JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

A Brief Review on the Management Options Available for Sickle Cell Anemia

Chirag Desai[1], Janam Desai[2], Sanket Desai[2], Rana Kajal[2]

1. Research Scholar, JJTU, Jhunjhunu, Rajasthan.

2. Student: Smt.BNB. Swaminarayan Pharmacy College, Salvav

ABSTRACT:

Sickle cell anemia is an autosomal recessive disorder with which every year 300000 children are born. Because of reduced life of red blood corpuscular the devastating and life threatening clinical sign and symptoms of this disorder the management is major health concern. The current challenge is to improve the prospects of quality of life of the patients with low toxicity and safer and easy to administer therapy as it relatively affect tribal population belongs to lower economical class and spare of education and healthcare facilities. The understanding of pathology helps in designing newer treatment approaches like Fetal hemoglobin augmentation, red cell rehydration, anti-oxidant therapy, acting on adhesion pathway, transfusion and transplantation therapy, and gene therapy have been discussed in this review. The purpose of this review is to spark the light on awareness amongst the healthcare professionals and initiate the research work in the herbal field which might be the safest option for the maintain the quality of life of sickle cell patients.

Keywords: sickle cell anemia, quality of life, gene therapy, transfusion, red cell rehydration

Article history:
Received 01 March 2015
Accepted 24 March 2015
Available online 01 April 2015

Citation: Desai C, Desai J, Desai S, Kajal K. A brief review on the management options available for sickle cell anemia**J Pharm Sci Bioscientific Res**. 2015 5(2):230-238

For Correspondence:

Mr. Chirag Desai

Research scholar, JJT University, Jhunjhunu, Rajasthan, India

Email: cddon007@gmail.com

Special Awareness Issue
(www.jpsbr.org)

INTRODUCTION:

Sickle cell anemia is an autosomal recessive disorder which affects almost 5% of world population. It is most commonly pronounced in poor countries located in subtropical regions, in India most commonly the tribal areas are mostly suffered from this condition. Clinical features of this conditions are common like fever, cough, abdominal pain, pallor, dizziness, giddiness, weakness, fatigue can be devastating if remain undiagnosed or untreated. Pain-full crisis are characteristics observation in patients of sickle cell anemia. As far as management is concern because of inadequate diagnosis and available treatment it is the major health concern. As it is autosomal recessive type any drug designed by keeping the points in mind that it would have to be tolerated throughout the life by the patients with low toxicity and easy availability and affordability. As we know treatment of sickle cell anemia is still evolving like some of its advances in management in this review we discussed the recent management advances and its pros and cons.

Patient education and Counseling for newborn screening: Newborn screening program activities are mechanisms by which public health has control to reduce morbidity and mortality and improve the well-being of people with Sickle cell anemia. The new born screening and detection of health problems, implementing policies and to deal with these promoting partnerships and coordination among various entities, informing and educating the public and linking people to health services might be the good option especially when dealing with hemoglobin disorder. These activities are consistent with the essential services of public health.

However, more work and efforts needs to be done in this department because it will be more economical and more fruitful. Currently, there are no standardized new born screening follow-up guidelines for sickle cell anemia.[1-6]

Surveillence and monitoring of sickle cell anemia patients:

Epidemiological information like incidence & the prevalence of disease, various risk factors, and health impact helps in developing and strengthening strategies for reducing morbidity and mortality from sickle cell anemia. Population-based disease surveillance activities and disease registries are also needed. Surveillance information is needed for the development and implementation of programs and strategies for reducing morbidity and mortality, such as through appropriate follow-up, proper referral, and delivery of services. Public health activities need to be implemented at state and local levels for continued collection, assessment, and use of information related to sickle cell anemia occurrence. Due to entire focus on research and development the attention on surveillance and monitoring on sickle cell patients by health care team is not up to the mark as it needs to be.

