Splenectomy In Management Of Thalassemia Major - A Boon For The Little Angel.
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Citation

Abstract
Thalassemias are one of the most common inherited hematological disorders. Today thalassemia remains a major health problem throughout the world. It is seen practically all over the world. This study was conducted on patients admitted and operated at Guru Gobind Singh Hospital, Jamnagar in various surgical units between June 2007 and March 2009. This is a study of 50 cases operated on elective basis. The main indication for splenectomy was higher blood transfusion requirement. After splenectomy, a dramatic increase in the Hb level occurred. All the patients had Hb >8g% with an average of 10g%. Most of the patients had a decrease in blood transfusion requirement with 96% of patients having blood transfusion requirements <150ml/kg/year. The frequency of blood transfusion requirement also decreases. Quality of life improved after splenectomy because of improved hemoglobin. The patients felt less fatigue and were able to carry out their daily activity in a better way. Decreasing blood transfusion requirement helped them reduce the hospital visit. The cost of iron chelation therapy was also reduced. Most patients had improved school attendance and better academic performance. Their family members also benefited due to decreased hospitalization. Overall, quality of life of the entire family improved and thus it proved to be a boon for the patient and his family. So, we strongly recommend that, as splenectomy improves quality of life, surgery should not be withheld if indicated.

INTRODUCTION
The spleen was regarded by Galen as “an organ of mystery”, by Aristotle as unnecessary, by Pliny as an organ that might hinder the speed of runners and also as an organ that produced laughter and mirth, a concept reasserted in the Babylonian Talmud.

Although posttraumatic splenectomy may have been performed by military surgeons earlier, the first recorded splenectomy was performed by for splenomegaly on a 24-year-old Neapolitan woman in 1549 by Adrian Zacarelli. However, survival was not achieved. In 1866, Sir Thomas Spencer Wells gave an account of the first successful splenectomy in England.

Thalassemia results from a wide variety of mutations of the genes which code for hemoglobin synthesis leading to reduced or absent synthesis of globin chains.

The spectrum of the clinical manifestation of beta-thalassemia varies widely. One end of the spectrum is the serious homogenous form or thalassemia major presenting in early infancy with progressive pallor, splenomegaly, bony changes and, if untreated, invariably fatal in first few years of life.

The other end of the spectrum is the heterogeneous form or thalassemia minor with which the patient can live practically a normal life without much disability except for mild persistent anemia.

In between these extremes are forms with varying degree of clinical manifestations of anemia, splenomegaly and bony changes that can maintain life fairly comfortable and are known as thalassemia intermedia.

The mainstays of diagnosis under surgical aspects are peripheral smear, hemoglobin electrophoresis and abdominal ultrasonography to rule out associated gall stones.

In thalassemia patients, packed cell transfusions have improved survival but transfusions also have their own complications of iron overload and so iron-chelating agents are given concurrently with transfusion.

Spleen involvement is known to occur in thalassemia. The spleen is most commonly affected in form of splenomegaly because of excessive destruction of abnormal RBCs, extramedullary hematopoiesis and transfusional overload.
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Splenomegaly further increases transfusional requirement. So these patients benefit from splenectomy.

Other modalities of treatment include bone marrow transplantation, peripheral blood stem cell transplantation, cord blood stem cell transplantation, gene therapy and stimulation of fetal hemoglobin synthesis.

AIMS AND OBJECTIVES

The aim of this retrospective study carried out on thalassemic patients operated for splenomegaly between June 2007 and Sept. 2009 was

1. To determine the preoperative blood requirement and to know the efficacy of splenectomy in reducing postoperative blood requirement.

2. To identify the efficacy of prophylactic vaccination in reducing the incidence of post-splenectomy infection.

3. To identify the morbidity of splenectomy with special reference to opportunistic infection.

4. To evaluate quality of life after splenectomy.

THALASSEMIA IN INDIA

The first case of thalassemia in India was reported by Mukharji in 1938 in a Bengali boy and later cases of thalassemia had been reported all over India. The frequency of the thalassemia trait ranges from 3-15% in Northern and Western India to 1-2% or less in South India.

A higher incidence has been noticed in Bengal, U.P. Madras, Punjab, Gujarat, Bihar, Orissa and Kerala.

A higher frequency of the carrier state is also noted in certain communities, viz. Sindhis, Kutchis, Lohanana, Bhanusalis, Punjabis, Mahars, Agris, Goud and Gowads.

MOLECULAR BASIS OF BETA-THALASSEMIA

The deficiency or absence of β-chains that characterize beta-thalassemia could potentially result from defects affecting transcription, RNA processing or RNA translation, or modifying codons into “nonsense” codons that leads to premature termination of translation.

