

A Systematic Review of Pharmacological Therapies for Sickle Cell Disease

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ABSTRACT

This review was carried out to understand various issues concerned with the patients of sickle cell disease (SCD). An attempt has been made to review the literature with respect to the multiple complications experienced by the SCD patients, variety of pharmacological therapies used throughout the world for SCD management. The literature highlighted the lack of reliable prevalence statistics, lower use of diagnostic measures, especially in rural areas. The literature indicated that varieties of medicinal plants are used regularly for the management of SCD related complications, such as sickling, infections, pain crisis, etc. Although, Bone marrow transplant, the only curative therapy and genetic counselling, have shown promising results for effective management of SCD, now a days people are using alternative pharmacological therapies for SCD management.

Key words: Sickle cell disease; pharmacological therapies;
sickling; pain crisis; Bone marrow transplant

INTRODUCTION

Human genetic diversity poses a great challenge to community health care in India. Although many diseases present varied level of complexity, haemoglobin disorders constitute the most common genetic and public health burden on people¹. Sickle cell disease (SCD) a common genetic haemoglobin disorder has been reported worldwide. Amino acid substitution that causes SCD is a mutation of the sixth amino acid from glutamic acid to valine². Inheritance of mutant haemoglobin genes from both parents results into SCD. So far many studies³ aimed at determining the prevalence estimates of SCD. However, a comprehensive and reliable data for India context is not available. SCD disorder is largely ignored in many parts of the world including India, though the techniques for diagnosis of the disorder are well known, its treatment has limited scope. Also, it is not a public health priority in many countries where it is prevalent. Furthermore,

in countries where SCD is prevalent, health systems are often strained and the main hurdle for management of the SCD sufferers is the lack of resources and understanding of the disorder, which results in increased severity of the condition and drastically shortens life of the affected individual. Majority of children die undiagnosed, untreated or undertreated⁴.

The current global economic activity and the relatively newer phenomenon of global migration for work have presented an entirely new aspect to the SCD research. For most healthcare professionals (haematologists), such issues may look far different from regular practice. However, as genetic diseases are increasingly recognized as a major global health problem, haematologists are needed to be equipped with adequate knowledge for dealing with a new spectrum of SCD, which they need to be able to identify and manage.

Numerous studies⁵ confirmed that early diagnosis and treatment of newborns can reduce many complications and increase life expectancy and quality of life of an SCD patient. Furthermore, Regular blood tests along with prenatal counselling also reduce the number of births of SCD affected children⁶. There are promising techniques such as solubility test, full blood count, haemoglobin electrophoresis, isoelectric focussing, high performance liquid chromatography, DNA analysis, prenatal diagnosis, chorionic villus sampling, amniocentesis and fetal blood sampling etc. which support in diagnosis of SCD and thereby help in managing and improving SCD patients' quality of life. Apart from this, now a day's people are using alternative therapy for SCD management. Medicinal plants have been a source of succour in the control of many diseases and SCD is one of them. Local people from Africa and Asia with high incidence of the SCD have learnt to manage the problem by using plants which have medicinal properties. In Nigeria and most parts of developing countries, medicinal plants have been used in the treatment of painful crises associated with SCD, especially among the lower socio-economic class who cannot afford the high cost of medicine. In the backdrop of the above information, this article attempts to review pharmacological therapies for SCD treatment and other related aspects.

A survey was conducted⁷ in Lubumbashi city (Democratic Republic of Congo) in order to identify medicinal plants used by traditional healers in the management of SCD. Authors used the Emmel test in vitro, for the antisickling activity assays of aqueous and ethanolic extracts of different parts of these plants. The survey revealed that 13 medicinal plants were used in the treatment of drepanocytosis among which 12 plants exhibited the in vitro antisickling activity for at least one of the used parts or extracts. These plants are *Bombax pentadrum*, *Bougainvillea* sp., *Byarsocarpus orientalis*, *Dalbergia boehmiantaub*, *Diplorrhynchus condolocarpus*, *Euphorbia heterophylla*, *Ficus capensis*, *Harungana madagascariensis*, *Parinari mobola*, *Pothmania witfchidii*, *Syzygium guineense*, *Temnocalys verdickii* and *Ziziphus mucronata* of which four (*Bombax pentadrum*, *Ficus capensis*, *Parinari mobola* and *Ziziphus mucronata*) revealed a high antisickling activity. The authors concluded

that in vitro Antisickling activity justifies the use of these plants by traditional healers and this activity would be due to anthocyanins.