Hydroxyurea: A Fetal Hemoglobin Inducer:

Fetal hemoglobin interferes with the polymerization of deoxygenated sickle hemoglobin in vitro. Based on all these studies, it was anticipated that pharmacological induction of fetal hemoglobin production may be an effective therapeutic strategy for ameliorating the severity of sickle cell anemia. DNA methylation and histone acetylation played important roles in the developmental regulation of globin gene expression.[9] So, it was proposed that pharmacological agents that alter the epigenetic configuration of the γ-globin genes may provide a viable therapeutic approach to the induction of fetal hemoglobin level. Hydroxyurea, an S-phase–specific chemotherapeutic agent which does not inhibit DNA methyl-transferase enzyme, but generally it is an inhibitor of ribonucleotide reductase enzyme that had been in use for many years in the treatment of myelo-proliferative disorders. The main advantage is it's an orally available drug which is relatively well tolerated. It was originally proposed that hydroxyurea may elevate level of fetal hemoglobin by accelerating erythroid differentiation in the bone marrow, leading to the appearance of "fetal-like" cells in the peripheral blood.[10] But more recent studies have shown that hydroxyurea generates nitric oxide in vivo, which results in the activation of the signaling pathway and the up-regulation of γ-globin gene expression in patients with sickle cell anemia.[11] Anticancer agent hydroxyurea also has other effects that may also benefit patients like it decrease the adhesion of sickle cells to endothelium and also decrease the expression of soluble vacular cell adhesion molecule level.[11-12]

Due to its bone marrow suppression effect, hydroxyurea reduces the circulating white blood cell counts and likely the number of adherent leukocytes recruited to the wall of small vessels. The decreases in white blood cells were correlated with the clinical benefit from hydroxyurea.[13] But it is still not completely clear how much of the clinical benefit from hydroxyurea could be attributed to its effect on fetal hemoglobin levels compared with its other activities. However, it has been reported that hydroxyurea has mixed effects on erythroid precursors, depending ongenotypic variation14 and all patients do not respond equally well to hydroxyurea so it require time being monitoring by physicians through checking changes in blood parameters.

One possible mechanism of hydroxyurea toxicity is the reduction of intracellular dNTP pools resulting from the inhibition of RR, which impairs DNA repair mechanisms due

to the lack of nucleotides for DNA polymerase. Therefore, DNA instability potentially accumulates and leads to carcinogenesis, mainly by leukemic transformation. Cancer and leukemia have been reported in patients of sickle cell anemia treated with hydroxyurea, but still the incidence is higher than in the general population which is still not known.[15-17] That's why to induce maximal Fetal hemoglobin with hydroxyurea treatment, dose escalation to the maximum tolerated dose is required. As a result, there are risks of infection and bleeding relating to drug induced cytopenia as well as concerns relating to the potential side-effects of the drug. [15-17]

Hydroxyurea therapy might be start with initial dose of 15mg/kg/d and increased up to 20-30mg/kg/d by 6-8 weeks. The optimum dose will be determined on the hematological toxicity and level of fetal hemoglobin. Increase value of mean corpuscular volume parallel to the increase in fetal hemoglobin. This makes mean corpuscular volume as a useful marker for fetal hemoglobin. [15-17]

Hydroxyurea therapy fails in 20% patients might be due to abnormal marrow function, genetic factors or metabolism of drug. Mutagenic agent hydroxyurea must be used carefully and with full appreciation of its toxicity and possible long-term adverse effects in patients. As we know it is carcinogenic drug. Sickle cell is not a malignant disease and hence needs to be cautious in using anti-cancer drug. Various trials suggest it is a harmless drug at least for short period. [15-17]

Although the bone marrow suppression effects are readily reversible one has to still do the frequent blood counts to prevent serious myelotoxicity which might have an undesired impact on quality of life in sickle cell anemia patients. Hydroxyurea known to cause ankle ulcers and patients with sickle cell anemia often develop leg ulcers so pharmacological use in that cases are still not cleared yet. Hydroxyurea is still not the final choice in field of pharmacology for sickle cell anemia but might be the beginning to think over the impact of drug on balancing the hemoglobin level. [15-17]

Management of pain: Acute pain observed in case of acute chest syndrome, cholecystitis, hand-foot syndrome, priapism, right upper quadrant syndrome, splenic sequestration crisis while chronic pain syndrome observed in case of arthritis, arthropathy, aseptic (avascular) necrosis, leg ulcers, and vertebral body collapse.

Over-the-counter medicines like the analgesics such as non-steroidal anti-inflammatory drugs for example acetaminophen, ibuprofen, as well as central analgesics opioids for example drugs like codeine, morphine, are used to control sickle cell pain. Non steroidal anti-inflammatory drugs are prostaglandin-synthesis inhibitors, prescribed for the management of mild to moderate pain. Non steroidal drugs can be used in conjunction with opioid class drugs to reduce the dose of opoid class which may provide additional analgesia too. The opoids may be slight sedative in nature but it may provide rest which may be beneficial in most cases. These non steroidal anti-inflammatory drugs prevent the conversion of arachidonic acid to prostaglandins by interfering with the function of the enzyme cyclo-oxygenase.

