Therapeutic Strategies in Sickle Cell Disease

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Sickle cell disease (SCD) is one of the commonest inherited diseases worldwide affecting mostly persons whose ancesters originated from sub-Saharan Africa, the Eastern Mediterranean basin, the Arabian peninsula & Indian subcontinent[1]. Sickle cell disease results from an aminoacid substitution of Valine for Glutamic acid at position 6 of the betaglobin chain. This alteration causes deoxygenated sickle hemoglobin to form polymers that ultimately destroy red cells there by producing anemia.[2] The key difficulty with sickle cell disease is damage to tissues & organs produced when deformed sickle erythrocytes occlude the microcirculation. Manifestations of sickle cell disease are due ultimately to this problem[3].(See Fig).

Management of SCD is very crucial & to be targated on every aspect like preventive, during acute complications & chronic complications.

Preventive strategies :

Screening :

Treatment of SCD begins with diagnosis in newborn. Antenatal & neonatal screening programmes to detect SCD carriers & affected infants were initially targeted only at those considered to be at risk by virtue of ethnicity. The purpose of this programme is to make informed reproductive decisions. The process of newborn diagnosis combined with family education, comprehensive care & prophylactic penicillin has been the most important treatment advance in the history of SCD. Early diagnosis (by neonatal screening) shown to reduce mortality.[4]

Infection :

Hyposplenism due to repetitive VOC lead to SCD patient at risk of infection. Vaccination against Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides & influenza in conjunction with prophylactic penicillin to prevent the sepsis is indicated. It is recommended in children in whom fever is common . Penicillin should be initiated from 3months of age. Rigororous antimalarial chemoprophylaxis is recommended when visiting areas where malaria is endemic.

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Immunization:

Polyvalent pneumococcal vaccine every 5 yrs in children having <2 yrs is recommended. No much benefit of this vaccine is observed in adults.

Immunization against hepatitis B should be universal.

Hemophilus influenzae vaccine is also beneficial in children but it's role in adults is controversial.

Genetic counseling:

It should be done by trained professionals. Partner & patient should make informed decision about reproduction

Supportive measures during Acute complications:

Main therapeutic strategy in acute complication is Hydration, oxygenation & treatment of infection. VOC is most important complication, usually precipitated by infection, exposure to heat/ cold, inadequate fluid intake & adverse living conditions.[1]

- Avoidance of these factors can lead to reduce the rate of complications.
- Hydration should be corrected with hypotonic solution like 5% Dextrose.(It reverses erythrocyte dehydration which favors polymerization of Hbs) .
- O2 therapy may be beneficial in relieving VOC though there is no clear evidence about benefit of O2 therapy in absence of hypoxia.
- Infection should be treated with broad spectrum antibiotics.

Pain control :

Pain is the most common clinical problem encounters in care of SCD patient

Pain management at home:

Combination of relaxation, local warmth, hydration & oral analgesics.[5]

- Opiate analgesia is often the only effective therapy.
- Weak opiate (Codeine) can be used in mild pain
- NSAIDs to be avoided (ill effects on renal vasculature) Use judiciously.
- Exclude other medical complications that

masquerade as pain episode (osteomyelitis, Appendicitis, evolving stroke, other abdominal catastrophe).

Pain management in hospital set up:
Failure to home measures requires parenteral analgesics, usually in severe pain

- Use of patient controlled infusional device "PCA"is advisable.
- PCA with a continuous basal delivery of morphine or di morphin (heroin) is very effective in dose of .1-.15/kg every 3-4 hrs .[1]
- Meperidine (Demerol) to be avoided since causes seizures.
- Respiration, O2 saturation, sedation should be monitored when on opiate therapy.
- Toradol : only injectable non steroidal & extremely effective single agent. having narcotic sparing effect. Can be used with morphine PCA. for 5days along with H2 receptor blocking agent. Toxic effect is GI ulceration.[6]
- Ketorolac 30-60mg initially followed by 15-30mg 6-8 hrly used I for bony pain.
- Epidural analgesia with local anaesthetics with /with out narcotics can be beneficial in severe refractory pain [7]
- Inhalation of nitrous oxide can provide short term relief.

Transfusion :
Red cell transfusion is widely used in the management of SCD.50% of all SCD patients have received a blood transfusion (BT) in their life time & 5% require a chronic transfusion programme.

