiliar questions, inform polices and regulate the use of HU.

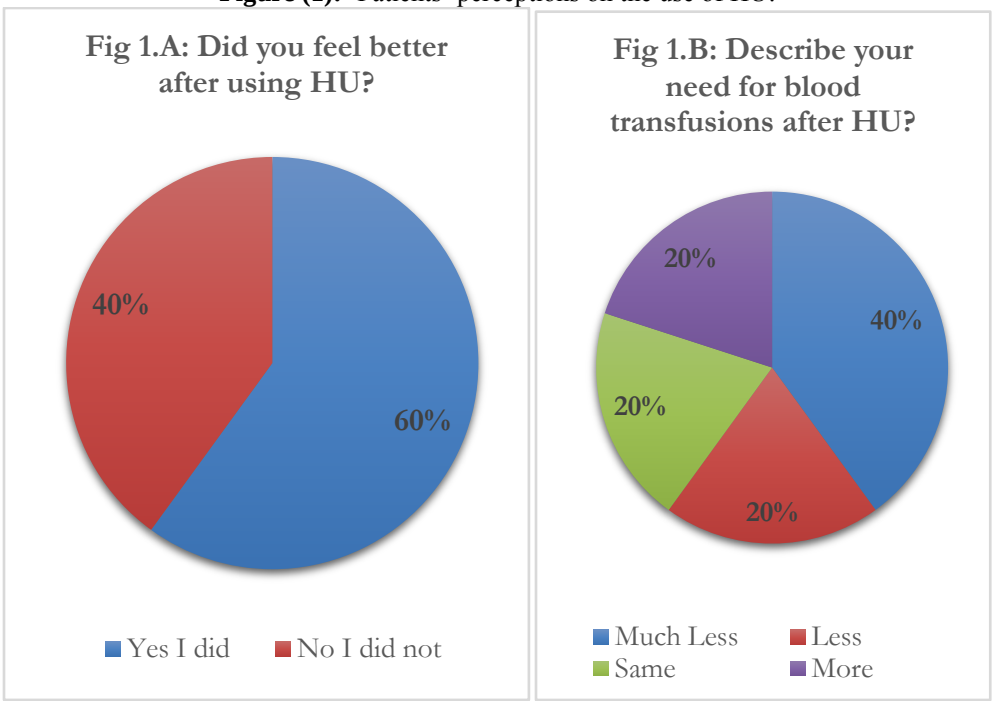
Table (1):- Hematological profile of patients

Characteristics	Study Group (on HU)	Control Group	P-Value
Hb (g/dL)	7.95 ± 1.3	8.44 ± 1.3	0.018
MCV	88.25 ± 14.3	78.78 ± 12.77	<0.001
Platelet	407 ± 155	478.34 ± 177	<0.001
Reticulocytes	0.21 ± 0.75	0.22 ± .110	---
WBC	12.20 ± 3.861	18.15 ± 8.799	<0.001

Table (2):- Measures of Organ Damage

Parameter	Study Group (on HU)	Control Group	P-Value
Total Protein	78.17 ± 5.661	75.08 ± 6.803	---
Serum Albumin	37.41 ± 3.51	35.80 ± 7.72	---
Bilirubin	51.59 ± 52.49	44.34 ± 31.62	---
ALT	57.70 ± 35.90	48.03 ± 23.00	---
ALP	121.36 ± 52.15	204.56 ±24.88	<0.001
AST	53.61 ± 26.51	49.48± 21.94	---
Gamma-GGT (GGT)	55.75 ± 32.850	53.71 ± 45.627	---
Serum Creatinine	41.79± 11.37	35.74 ± 9.37	<0.001

Figure (1):- Patients' perceptions on the use of HU:



Conclusion:-

HU use in SCA cases presenting with VOC was associated with appreciated improvement, stabilty of hematologic parameters, and reduced hospitalization. More studies should be conducted to undesrtand the benefits and risks of HU use among local SCA patinets.

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