Acetaminophen is another popular drug use for the treatment of sickle cell disease. But it is not benign as acetaminophen has ceiling doses above which escalation does not result in increased relief. Acetaminophen may be toxic when liver disease is present. Non steroidal anti-inflammatory drugs are contraindicated in patients with peptic ulcer, coagulopathies and renal failure. All non steroidal anti-inflammatory drugs are associated with renal failure when used on a long-term basis and that's why patients must be informed not to exceed safe doses of these medications. Opioids are a popular analgesic used for the treatment of moderate and severe acute pain due to pain episodes. When opioids are given for the first time for severe pain, usually morphine sulfate or hydromorphone should be used for hydration. [18-20]

Transfusion: Red blood cells for transfusion in sickle cell anemia can be given as a simple additive transfusion, in which case it is generally inadvisable to take the total hemoglobin above 10 g/d1 because of the risks relating to blood viscosity. Indeed, in most cases transfusion to raise the hemoglobin to that particular patient's stable state level (generally 6-10 g/dl) is usually sufficient.[21-23] In patients with sickle cell anemia, the viscosity of red blood cell suspension at full oxygenation is already higher than that of adult hemoglobin, red blood cell suspension, and the viscosity of the sickle red blood cell suspension rises progressively with deoxygenation, a feature which is evident well before morphological sickling can be demonstrated.[22-23] Relating to

the complications of transfusion in sickle cell anemia, it is essential that a clinician considers carefully four main areas before embarking on any transfusion. In sickle cell complications like acute chest syndrome, stroke, splenic sequestration crisis, cerebro-vascular accident, cardiovascular complications, leg ulcer, priapism, multi-organ failure due to sickle cell anemia where transfusion is the treatment of choice so before considering it clinicians must consider the four main areas as the prime objective of transfusion[21]

1. To improve oxygen carrying capacity, to remove sickle cells, diluting those remaining and improving blood viscosity and flow, to increase the hematocrit, decreasing erythropoietic drive and as a result minimize or prevent autologous erythrocyte production.

2. The potential adverse consequences.

3. The evidence of efficacy for transfusion in the particular clinical situation.

4. Alternative therapeutic options.

Top-up, or additive, transfusions are required when a sickle cell anemia patient drops their hemoglobin sufficient to give rise to, or risk, clinical compromise such as congestive cardiac failure and hypovolaemic shock. Exchange transfusion has been shown to be lifesaving in severe cases, like cerebro-vascular accident, acute coronary syndrome.[21, 24-26] Hyper transfusion therapy is generally used to prevent continued end organ failure related to sickle cell anemia or its symptoms.[21] It has a proven place in the management of central nervous system disease in sickle cell anemia and is probably useful to prevent progression of early to moderate chronic sickle lung disease. When a patient with sickle cell anemia receives a simple blood transfusion, the increase in hematocrit with a constant sickle crit leads to an increase in viscosity and thus limiting the improvement of oxygen delivery, in spite of the improved oxygen carrying capacity.[22-23] It appears that a Sct of ≥25% causes a disproportionate

increase in whole-blood viscosity related to increasing hematocrit, as compared with adult hemoglobin patients.[27-28]

It is probably the combination of increased blood viscosity with decreased efficiency of oxygen delivery to the tissues that causes the sickle complications that have been reported to occur during, or soon after, transfusion for acute complications as well as after the cessation of hyper transfusion. These complications are, generally, either painful vaso-occlusive crises[6] or It is probably the combination of increased blood viscosity with decreased efficiency of oxygen delivery to the tissues that causes the sickle complications that have been reported to occur during, or soon after, transfusion for acute complications as well as after the cessation of hyper transfusion. These complications are, generally, either painful vaso-occlusive crises[6] or neurological events, well as, possibly, the hypertension, convulsion, and cerebral hemorrhages syndrome.[29-32]

Immunological effects: The respective ethnic origins of the sickle cell anemia patient population and the blood donor population are important because, in most of the developed world where transfusion is freely available, these two groups are, predominantly, of different racial origins. As a result of it the risks of allo-immunization are high. The development of antibodies appears directly related to the number of transfusions. Blood transfusion in sickle cell disease and the frequency continues to increases as the number of transfusions also increases. Generally two-third of the antibodies was within the Rh or Kell system. Up to one third of antibodies to red blood cell antigens in sickle cell anemia are transitory and, therefore, may not be detected on pre-transfusion testing, so that there is a risk of development of delayed hemolytic transfusion reactions, which can mimic the clinical complications of sickle cell anemia, including painful crisis and hepatic sequestration. The risk of alloimmunization to red-cell antigens can be minimized by the implementation of careful and conservative red blood cell transfusion guidelines for sickle cell anemia.[33-36]