Indications for BT in SCD:[1]
1) Top up Transfusion -

*Aplastic crisis	* Hepatic failure
*Sequestration syndrome	* Multi organ failure
* Exchange BT	* Stroke
*Acute chest syndrome	*Priapism (role not proven)

2) Hypertransfusion/ chronic exchange transfusion
* Chronic lung or cardiac disease.
* Leg ulcer
*Recurrent VOC
*stroke

Preoperative BT is recommended for major orthopedic, abdominal & chest surgery & for neuro surgery as per various trials it is observed that intensive chronic BT can render the disease nearly quiscent Early BT preserves life.

Isovolemic exchange transfusion should be performed by automated apheresis.

Complications related to red cell transfusion: [8]

- Development of antibodies against transfused RBC.
- Secondary hemochromatosis.
- Hemolytic crisis rarely.

How to avoid this?

- Automated red cell transfusion but high cost.
- Use of blood substitutes.
- Use of polymeric hemoglobin solusions (bovine, porcine or human origin) which do not require compatibility testing.
- Hemolytic crisis due to BT should be treated with high doses corticosteroids & IV immunoglobulins.
- Iron chelating agent (Deferoxamine) / Exchange transfusion for hemochromatosis.
- Hydroxyurea: Results of 1995multicentric study in SCD revealed 1st drug proven to prevent sickle cell crisis.

Screening criteria to start Hydroxyurea. [9]

1. Age 18yrs or older.
2. Frequent painful VOC ie. 3 or more crisis / year requiring hospitalization
3. Use of accepted modes of contraception to prevent conception while on drug.

Contraindications:
Prgnancy, allergy to drug, Thrombocytopenia / Neutropenia.
Bimonthly blood counts are mandatory on hydroxyurea therapy. Dose 10-30mg / kg/day.

Bone marrow/stem cell transplantation: [10]
It is curative treatment.

Indications :
Age < 16yrs.
HLA matched sibling donor.
CNS disease.
More than two episode of acute chest syndrome.
Recurrent, debilitating painful crisis.
Manifestations caused by reduced Erythrocyte survival & increased turn over.

Anemia: 6-9gms/dl hemoglobin level is seen commonly **with homozygous SCD or those with S**ickle **thalassemia. These Hb levels are better tolerated. Folic acid supplementation in children / pregnancy** is needed to prevent megaloblastic anemia.[1]

Gall stones:
Early surgical intervention in symptomatic patient is the treatment of choice.[1]
Aplastic crisis: Parvo virus B19 is the common cause for aplastic crisis in SCD. Requires BT & antibiotics if patient febrile.

Manifestations due to VOC:[1]
Acute bone complications :
- Bone marrow necrosis.
- Dental complications.
- Osteomyelitis.
- Stress #.
- Vertebral collapse.
- Dactylitis.

Chronic bone disease:
Avascular necrosis
Chronic arthritis.
Impaired growth.

Treatment :
- Analgesia
- O2 inhalation
- Hydration
- Controlled analgesia device
- Acetaminophen (Tylenol) & NSAIDs may be useful.
- Thromboprophylaxis is recommended during period of immobility.
- 3rd generation Cephalosporin & Ciprofloxacin is the rational choice combination (required for 6weeks-3months)
- Joint replacement almost always required in a vascular necrosis.

Pulmonary disease:
Acute chest syndrome: commonest cause of death in adults. Incidence is 50% in SCD.

Causes :
Infection, Bone marrow fat embolism, Atelectasis.

Treatment :
- Main stay of treatment is BT to reduce HbS levels to <20%
- Broad spectrum antibiotics (3rd generation cephalosporin, Beta lactam with macrolide.).
- Avoid overhydration (can precipitate pulmonary edema)
- O2 inhalation.
- Respiratory support (PEEP), CPAP (continuous positive air way pressure)
- Mechanical ventilation.
- Extracorporeal membrano-oxygenation.
- Hydroxyurea may reduce 50% decrease in acute chest syndrome[1].

Chronic lung disease: chronic pulmonary damage is a Common complication.

Pulmonary hypertension is emerging major cause of morbidity/mortality.

Treatment:
- Intensification of SCD specific therapy
- BT.
- Hydroxyurea
- Sildenafil (Viagra)
- Prostaglandins & inhaled nitric oxide currently under study.

Stroke: common in children
Exchange blood transfusion followed by maintenance hyper transfusion or exchange Transfusion.[11]

Sequestration syndrome:
- BT/fluids/analgesia
- Splenectomy after 2episodes.

Sickle Nephropathy:
- Hydratation
- ACE inhibitors.
- Recombinant erythropoietin
- Rest of treatment same like renal failure.

