Safe Marriage for Prevention of Thalassaemia: Sri Lankan Experience, Appraisal of the Concepts and Challenges of Implementation

ABSTRACT Thalassaemia prevailing mostly in the Mediterranean region has gradually distributed all over the world due to migration and cross-cultural marriages. It is caused by the deficiencies of production of alpha or beta globin chain required for the stability of haemoglobin molecule. Lack or inadequacy of globin chains leads to a chronic haemolytic anaemia with a wide spectrum of phenotype ranging from asymptomatic normal life to total transfusion dependency for survival. Bone marrow or stem cell transplant and genetic therapy are not accessible to majority. Therefore, management is entirely based on regular blood transfusion and chelation of iron that accumulate due to blood transfusions. Provision of required amount of blood has become a concern in some countries while the cost escalation due to accumulation of cases due to the palliative nature of management has strained health budget, making thalassemia prevention inevitable.

Most popular and successful method of thalassemia prevention by antenatal diagnosis and abortion of affected babies is not practiced widely in many parts of the world due to legal sanctions on abortions, lack of facilities or due to self imposed restrictions based on socio-cultural or religious belief. The concept of safe marriage has been introduced in Sri Lanka. A marriage is considered safe when at least one of the partners of the couple is NOT a thalassemia carrier. Public education, voluntary screening of school leavers and providing them with a pink or a green card indicating carrier or non-carriers status has been initiated. Screening protocol and a visual aid depicting the popular concept of matching horoscope has been deployed.

The thalassemia prevention programme in Sri Lanka has two main challenges; inadequacy of screening coverage due to voluntary nature of screening and doubts about the merit of the MCV and MCH as a screening test due to the possibility of missing some E beta thalassemia carriers. The screening coverage could be addressed by incorporating thalassemia screening in to the routine practice and monitoring at risk marriages at the time of registration to offer them medical counselling. Impact of missing some of the E beta thalassemia is probably over emphasised. The rare chances of inadvertent birth of a baby with E-beta thalassemia can happen only once in several years and should not thwart screening and counselling to promote safe marriages in a country.

KEYWORDS thalassemia prevention, safe marriages, sensitivity of screening test, criteria for population screening

INTRODUCTION

Thalassaemia is widespread all over the world. Eighty nine per cent of births in the world in 71% of 229 countries have the risk of thalassemia. Annually 3,30,000 babies are born with thalassemia. Out of them 2,75,000 are sickle cell disease and 56,000 are thalassemia major. Out of 42 thousand babies born with beta thalassemia in the world 50% are born in South East Asian region. Sri Lanka the 65 thousand sq km island, middle income country situated south of India with a population of 20 million has a carrier rate of 2–4%, estimated prevalence of 2,000–3,000 cases and annual incidence of 80–100 cases out of 3,50,000 births.

Thalassemia is a group of disorders with diverse severity caused by a qualitative and/or quantitative imperfection of either alpha or beta globin chains due to genetic disorder that results in premature destruction red blood cells. Severity of red cell destruction and several other pathophysiological process
will determine the severity of the disease spectrum that expand from near normal life to premature death.6

Beta thalassemia caused by a genetic defect in the beta thalassemia gene located in chromosome 11 has a wide spectrum of disease severity depending on the rate of production of beta globin chains and many other factors affecting the disease progress.7 E-beta thalassemia is also caused by the defect in the same gene but the result of this mutation leads to reduced rate of production of a beta chains with different configuration of the haemoglobin having better capacity of oxygen transport. Beta-thalassemia and E-beta thalassemia are the two commonest forms of thalassemia in Sri Lanka and several cases of sickle cell disease also have been reported.8

Management of major forms of beta-thalassemia involves life long regular blood transfusion with heavy psychosocial and financial burden on the affected persons and families and this constant demand for blood will strain the transfusion services in the country. Blood is laden with iron leading to accumulation of toxic levels of iron within the system of thalassemia patients leading to devastating cardiac, hepatic, bone and endocrine disorders. There is no natural mechanism of removal of iron from the body. Therefore, iron chelation is an essential component of management of thalassemia that will add to cost and pain of patients and their families.

Thalassemia management is mostly confined to blood transfusion and chelation or bone marrow transplant. Bone marrow transplant is becoming popular; however, the cost and the lack of compatible related donors are restraining this approach.9 Gene therapy is at its early stages. Blood transfusion and chelation offered for all thalassemia patients is palliative leading to accumulation of cases causing escalation of costs to nations. This problem is contentious in countries striving to provide free health care for all with limited resources. Therefore, thalassemia prevention is mandatory.