Bone marrow transplantation: World-wide over 100 child with sickle cell anemia have been treated with bone marrow transplantation mainly indicated in acute chest syndrome, stroke, vaso-occlusive crisis with overall survival rate of 90-95% and 10-15% graft rejection rate.[37] It is estimated that only 10% of children with sickle cell anemia have fulfill the criteria for bone marrow transplantation of whom only about 1 in 5 will have a match of same human leukocyte antigen siblings. Bone marrow transplantation was overlooked as a possible treatment approach for sickle cell disease is not at all surprising. It's a serious procedure entails substantial risk to the patient. Prior to transplant it, patient must undergo a chemotherapeutic regimen to destroy their own bone marrow and immune system. Before transplantation and during immune suppression some patients do not survive the chemotherapy.[37] Others suffer from life-threatening infection before their bone-marrow and immune system are sufficiently regenerated. Some bone marrow transplant does not work. Still others seen to work initially but then fail because the the immune cells produced by the transplanted marrow attack the tissues and organs of the patients (graft versus host defenses) or because the patient succumbs to other complications, such as hemorrhage. Sibling allogeneic bone marrow transplantation is curative and is important to consider and discuss with all parents. Important drawbacks include:[37]

1. The need for a human leukocyte antigen-matched sibling

2. The high probability of sterility after the procedure on account of the toxic conditioning regimes currently used

3. The small risk of treatment associated mortality (about 5%) and of long-term morbidity from chronic graft versus host disease. Even if a donor is available, the decision to go for Bone Marrow Transplantation is not an easy one. Disease severity in the long-term is very difficult to forecast and bone marrow transplantation might be an unnecessarily hazardous therapy for mildly affected patients (25%). [37] Till date great studies have been made in conservative management of sickle cell anemia. However, the medical and psychological cost of supporting patients with this disease is enormous and spans a lifetime. The hematopoietic stem cell transplantation can abrogate sickle cell anemia manifestation and is the best option for cure today but this treatment modality is underutilized as less than 500 transplants were reported in the centre for international blood and marrow transplant research because of the significant risk of morbidity and mortality.[38] Bone marrow transplantation is an experimental approach limited to patients below 16 years of age and who exhibit sickle cell complications, such as a stroke, acute chest syndrome and refractory pain. Studies show that only 1% of patients with sickle cell anemia actually meet the set requirements for bone marrow transplantation.[16]

Gene therapy: Gene therapy is the relatively new idea of inserting genes into the cells of an individual's tissues and cells in order to treat a hereditary disease, such as sickle cell anemia, in which a defective mutant allele is replaced with a functional one. In current treatment options gene therapy would be the best cure for sickle cell anemia, but work in this method of treatment is still very new. [37]

What It Involves: Two methods of gene therapy are being explored.

1) Correction of Gene
2) Turning Off Gene

Correction of Gene: Scientists are looking at whether correcting the defective gene in sickle cell anemia and inserting it into the bone marrow of people with sickle cell anemia will result in the production of normal adult hemoglobin.[37]

Turning off Gene: few other scientists were looking at the possibility of turning off the defective gene and on the other hand reactivating another gene to lift up the production of fetal hemoglobin level. The cost of gene therapy is very high at this point in time. However, Gene therapy will probably be cheaper in the long run since it is a onetime only procedure and it will eliminate the cause of suffering from the individual.[37]

and it will eliminate the cause of suffering from the individual.[37]

Folic Acid Supplements: - Folic acid supplementation compensate for the increased red blood cell production. Folate supplementation safely reduces elevated homocysteine levels and thereby appears to ameliorate endothelial dysfunction. Even though folate supplementation seems to have no effect on the occurrence of clinical vaso-occlusion, the accumulating detrimental effects of homocysteine on the endothelium could easily be avoided.