Retinopathy:
Laser photocoagulation.

Priapism:
- Vasodilator-pseudoephedrine (Sudafed) or etilnephrine hydrochloride[1].
- Antiandrogen, cipoterone acetate for persistent recurrence.
- Sildenafil may be effective.

Leg ulcer:
- Topical dressing.
- Compression stocking.
- Zinc supplementation.
- Topical granulocyte- macrophage coloney stimulating factor (GM-CSF).
- Treatment of secondary bacterial infection

Old traditional therapy:
Myth :
use of Sodabicarb intravenous / oral in SCD crisis improves acidosis leading to relief in symptoms.
Facts :
There is no role of IV/oral sodabicarb inSCD crisis as per

literature.

Myth :

Zinc is membrane stabilizer drug used in treatment of Sickle cell disease .

Facts:

Role of zinc in treatment of leg ulcer has been found beneficial. But it's role in regular treatment of SCD is not been mentioned.

Novel therapy: [12,3]

Erythropoietin :

Can be beneficial by increasing HbF.

Butyrate :

Arginine butyrate & similar compounds have been tested in SCD in 1989 & found to increase HbF. Route of administratin is IV but half life is only 5min, so became unpopular.

Clotrimazole:

Clotrimazole & other imidazoles antimycotics specially inhibit the Ca^{2+} activated K^{+} channel thereby inhibiting Hb polymerization in SCD.

Magnesium / clotrimazole used as adjunct with Hydroxyurea.

Nitric oxide :

Inhaled gas tha has been used in neonatal pulmonary hypertension & ARDS.

Data suggested nitric oxide breathed at a concentration of 80ppm. reduces polymerization and tendency of sickle Hb.

Flucor TM, Decitabine (Decogen) hypomethylating agent Clinical trials under progress.

Gene replacement therapy :

In any event gene therapy for SCD ,the ultimate cure for the disorder is not imminent . Several other agents have shown to reduce cell adhesion in vitro & might hold clinical promise.

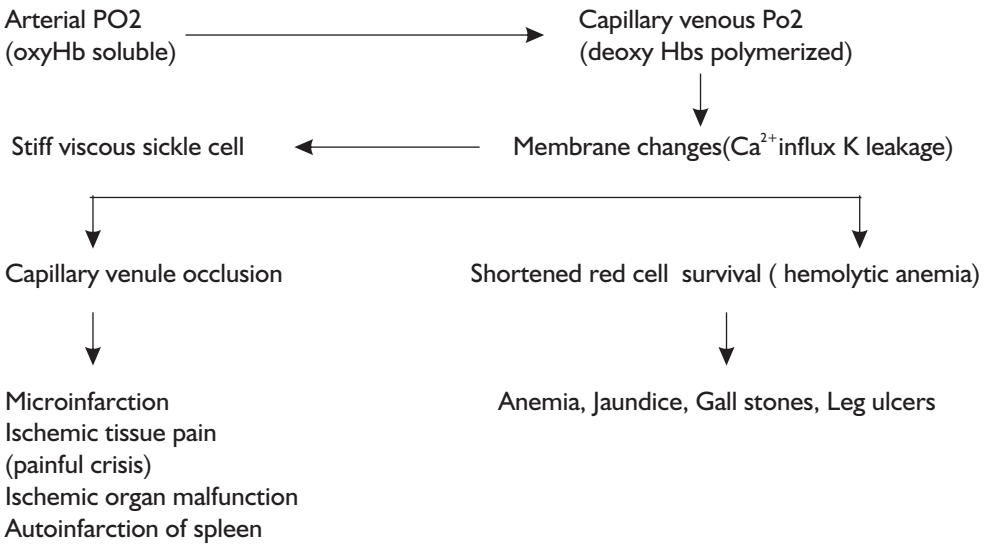
Treatment goal	Cure	Maintenance	Acute pain management
	BM Transplant	Hydroxyurea	Nitric oxide
	Gene therapy	Clotrimazole	Fluocor TM
		Magnesium pitolate	Inhibitors of endothelial adhesion
		Arginine butyrate	Anti inflammatory agents

Conclusion:

Without major breakthrough in gene therapy or BM transplantation that make these treatments applicable to a large number of patients, drug intervention will remains the major therapeutic option for sickle cell disease.

The likelihood is low of finding a " Magic bullet " medication that substantially improves SCD for all or even most patient. Prevention must be the watch word as we seek to improve the management of patient with sickle cell disease.

Fig: Pathophysiology of Sickle cell crisis



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