The author⁸ studied the role of *Cajanus cajan* methanolic extract in inhibition of sickling and suggested that the additive antisickling effect of both compounds (phenylalanine and p-hydroxybenzoic acid) can be therapeutically exploited for the treatment of SCD. The leaves of *Hymenocardia acida* are commonly used alone or in combination with other plant parts to manage SCD⁹. They found that the antisickling activity was dose dependent. The fractions containing flavonoids, saponins and carboxylic acids were found to be responsible for reversal of the sickled RBC. The anti-sickling activities of the extracts of the roots of a plant *Cissus populnea* L. (CPK) was examined in one of the study and reported¹⁰ that extract showed presence of anthraquinone derivatives, steroidal glycosides and cardiac glycosides. The chloroform and water partitioned fractions of the cold methanol extracts of CPK exhibited a 62.2% and 52.9% inhibition of sickling, respectively, at 180 min.

Pathophysiology and Medical Complications

Pathophysiology is the study of the changes of normal, mechanical, physical, and biochemical functions, either caused by a disease or resulting from an abnormal syndrome is of utmost importance in case of SCD. Pathophysiological changes observed in the patients with SCD are reported in many studies¹¹. For example, confirmatory studies¹² revealed that SCD is a genetic disorder of blood which produces abnormal Hb and causes vasoocclusion as well as the disruption of oxygen to body tissues, because of which innumerable SCD patients suffer from other medical complications that include but are not limited to delayed growth and delayed sexual maturation; acute chest syndrome, priapism, stroke, Dactylitis, Renal Disease, sickle cell retinopathy, dermal ulcers, severe chronic pain and oxygen etc. These were the major clinical reasons for hospitalization as well as death in some cases. The authors advocate the need for management of patients with SCD with a multi-disciplinary approach¹³.

Role of Antioxidants

Studies¹⁴ carried out in Central India

reported lower vitamin E levels in SCD patients. Homozygous SCD had lower levels of all three vitamins, such as vitamin E, vitamin C and beta-carotene levels. Significant depletion of the antioxidant vitamins, particularly in severe forms of SCD has also been reported indicating the necessity to provide appropriate food supplements and medication.

Oxidative phenomena play a significant role in the SCD's pathophysiology¹⁵. They evaluated the antioxidant effect of garlic (*Allium sativum*), AGE on sickle red blood cells. Their study data suggest that AGE has a significant antioxidant activity on sickle RBCs, which may be further evaluated as a potential therapeutic agent to ameliorate complications of SCD.

Another study reported¹⁶ that certain erythrocytes with an elevated density are believed to be the root of the painful crisis and anemia of the patients. On the basis of *in vivo* and *ex vivo* studies, the authors proposed that a cocktail of antioxidants would have beneficial effects in lessening the incidence and severity of crisis and reducing anemia in SCD.

Fetal haemoglobin

The newborn infant is protected by the high level of fetal hemoglobin in the red cells during the first 8 to 10 weeks of life. As the level declines the clinical manifestations of sickle cell disease appear, and the hematologic manifestations of SCD are apparent by 10 to 12 weeks of age¹⁷. High level of fetal Hb in the red cells, which persists during the first year of life, somehow protects the infant. In view of this, it is obvious that the infants should be screened at appropriate time to determine the clinical complications.

Physical growth

It's a common clinical feature of SCD (SS pattern) is reported^{18,19} as poor growth, weigh less, shorter and poor nutritional status in combination with delayed sexual and skeletal maturation. The nature and magnitude of body-compartment shortage are important in understanding the nutritional needs of children with SCD and for monitoring the outcomes of nutrition interventions. Children with SCD have impaired growth, delayed

puberty, and poor nutritional status. Body-composition abnormalities suggested the nutritional need.