**Thalassemia prevention**

Antenatal diagnoses by chorionic villi sampling of at risk pregnancies and abortion of affected fetuses have been recorded as the most successful approach in thalassemia prevention. Screening and counselling have been successful in many countries in implementing thalassemia prevention programmes such as Cyprus, Iran, China, Israel, and Jedah. However, this approach has been prohibitive in many countries due to either legal sanction of abortions, social un-acceptance due to religious belief or due to lack of resources. Therefore, alternative approaches have been considered by many countries with some success. Iran thalassemia prevention project has tried screening couples and counselling at risk couples, achieving 80% reduction of incidence of some parts of the country. Pre implantation diagnosis is a more technically advanced method of thalassemia prevention that demands technically advanced facilities for IVF technology and genetic diagnosis. In Sri Lanka, law prohibits abortions. The religious and cultural belief is likely to retain this sanction longer, in spite of constant lobbying by experts to legalise abortions for foetal pathologies. Therefore, the concept of safe marriage has been advocated as the national policy of thalassemia prevention in Sri Lanka.

**SAFE MARRIAGE**

Adopting safe marriage concept would be a voluntary process promoted by public education, monitoring and counselling at risk marriage proposals. A safe marriage is defined, as a marriage where at least one of the partners is not a thalassemia carrier. When one of the partners in a couple is not a thalassemia carrier, chance of their offspring having thalassemia major become zero. Therefore, at least one of the partners should be screened and confirmed to be a non-carrier before a couple and the family pursue on a relationship leading to marriage.

Developing a screening protocol (Fig. 1) and culturally sensitive method of dissemination of the concept supports the prevention strategy. The government provides island-wide free facilities to perform MCV and MCH using automated haematological analysers as the screening test, which is feasible and cost effective, and confirmation is done by HPLC available in four referral centres located in three provinces with highest thalassemia burden.

Those who have MCV above 80 fl and MCH above 27 pg are considered minimal chance of been thalassemia carrier and counseled, and given green card that will state that the card holders marriage with any body will have minimal risk of having offspring with thalassemia.

Those who are having MCV less than 80 fl or MCH less than 27 pg are given iron 6 mg/kg/day for a period of 3 months after evaluation by a qualified medical officer. The tests will be repeated at the end of the iron therapy, and if the MCV and MCH have recovered they would be given green cards and counselled accordingly.

Those who persist to have MCV less than 80 fl and MCH less than 27 pg would be referred for HPLC and once the thalassemia carrier status is confirmed they would be given a red card indicating that they should select a partner with a green card.

The counselling process is facilitated by the concept of horoscope entrenched by many Asian cultures. Pictorial depiction helps primary care workers to discuss the options and risks (Fig. 2).

This population-based intervention needs stringent monitoring to steer project for its success. Screening coverage among adolescents and adults ready for marriage, number of at-risk marriages at the time of registration and number of at-risk pregnancies and incidence are possible indicators. However, acceptance of the policy has not produced expected results so far due to lack of monitoring. Therefore, this article intend to appraise the concept of safe marriage based on Wilson and Jungner.
Prevention of thalassaemia

Fig. 1 National thalassemia screening protocol of Sri Lanka.

If the MCV equal or less than 80 fl or MCH equal or less than 27 pg
- Treat with iron for 3 months after evaluation by a qualified medical officer
- Repeat full blood count to check red cell indices
- If the repeat MCV more than 80 fl or MCH more than 27 pg
- Perform HPLC
- If thalassemia carrier state is not confirmed refer for haematologists opinion
- Issue a pink card if carrier state is confirmed
- Issue a green card
- Offer counseling based on thalassemia horoscope shown in the figure one

Fig. 2 Thalassemia horoscope; an aid to decide whether a proposed couple is safe or at risk with regards to risk of having offspring with thalassemia*.

*Box number 2 and 4 is highlighted to indicate that those who select a known thalassemia carrier as his/her partner for the marriage should check their blood by HPLC to confirm that they are nor thalassemia traits.
The condition sought should be an important health problem.

There should be an accepted treatment for patients with recognised disease.

Facilities for diagnosis and treatment should be available.

There should be a recognisable latent or early symptomatic stage.

There should be a suitable test or examination.

There should be an agreed policy on whom to treat as patients.

The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

Case-finding should be a continuing process and not a “once and for all” project.

The condition sought should be an important health problem. The condition is not without implications. Evaluating the population-based screening of thalassemia carriers is evaluated based on Wilson and Jungner principles.

1. The condition sought should be an important health problem. Thalassemia is an important condition in the society due to the life-long pain and suffering to the patient and the family and the costs involved to the government and family.

2. There should be an accepted treatment for patients with recognised disease. Here the thalassemia carrier status is the disease. Once a thalassemia carrier is detected they have several options: (1) they can select a partner who is not a carrier; (2) they can plan ante-natal diagnosis and abortion of affected fetus; (3) they can explore the possibility of pre-implantation diagnosis and (4) plan the family.

3. Facilities for diagnosis and treatment should be available. Screening using FBC and based on MCV and MCH is available free of charge for all.

4. There should be a recognisable latent or early symptomatic stage. Thalassemia carriers have a distinct latent period; time from birth to the time of recognising their own son or daughter becoming pale around 6 months of age.