Propphylactic Antibiotic Treatments

The most important intervention in the routine management of children with sickle cell anemia is Penicillin prophylaxis to prevent pneumococcal infection[37], which justifies the importance of newborn screening. This broad spectrum drug penicillin is given twice daily from as early as 2 months of age, this treatment was supported by the hallmark penicillin prophylaxis studies of the 1980s.[37] Than it was recommended that children with sickle cell disease be given penicillin VK: 125 mg by mouth twice daily for those under 3 years of age and 250 mg twice a day for those 3 years and older. Penicillin may be given as a liquid dosage form or tablet; but finely crushed pills may be given to young children. Tablets and pills have an important advantage because they are stable for years as compared to liquid forms of penicillin that must be discarded after 2 weeks. A study in children older than 5 years of age and found no clinical benefit of penicillin prophylaxis compared with placebo treatment indicating that treatment may be stopped at that age.[37] Patients on penicillin had no increased infections with penicillin-resistant organisms or other adverse effects into them. Since splenic function is still absent in patients with sickle cell anemia older than 5 years of age, that's why parents should be given the option to continue penicillin if desired. For patients allergic to penicillin, the other option erythromycin ethyl succinate (20 mg/kg) divided into 2 daily doses can provide adequate prophylaxis in patients. The importance of prophylactic antibiotics should be emphasized at all visits because parents may become noncompliant with this essential management.[16, 37]

at all visits because parents may become noncompliant with this essential management.[16, 37]

Anti Adherence Therapy: This therapy targets the abnormal interactions between red blood cells, endothelial cells, white blood cells and platelets that are thought to play a role in pathophysiology of sickle cell anemia.[39] Potential anti adherence agents have been studied in acute painful events through inadequately understood mechanisms that they restore the microvascular circulation and improve tissue ischemic condition.[40-41] In phase-2 studies of a non-ionic surfactant copolymer drug poloxamer-188 reduced the duration and increased the resolution of acute painful episodes and its effect was especially notable in children below 15 years of age and patients receiving hydroxyurea.[39] Whether poloxamer 188 exerts its effects by modifying interactions of sickle cells or other blood cells to endothelium is not known.

Nitric Oxide: - Nitric oxide binding to hemoglobin may play a role in the regulation of vascular tone with nitric oxide binding and release tied to oxygen- induced allosteric structural transitions.[37] In the lungs, hemoglobin is highly saturated with oxygen and nitric oxide which is produced in the lungs is thought to bind to cysteine-93 on the beta-chain of hemoglobin. This S-nitroso hemoglobin is carried by the red cells to the micro vascular system, where the oxygen tensions are reduced. Following to deoxygenation allosteric structural changes in the hemoglobin molecule favor the release of nitric oxide; this diffuses to the arterial wall and causes vasodilation. Heme of the deoxygenated hemoglobin is then capable of binding nitric oxide, favoring the formation of alpha-nitrosyl hemoglobin. This observations suggest that therapeutic delivery of nitric oxide may be beneficial to patients with sickle cell anemia who have impaired microvascular perfusion because of a direct vasodilation effect of nitric oxide in the periphery.[37, 40-41]

Inhibition of Gardose Channel: The Gardos channel appears as a major contributor to the dehydration of erythrocytes of sickle cell anemia patients and has long been recognized as a potential therapeutic target for this disease. Several triarylamides have been identified as potent inhibitors of the channel and active in mouse model of sickle cell anemia. Clotrimazole is an inhibitor of the human red cell gardos channel but its use was associated with dysuria and reversible hepatic toxicity. Senicapoc (ICA 17043) is a clotrimazole derivative lacking the toxic imidazole residue, was a 10 fold more potent blocker of Gardos channel than the native drug. But failed to reduce the frequency of vaso-occlusive crises.[42, 43] Chemokine blockages may potentially be used as a targeted therapeutic approaches for the sickle cell positive patients to optimize the gardos channel inhibition

Inhibition of K^+-Cl^- cotransport

Oral magnesium supplementation inhibits erythrocytes K^+-Cl^- co-transport in vivo.[44] Following studies that showed a beneficial effect on the erythrocyte membrane of transgenic sickle mice, a 6 month trial of oral Mg pidolate improved erythrocytes hydration and was associated with a reduction in the number of painful days.[45]

A new dimension towards ayurvedic approach: Although Sickle cell anemia has not been mentioned in the ayurvedic literature but in the literature it was mentioned that changing nature and environment with time may be the chief contributor in emergence of new disease. As sickle cell anemia is an autosomal recessive type 'Sahaj' word in Sanskrit known as belonging to family or community has been added to Pandu Roga. The study of effectiveness Dadam Ghrita on sickle cell anemia in comparison to folic acid as standard was carried out showing that there has been work in a direction of Ayurvedic medicine for this disease has already started.[47] While in another other trial Yogaraj and Laxadi guguly has been tried clinically for the maintenance of level of hemoglobin in sickle cell anemia patients.[47] Another study in Nigeria documented a potent anti-sickling activity of Ciklavit a newer herbal formulation.[48] Lot of work on herbal approach towards the enhancing the life span of red blood corpuscle by preventing them from lysis has been going on so ayurvedic medicinal plants extracts.[49] This newer approach can be a good alternative system of medicine for the patients of sickle cell anemia.