Iron deficiency anaemia

Earlier study²⁰ documented the Iron Deficiency Anaemia (IDA) in Indian population. Furthermore, another past study²¹ reported that children with IDA show significantly higher red blood cell counts and higher total iron binding capacity but significantly ($P < 0.05$) lower reticulocyte counts than children without IDA²², which clearly indicated that IDA is a clinical problem of children with SCD.

The oral administration of aqueous extract of *Sorghum bicolor* (L.) Moench stem bark administration produced significant increase in haemoglobin, packed cell volume and red blood cells in iron sufficient and iron deficient groups ($P < 0.05$)²³. The results revealed that extract administration has restored the anaemic condition in the iron deficient group and thus presents credence to its use as a medicine in the management of anaemia. Wild plant *Pfaffia Paniculata* (PP) functions as a sodium ionophore on sickle cells and improves their hydration status and rheological properties²⁴. Author further noticed that the PP Improves the deformability of sickle cell, as well as it increases sodium content and mean corpuscular volume (MCV).

Pain

Acute episodes of pain have been extensively reported²⁵ in SCD patients. Patients who had more pain episodes tend to die early, which could be because of high Hematocrit and low Hb F level. From these observations, it may be noted that pain rate correlates with early death in SCD. Hence prevention of pain episodes is necessary to increase the life span of SCD patients. Management of pain associated with SCD consists of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant medications²⁶. However, to improve the quality of life, the medical professionals should be sensitized regularly regarding the therapeutic developments for combating the pain crises. Author supported²⁷ the decision of pharmacological screening of siculine syrup (a traditional herbal remedy purported to be useful in the prevention and treatment of sickle cell pain –

crises), which has antisickling and analgesic activities as well as antimicrobial and diuretic effects. The author reported that siculine syrup is used by the local population of Nigeria for the prevention and treatment of sickle cell pain crises.

Leg ulcer

The ulcers usually appear between ages 10 and 50 years and are seen more frequently in males than in females²⁸. It has been reported²⁹ that often decreased oxygen capacity in the blood results in the leg ulcer complications in SCD patients, where anti sickling drug and chemical manipulation of the haemoglobin helps manage the leg ulcer. The earlier studies³⁰ highlighted that there are no controlled clinical trials available to define the pharmacologic approach to cure the leg ulcer, which often goes undocumented. Therefore, as a preventive measure, the affected people should be made aware of the problems regarding leg ulcers. Recent studies appear to show topical and orally administered aloe vera preparations in patients with chronic venous leg ulcers may aid healing³¹.

Dactylitis or hand-foot syndrome

Dactylitis affected 45% of the children by the age of 2 years³². Children are always at high risk of severe complications, if dactylitis occurs before 6 months of life. Episodes were significantly more common during colder months of the year and are related to intravascular sickling. Dactylitis commonly occurs in patients with homozygous hemoglobin S disease sickle cell-hemoglobin C disease or sickle cell-beta-thalassemia, but one of the case of dactylitis also reported³³ in sickle cell trait which is a very rare.

Cassia occidentalis Linn. mast cell degranulation at a dose of 250 mg/kg, showed dose dependent stabilizing activity towards human RBC, with is widely used in traditional medicine of India to treat a number of clinical conditions including allergy and inflammatory manifestations. *C. occidentalis* whole plant ethanolic extract inhibited mast cell degranulation stabilized HRBC membrane thereby alleviating immediate hypersensitivity besides showing anti oxidant activity³⁴.

Spleen

It has been reported³⁵ that about 7% of

the SCD patients possess acute splenic sequestration crisis. Frequent splenic infarcts were also reported to be a common episode in patients with SCD, which ultimately led to autosplenectomy³⁶. Massive splenic infarction is a rare and unique complication of SCD, and for early diagnosis and treatment, physicians should be made aware of such a complication.

Qiulirunfei extracta shows antiviral effects, and it is a good immune system enhancer, which should be explored as a potential therapeutic agent³⁷.