5. There should be a suitable test or examination. The screening test, MCV and MCH, are reliable and sensitive enough for screening for thalassemia trait. The possibility of missing some of the E-beta thalassemia carriers has been considered a problem and the option of performing HPLC as the screening test has been suggested. The perfection of the sensitivity and its implications on the proposed thalassemia prevention is discussed later in this article.

6. The test should be acceptable to the population. Acceptability in the society depends on the understanding of the society. Population education and establishing screening as the norm of the society will help to eliminate possible stigma. The benefit of screening that will be provided to 2–4% of the population of thalassemia carrier is invaluable. Until a screening test is performed no body could be certain about his or her thalassemia status. Therefore, screening should be acceptable for the entire society.

7. The natural history of the condition, including development from latent to declared disease, should be adequately understood. The natural history of the condition is well understood. As the condition is the thalassemia trait, the natural history is that the person with the condition will have the 2–4% risk of marrying another carrier and if they do so they have the 25% risk of producing a child suffering with thalassemia at each conception.

8. There should be an agreed policy on whom to treat as patients. The screening policy should be within the society. The best would be to test adolescents well before they select their prospective partners for marriage. The agreed policy regarding thalassemia traits would be to counsel them and offer a range of options mentioned above.

9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. There are many studies that demonstrate the cost benefit of thalassemia screening. Management of one thalassemia patient in Sri Lanka estimated to be 15 million rupees. The cost of voluntary screening would be minimal, as the tests would be performed within the existing health-care delivery system. The expenditure will involve provision of reagents and maintenance of machines.

10. Case finding should be a continuing process and not a “once and for all” project. Thalassemia screening should be an on going process in the society coupled with population and school education system, counselling and monitoring.

Based on Jungner’s principles, the screening criteria and discusses some of the controversies involved in implementation of this prevention strategy.
for thalassemia carriers does fulfill all these criteria. The need for screening has been recognised; objective and the target population are well defined. Effectiveness of thalassemia screening is established. Thalassemia screening could be integrated in school curriculum, public education and counselling. The systems have the capacity for testing, counselling and programme monitoring for quality assurance. The potential risks of screening; social stigma should be addressed logically.

**Challenges of implementing the strategy**

The slow progress and lack of much needed political support in implementing this theoretically sound concept deserve an appraisal. An elusive sense of violation of rights of thalassemia carriers is discussed by some while others talk about the right of those who are not carriers. The cost of carrier screening is not considered a major problem. Most challenging scientific reservation is regarding the sensitivity of MCV and MCH with regard to screening for E-beta thalassemia.

**Rights of thalassemia carriers and others in the society**

Thalassemia carriers have a hidden risk of having offspring with manifest thalassemia disease. Therefore, screening will be beneficial for carriers of thalassemia. Screening the entire population would be essential as there is no external physical signs to indicate thalassemia carrier status. On the other hand, soliciting the carrier status of proposed marriage partner should be established as a routine practice to safeguard the rights of thalassemia carriers.

**Sensitivity of the screening test**

Even though MCV and MCH are 100% sensitive to detect beta-thalassemia carriers, the possibility of missing small percentage of E-beta carriers during pregnancy has been reported. In Sri Lanka, 40% of thalassemia would be E-beta type. Therefore, a concern about the possible failures in the programme is highlighted and doubts about the safety of a safe marriage have been raised.

However, it is important to evaluate the possible outcomes of the small percentage of E-beta thalassemia carriers who may fail to detect at the screening due to MCV and MCH values falling within normal range. In a society like Sri Lanka E-thalassemia carrier incidence of 0.5% and missing small percentage of that group would end up as even smaller E-thalassemia carriers in the society contributing for the genetic pool. Such a small number would cause only an insignificant risk. Therefore, possibility of missing small percentage of E-thalassemia carrier should be ignored.

**Doubt about acceptance of the entire population**

Thalassemia screening will have exponential impact on the society. If we could screen 50% of the population outcome would be 75% reduction of incidence rather than 50% reduction of incidence. Considering the Sri Lankan scenario, after screening 50% of the population incidence of 80 births per year would be reduced up to 20 births per year. Prediction of the outcomes of genetic disorders is complex and best evaluated using the Hardy-Weinberg calculation (Fig. 3).

If we consider a situation of detecting 50% of the carriers from a population with 4% carrier rate the population should behave like 2% carrier rate. Accordingly 4% carrier rate will contribute to 0.4 affected babies per 1,000 births. In Sri Lanka, with 3,00,000 birth per year expected total number of births would be 120 cases. When population screening reduces the effective genetic pool to 2% expected number of affected births would be only 0.1 per thousand; only 30 affected babies per year. This reduction of incidence from 120 per year down to 30 cases per year will help to minimise predicted caseload of 2,000 and huge cost of care extend up to 5% of entire health budget of Sri Lanka.

**CONCLUSION**

Thalassemia screening should not be delayed pending evolution of more precise methods in any society. Methods available at present can offer significant...
benefits to the society. However scientists should strive to develop better solutions that are cost effective and acceptable to the society.

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