Newer research:

Umbelical-cord blood is one promising area of investigation. Increasing evidence suggest that donors of umbilical cord blood do not need to match recipients as closely as bone marrow donors do. In addition to indicating that use of cord blood may reduce the risk of rejection and graft versus host disease, this also suggest that transplantation of unrelated cord-blood may provide a source of stem cells for children with hard to match tissue types.[50]

Vasoactive drugs (e.g., Nitric oxide, sildenafil, endothelin antagonists) are being evaluated for the treatment of pulmonary hypertension. Statins are therapeutically of great interest since they can increase Nitric oxide production and reduce leukocyte adhesion.[51]

Additionally, there is growing interest in the prevention and treatment of vaso-occlusion by novel selectin antagonists since they appear to participate in multiple pathways involved in sickle vaso-occlusion, including the adhesion of leukocytes, red blood cells and platelets to the endothelium and to each other.[52]

Future non-pharmacological approach: Good care requires a multi-disciplinary team approach incorporating hospital and community as well as general primary and secondary pediatric services linking into educational and welfare systems. The majority of families affected with sickle cell anemia have African or Caribbean family origins and they often face additional difficult socioeconomic challenges which can impact negatively on the experience of sickle cell anemia. It is important to gain an understanding of the different cultural background, and to develop a service for long-term care which recognizes and interests itself in the diverse cultures, and works hard to remove stigmatization, acknowledges the diverse support that many families diverse support that many families need in order to give their child the optimal chances in life, directs parents to the right agencies for gaining their welfare entitlements and raises understanding of Sickle cell anemia in the healthcare system and local community.

ACKNOWLEDGEMENT: Authors like to thank the scientists directly or indirectly involved in sickle cell research since last 100 years.

REFERENCES

1. CDC. National Public Health Performance Standards Program: 10 essential public health services. www.cdc.gov/od/ocphp/nphpsp/essentialphservices.htm.

2. Olney RS (2000). Newborn screening for sickle cell disease: public health impact & evaluation. In: Khoury MJ, Thomson EJ, Burke W, eds. Genetics and public health in the 21st century: using public genetic information to improve health and prevent disease. NewYork NY: Oxford university press, http://www.cdc.gov/genomics/ resources/books/21stcent/index.htm.

3. Lerner NB, Platania BL, La Bella S (1989). Newborn sickle cell screening in a region of western New York State. J Pediatr 2009; 154:121–5. 12. Harris MS, Eckman JR. Georgia's experience with newborn screening: 1981-1985. Pediatrics 83(5 Pt 2): pages: 858–60.

4. Therrell BL, Simmank JL, Willborn M (1989). Experiences with sickle hemoglobin testing in the Texas newborn screening program. Pediatrics; 83: pages: 864 –7.

5. Lloyd-Puryear MA, Mann MY, Therrell BL, Eckman JR, Telfair J (2009) The role of the federal government in supporting state newborn screening programs. In: Baily MA, Murray TH, eds. Ethics and newborn genetic testing - new technologies-new challenges. Baltimore MD: Johns hopkins press.

6. Pass KA, Lane PA, Fernhoff PM, et al (2000). U.S. newborn screening system guidelines II: follow-up of Children, Diagnosis, Management & evaluation. (Statement of the council of regional networks for genetic services). J Pediatr ; 137(4S):S1– 46.

7. Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG (2010). The number of people with sickle-cell disease in the United States: national and state estimates. Am J Hematol; 85(1): pages: 77– 8.

8. Hassel KL (2010). Population estimates of sickle cell disease in the U.S. Am J Prev Med; 38(4S):S512–21.

9. Balfour IC, Covitz W, Davis H, et al (1984). Cardiac size and function in children with sickle cell anemia. Am Heart J; 108: pages: 345-50.