Retinopathy (Eye Disease)

SCD children must check their eyes routinely to prevent vision-threatening complications³⁸. Author studied 263 pediatric SCD patients and mentioned the Proliferative retinopathy (PR) was rare. But Six cases (8.2%) of PR were seen in the SC genotype, 1 case (0.6%) in the SS genotype, and no cases in the SB-Thalassemia genotype. SC genotype patients at the age of 9 years and 13 years of age for SS and SB-Thalassemia genotype patients should under go for retinopathy screening. Fluorescein angiography for Patients with an abnormal examination is also recommended³⁸. Another study³⁹ of 55 adult SCD patients also reported severe sickle cell retinopathy is more common in SC genotype than the SS and SB genotypes. Proliferative retinopathy is more common in SC patients than SS and SB patients. Screening is useful in detecting sickle cell retinopathy.

Stroke

Stroke is one of the major complications in patients with SCD^{40,41}; however, it has been reported that the risk of stroke in childhood can be reduced through chronic blood transfusions⁴². Besides, prevention of the first stroke (primary prevention) was through the use of transcranial Doppler (TCD) was also reported. Previous studies⁴² strongly emphasized that TCD must be performed in all children at 12-18 months of age to detect cerebral vasculopathy and prevention of stroke.

From the literature, it is evident that there is a dearth of studies reporting results for acute stroke treatment for SCD patients, however,

hydration and exchange transfusion were found to be often recommended practices.

Acute Chest Syndrome (ACS): ACS is a leading cause of hospitalization and death of children with SCD. ACS is an acute illness characterized by fever and respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest x ray. Younger children with greater blood and heat loss during surgery appear to be more prone to ACS. Splenectomy also seems to increase the risk of ACS. Inhaled nitric oxide and exchange transfusion therapy shown successful effects⁴³. A major finding⁴⁴ of risk factor for the development of ACS is the hemoglobin genotype and the highest incidence is seen in Hb SS genotype (12.8 events/100 personyears) and the lowest in Hb-S + β -thalassemia genotype (3.9 events/100 person years)

Oxygen

Arterial blood gas (ABG) analysis is used to measure the partial pressures of oxygen (PaO₂) and carbon dioxide (pacO₂)' and the pH of an arterial sample. Earlier study documented⁴⁵ that Pulse oximetry is an accurate and effective non-invasive method for monitoring the arterial oxygen saturation in SCD. The lowest oxygen saturation to 86.5% +/- 0.9% was observed during sleep. It has been reported⁴⁶ that in a fall in oxygen saturation was associated with a decrease in respiratory depth without a change in respiratory frequency. Oxygen saturation was lower during sleep than during wakefulness and that hypoxemia can be attributed to a fall in tidal volume is also reported in SCD patients.

Renal disease

Many renal structural and functional abnormalities reported in SCD. The prevention of the renal complications of SCD will required a cure for this genetic disorder is recommended⁴⁷. The patients have impaired urinary concentrating ability, defects in urinary acidification and potassium excretion, and supranormal proximal tubular function. Recurrent hematuria is a relatively common problem in patients with SCD⁴⁸ and it is also observed in SCT. For the prevention of renal damage, routine screening of SCD patients is recommended.

SCD in males

Priapism

Priapism is one of the complications of SCD that receives very little attention but can be particularly bothersome for a large number of patients. If left untreated, irreversible fibrosis and impotency may occur. Other effects of priapism include pain, hospitalizations, and days missed from work, school, or other activities. Priapism is a rare urologic emergency in pediatric as well as in young population. It is a major consequence of SCD⁴⁹. There are two types of priapism: low-flow and high-flow and the treatment is different for each type. Priapism is considered a medical emergency, where the patient should receive appropriate treatment by a qualified medical practitioner as the functional recovery of the patient is dependent on early treatment.

SCD in females

Women with SCD experience multiple complications which can affect each and every organ system and are often worse in pregnant women. It is often noticed that more than one third of pregnancies in women with sickle syndromes terminate in abortion, stillbirth, or neonatal death. Past studies⁵⁰ report that over seventy-two thousand Americans were homozygous for the sickle cell gene and 2 million were carriers.

Pregnancy

Earlier longitudinal studies⁵¹ reported that the first pregnancy loss among SS women was much higher at 22% as compared to SC women at 12%. Similarly the percentage of foetal loss was high in SS women (19.2%) in comparison to SC women (8.9%). The specific finding⁵⁰ were that the prenatal mortality rate was very high in SS women than in SC women. The midterm/stillbirth death was negligible in SC women as compared to SS women. Overall it has been concluded that pregnancy loss is more in among SS women as compared to SC women.