10. Bridges, K.R., et al. (1996), a multiparameter analysis of sickle erythrocytes in patients undergoing hydroxyurea therapy. Blood, 88: pages: 4701-4710.

11. Charache S, Barton F.B, Moore R.D, Steinberg M.H, Terrin M.L, Dover G.J, et al (1996). Hydroxyurea and sickle cell anemia: clinical utility of a myelosuppressive 'switching' agent: the multicenter study of hydroxyurea in sickle cell anemia. Medicine; 75(6): pages: 300–25.

12. Gaston M, Rosse W.F (1982). The co-operative study of sickle cell disease: review of study design and objectives. Am. J. Pediatr. Hematol. Oncol. 4: pages: 197-201.

13. Benjamin LJ, Dampier CD, Jacox AK, et al (1999) Guideline for the management of acute and chronic pain in sickle cell disease. (APS clinical practice guidelines series), No. 1. Glenview, IL

14. United States Pharmacopeial Convention (1999), Inc. USP Dispensing Information Volume I: Drug Information for the Health Care Professional. Rockville, MD, pages: 1810.

15.Walters MC, Nienhuis AW, Vichinsky E (2002), Novel therapeutic approaches in sickle cell disease, Hematology, pages: 10-34

16. Stenberg MH (1999), management of sickle cell disease, N Engl J Mag; 340; pages: 1021-1030

17. Bunn HF (1999), induction of fetal hemoglobin in sickle cell disease, Blood; 93; pages: 1787-1789

18. Jacox A, Carr DB, Payne R, et al (1994). Management of Cancer Pain. Clinical Practice Guideline no.9 rockville, MD: (Agency for health care policy and research), public health service, United States department of health and human services. AHCPR ; 94-0592.

19. American pain society (1999), Principles of analgesic use in the treatment of acute pain and cancer; 4th edition. Glenview, IL.

20. Stinson J & Naser B (2003), Pain management in children with sickle cell disease. pediatric drugs, 5 (4); pages: 229-241.

21. S. C. Davies, M. Roberts-Harewood (1997), Blood transfusion in sickle cell disease, Blood Re~ie~t~.s , 11; pages: 57-71.

22. Jan K, Usami S, Smith JA (1982). Effects of transfusion on rheological properties of blood in sickle cell anemia. Transfusion; 22: pages: 17-20.

23. Schmeltzer EA, Lee JO, Brown AK et al (1987). Viscosity of mixtures of sickle and normal red cells at varying hemocrit levels: implications for transfusion. Transfusion; 27: pages: 228-233.

24. Emre U, Miller St, Gutieriez M et al (1995). Effect of transfusion in acute chest syndrome of sickle cell disease. J Pediatr; 127: pages: 90 l-904.

25. Bellet PS, Kalinyak KA, Shukla R et al (1995). Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med; 333: pages: 699-703.

26. Powars DR, Weidman JA, Odom-Maryon T et al (1988). Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. Medicine; 67: pages: 666-676.

27. Hasegawa S, Hiruma M, Uyesake N et al (1995). Filterability of mixtures of sickle & normal erythrocytes. Am J Hematol; 50: pages: 91-97.

28. Miller DM, Winslow RM, Klein HG et al (1980). Improved exercise performance after exchange transfusion in subjects with sickle cell anemia. Blood; 56: pages: 1127-l 13 1.

29. Keidan AJ, Marwah SS, Vaughan GR et al (1987). Painful sickle cell crises precipitated by stopping prophylactic exchange transfusions. J Clin Path; 40: pages: 505-507.

30. Rackoff WR, Ohene-Frempong K, Month S et al (1992). Neurologic events after partial exchange transfusion for Priapism in sickle cell disease. Pediatrics; 120: pages: 882-885.

31. Seigel JF, Rich MA, Brock WA (1993). Association of sickle cell disease, Priapism, Exchange transfusion & neurological events: Aspen syndrome. J Urology; 150: pages: 1480-1482.

32.Royal JE, Seeler RA (1978), Hypertension, Convulsions & cerebral hemorrhage in sickle-cell anemia patients after blood transfusions. Lancet; ii: pages: 1207-1208.

33. Rosse WF, Gallagher D, Kinney TR et al (1990). Transfusion and alloimmunization in sickle cell disease. Blood; 76: pages:1431-1437.

34. Cummins D, Webb G, Shah N, Davies SC (1991). Delayed hemolytic transfusion reactions in patients with sickle cell disease. Postgrad Med J; 67: pages: 689-691.

35. Heddle NM, Soutar RL, O'Hoski PL et al (1995). A prospective study to determine the frequency and clinical significance of alloimmunization post-transfusion, Br J Hematolgy; 91: pages: 1000-1005.

36. Sosler SD, Jilly BJ, Saporito C, Koshy M (1993). A simple, practical model for reducing alloimmunization in patients with sickle cell disease. Am J Hematol; 43: pages: 103-106.

37. Textbook of management and therapy of sickle cell disease National institutes of health, national heart, lung & blood institute, 3rd edition, 1994.

38. George Buchanan, Lakshmanan Krishnamurti, Elliott Vichinsky, Shalini Shenoy (2010), severe sickle cell disease-pathophysiology and therapy, Biology of Blood and marrow transplantation, olume 16, Issue 1, Supplement, pages S64–S67

39. Orringer EP, Casella JF, Ataga KI, et al (2001). Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: A randomized controlled trial. JAMA. ; 286: pages: 2099–106.

40. Walters MC, Nienhuis AW, Vichinsky E (2002), novel therapeutic approaches in sickle cell disease. Hematology, pages: 10-34

41.Rosse WF, Narla M, et al (2000) , new View of sickle cell disease pathophysiology and treatment, hematology; pages: 2-17

42. K.I. Ataga, W.R. Smith, P. Swerdlow, L.M. De Castro, O. Castro, E. Vichinsky, A. Kutlar, E.P. Orringer, Y. Saunthararajah, G.C. Rigdon, J.W. Stocker (2008), ICA-17043-05 Investigators Efficacy & safety of the Gardos channel blocker, Senicapoc (ICA- 17043), in patients with sickle cell anemia, Blood, 111, pages:3991–3997.

43. K.I. Ataga, J. Stocker (2009), Senicapoc (ICA-17043): a potential therapy for the prevention and treatment of hemolysis-associated complications in sickle cell anemia, Expert Opin. Investig. Drugs 18; pages: 231–239.

44. De Franceschi L, Bachir D, Galacteros F (1997). Oral magnesiumsupplements reduce erythrocyte dehydration in patients with sickle cell disease. Journal of clinical investigation; 100: pages: 1847–52.

45. De Franceschi I, Galacteros F, Bachir D, Cynober T, Tchernia G, Neuberg D, et al (2000). Oral magnesium pidolate: effects of long-term administration in patients with sickle cell disease. Br J Haematol; 108: pages: 284-9.

46. Shrivas Yogita Kamleshwar, Shamkuwar Manoj Keshaorao, Tiwari Gopinath, Shamkuwar Sujata Keshaorao, Chauhan Amit singh (2011), Therapeutic Efficacy of Dadim Ghrita in the management of Sahaj Pandu Roga (sickle cell disease): A human trial based study. IJRAP, Vol.2 (2), pages: 358-262.

47. Hemanta kumar panigrahi, hemant kushawa and Shyam sunder Sharma (1997), Treatment of sickle cell disorders by Ayurvedic medicine, Ancient Science of Life Vol. 17(1), pages: 15 – 22.

48. C.Wambebe, H.Khamofu, J.A.F Momoh, M. Ekpeyong, O.S Njoku, E.A Bamgboye, R.N Nasipuri, O.O Kunle, J.G Audam, J.I Okogun, M.N Enwerem, K.S Gamaniel, O.O Obodozie, B. Samuel, G. Fojule, O. Ogunyale (2001). Double-blind, Placebo-controlled, Randomized cross-over clinical trial of NIPRISAN® in patients with sickle cell disorder. Phytomedicine, Vol. 8(4), pages: 252–261.

49. P.T Mpiana, D.S.T Tshibangu, O.M Shetonde, K.N Ngbolua (2007), In vitro anti-drepanocytary activity (anti-sickle cell anemia) of some congolese plants. Phytomedicine. Vol. 14; pages: 192–195.

50. Locatelli, F, et al. (2003), Related umbilical cord blood transplantation in patients with thalassemia & sickle cell disease. Blood. 101: pages: 2137-2143.

51. Takemoto M, Liao J.K (2001), Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. Arterioscler. Thromb. Vasc. Biol. 21: pages: 1712-1719.

52. Chiang EY, Frenette PS (2005), Sickle cell vaso-occlusion. Hematol. oncol. clin. North Am. 19: pages: 771-784.

Journal of
Pharmaceutical Science and
Bioscientific Research Publication

www.jpsbr.org
jpsbronline@rediffmail.com