One of the study reported⁵² that medicinal plant use is common among the Brou, Saek and Kry ethnic groups of South Asia to facilitate childbirth, alleviate menstruation problems, assist recovery after miscarriage, mitigate postpartum haemorrhage, aid postpartum recovery, and for use in infant care.

Mortality and Morbidity

With the developments in science and technology, the lifespan of the mother and child has increased considerably. However, mortality and morbidity was reported to be higher in SS women as compared to AA women⁵³. One of the study reported⁵⁴ that with a proper combination of obstetrician and hematologist care, and using latest laboratory techniques there can be marked decrease in the maternal and perinatal morbidity rates and mortality in the pregnant SS women.

Infection

Apart from other complications, infection is a major complication in SCD and secondary infection, such as pulmonary infection has been extensively reported⁵⁵. Although special preventive measures against different infections exist in addition to routine immunizations; often treatment regimens are based on local formularies and antibiotic sensitivity tests. The single most common cause of death in children with SCD is *Streptococcus pneumoniae* sepsis^{56,57}. However, it has been observed that proper vaccination and course of prophylactic antibiotics can prevent pneumococcal disease.

Scientific research on the healing properties and bioactivity of natural compounds, especially of plant origin, has been extensive particularly in the Western world⁵⁸. However, a rich heritage of floral biodiversity is found in developing countries, which needs to be explored. A number of medicinal plants (of *Amaryllidaceae* and *Hyacinthaceae* families) have particular uses as disinfectants and anti-inflammatory agents, although there is still a lack of scientific research regarding their unique pharmacological compounds. *Allium sativum* (garlic) extract has broad-spectrum antimicrobial activity against many genera of bacteria and fungi. Because many of the microorganisms susceptible to garlic extract are medically significant, garlic holds a promising position as a broad-spectrum therapeutic agent, especially in treatment of SCD⁵⁹.

Psychological aspect of SCD

Depression and anxiety: Little is known about the impact of depression and anxiety on SCD adults⁶⁰. An epidemiological study showed that

27.6% SCD patients were depressed and 6.5% had one or the other anxiety disorder. Depressed subjects had pain on significantly more days than non-depressed subjects. It has been concluded that depression and anxiety predicted more daily pain and poorer physical and mental quality-of-life in adults with SCD, and accounted for more of the variance in all domains of quality-of-life than hemoglobin type. Cognitive behaviour therapy (CBT) is commonly used to treat, depression and anxiety.

Medicinal plants (*Bacopa monniera* and *Panax quinquefolium* have significant adaptogenic properties) can be used against mixed anxiety-depressive disorder (MAD)⁶¹. The authors reported that extracts of these plants can be used as a potent therapeutic agent in treating MAD. Other study reported⁶² that *Ocimum sanctum* is a promising anxiolytic agent, which may be useful in treatment of generalized anxiety disorder; however, more confirmatory studies are necessary.

Treatments for SCD

Medicinal plants: above section shows the utility of medicinal plants for possible use in the treatment of SCD. However, the knowledge that exists today needs confirmation through further systematic research investigation. Although the efforts by many scientists are underway, the exploration of medicinal plants for efficient treatment option shows promising future due to its low cost and no to negligible side effects.

Vaccination

Patients with SCD are susceptible to bacterial infections (*Streptococcus pneumoniae*⁶³), especially those caused by encapsulated organisms. The efficacy of oral penicillin prophylaxis against pneumococcal infections has been well established and is now recommended from 3 months of age⁶⁴. The high incidence and severity of bacterial infections in children with SCD justify prevention efforts by antibiotic prophylaxis and vaccination.⁶⁵

Hydroxyurea (HU)

Pediatric studies have shown that HU can be safely used in children as well as in adults for improving the QOL⁶⁶ who already suffer from moderate-to-severe SCD. The improvement in

laboratory parameters has also been reported⁶⁷ that suggests the beneficial use of HU in preventing acute clinical complications of SCD in children as well as in adults. In another study⁶⁸ regarding the safety and efficiency of HU, it was found that HU increased the fetal Hb production in previously ill children with SCD⁶⁸ and decreased morbidity from vaso-occlusive complications in patients with SCD⁶⁹. After the treatment for 32 months, it was observed that HU increased the level of Hb F in all children except one, who took 9 months. There was drastic reduction in pain crises and hematopoietic complications were not observed. In conclusion it was stressed that the use of HU is effective in reducing painful events in children with SCD. Results of studies⁷⁰, report that use of HU reduced the overall mortality rate by almost 40%. The survival was attributed to HbF levels and frequency of vaso-occlusive events.

Cognitive behaviour therapy (CBT)

CBT is a type of psychotherapeutic treatment that helps patients to understand the thoughts and feelings that influence behaviours. It has been reported that it is most effective in the management of SCD pain, which also reduces the psychological distress and helps to improve coping⁷¹. The CBT is economically efficient and is most cost effective during the first 6 months after the intervention. It has been recommended that CBT should be integrated as a part of the normal care available to the SCD patients and should be regularly offered every 6.

Bone Marrow Transplant (BMT)

Currently it is widely accepted that the only curative therapy for SCD is BMT⁷², which is rarely applied. The overall survival and disease free condition is greater than 80% following matched sibling BMT for SCD. Unfortunately, most patients with SCD do not have a suitable human lymphocyte antigen-matched sibling donor. So to increase the possibilities of match donor, several groups are beginning to explore the use of alternative sources of stem cells such as haploidentical donors and umbilical cord cell blood⁷². It has been reported that the cost of BMT was significantly less in India as compared to western countries⁷². In the support of BMT, the study⁷³ stressed the need to develop more transplant centers with adequately trained personnel

in India. Though the cost of BMT is less in India as compared to other countries but in India the SCD patients are mostly tribals and are from economically backward classes and the cost of the treatment is beyond their reach.

Gene replacement therapy

It is a process whereby the defective gene of the sickle hemoglobin is replaced with normal gene. Gene therapy for SCD, is the ultimate cure for the disorder, but is not imminent. Hence, research efforts need to be diverted for exploring further in the realm of gene replacement therapy for improving the problem of SCD.

Genetic counseling

The importance of genetic counseling is gaining momentum in fight against SCD⁷⁴. The need for providing sufficient information of SCD especially for students has been recommended in addition to genetic counseling. One of the problems reported elsewhere^{75,76} observed that the SCD patients participating in ethnographic survey while undergoing genetic counseling had a great concern about the confidentiality of their genetic information in public domain. Patients further suggested that the ethical principle of confidentiality needs to be seen as a human right and public health issue.

CONCLUSIONS

SCD a common genetic haemoglobin disorder has been reported worldwide with the developing countries having significantly higher prevalence rates. A comprehensive and reliable data for prevalence, however, is not available for Indian context and majority of children die undiagnosed, untreated or under treated. From the literature, it is evident that the early diagnosis and treatment of newborns can reduce many complications and increase life expectancy and quality of life of an SCD patient. Furthermore, numerous studies have reported effective use of medicinal plants for managing different complications of SCD patients. Specifically, the medicinal plants have been used for antisickling (*Bombax pentadrum*, *Ficus capensis*, *Parinari mobola* and *Ziziphus mucronata*), IDA (*Sorghum bicolor* (L.), *Pfaffia Paniculata* (PP)), pain (*Sicine syrup* (a traditional herbal remedy), ulcers (*Aloe vera*), *Dactylitis* (*Cassia occidentalis* Linn.),

spleen (Qiulirunfei extracta), infection (Amaryllidaceae and Hyacinthaceae families, *Allium sativum* - garlic) and depression and anxiety (*Bacopa monniera* and *Panax quinquefolium*). Furthermore, the treatment options most widely used are antibiotics, Hydroxyurea, Cognitive behaviour therapy, Bone Marrow Transplant, Gene replacement therapy, Genetic counselling, etc. In conclusion, this review indicates that variety of medicinal plants have been utilized throughout the world to address different physiological and other

complications of SCD sufferers. However, the knowledge of the use of these agents is in nascent stage and needs further investigations for using these medicinal plants as regular treatment option.

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