Thalassemia mutations which cause a complete absence or production of normal β-globin chains are called β°-thalassemia and those which cause reduced synthesis are known as β⁺-thalassemia.

MATERIAL AND METHODS

This study was conducted on patients admitted and operated at Guru Gobind Singh Hospital, Jamnagar, in various surgical units between June 2007 and March 2009. This is a study of 50 cases operated on elective basis.

SELECTION OF CASES

EXCLUSION CRITERIA

- Patients with ages <5 years were excluded from our study as in these patients the spleen still plays a major immune role.
- Patients with associated gall stones were excluded from our study.
- Patients with associated other disorders were also excluded.

CLINICAL MANIFESTATIONS

- Clinical manifestations of thalassemia major usually become apparent during the second six months of life and diagnosis is always evident by two years of age.
- Infants present with progressive anemia, failure to thrive, irritability, abdominal swelling, jaundice and bony changes.
- The further development of thalassemic features depends entirely on age of the patients and nature of treatment they received.
- Inadequately transfused or untreated patients develop typical features of thalassemia.
- There are prominent frontoparietal bossing and prominent zygoma, protuberant teeth and overgrowth of maxilla.
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Figure 1
Fig. 1. Typical thalassemic face

- Prominent zygoma leads to depression of nasal bridge and mongoloid slant of eyes giving a mongoloid appearance.
- The skin shows dirty brown pigmentation due to iron deposition.
- A thalassemic child has extremely poor musculature and little fat due to hypercatabolic state.
- The abdomen becomes protuberant due to enlargement of spleen and liver.
- Coagulopathy may result from impaired hepatic synthesis of clotting factors.
- These children are prone to recurrent infections, gall stone formation, pathological fractures and chronic non-healing leg ulcers.
- Inadequately treated patients may develop poor cardiac and hepatic function due to hemosiderosis.
- At the time of puberty, a thalassemic child may fail to grow further in height and show lack of development of secondary sexual characteristics.
- Endocrine dysfunction like hypothyroidism, panhypopituitarism and diabetes mellitus has been documented in some thalassemic cases.
- Thalassemic patients may succumb to death during the second decade of life due to cardiomegaly, chronic refractory cardiac failure, arrhythmia, cirrhosis, recurrent infections and progressive cachexia.
- The average survival of untreated patients of thalassemia major is <1 year and more than 80% die in first five years of life.
- Aggressive transfusion therapy permits near-normal growth and development during childhood but produces organ damage due to massive iron overload if not accompanied by iron chelation.
- A patient requiring aggressive transfusion definitely benefits by splenectomy because splenectomy reduces transfusion requirement.

DIAGNOSIS
1. Hemoglobin: reduced, usually between 2-6 g/dl.
2. Red cells: In the range of 1-3 million /mm³.
3. Reticulocyte count: elevated, may be up to 10%.
5. Haematocrit: reduced.
   MCV : 48-72 fl
   MCHC : 23-32g/dl
6. Peripheral smear:
   RBC series: Hypochromia, microcytosis, anisocytosis, poikilocytosis, leptocytosis, target cells, polychromasia, normoblastemia, Heinz bodies.
7. Fetal hemoglobin: raised up to 50-100%.
8. HbA₂: 1-2%
9. Bone marrow : BM is hyperplastic with erythroid hyperplasia with a number of stippled erythroblasts and sideroblasts. Hemosiderin deposit in the bone marrow increased.
10. Red cells osmotic fragility: increased
11. Serum iron concentration: increased
12. Serum iron binding capacity: reduced
13. S. bilirubin: elevated moderately between 1-3 mg/dl.
14. Urine urobilinogen: moderately increased.
15. S. protein S. albumin: decreased S. beta-globulin and gamma-globulin: decreased.
16. Hb electrophoresis Major band of HbF seen HbA\textsubscript{2}: HbA ratio is 1:2 (normal is 1:40)
17. Skeletal changes:
   - X-ray of the skull shows thickening of frontal bone with prominent bossing.
   - The thickened membranous bones of the skull do not expand adjacent to sutures leading to HOT CROSS BUN configuration.

**Figure 2**
Fig. 2. Skeletal changes

- The skull at first has a granular appearance but later perpendicular bone trabecula appear giving classical HAIR ON END appearance.
- Marked overgrowth of the maxilla results in malocclusion of teeth and prominence of the molar eminence.
- Metatarsals and phalanges are expanded producing a rectangular and then convex shape.
- Premature fusion of epiphysis of long bones is common in patients older than 10 years.
- Marked osteoporosis and cortical thinning may predispose to pathological fractures.

**MANAGEMENT**
Therapeutic strategies used in the management of transfusion-dependent patients with thalassemia have greatly improved during the past two decades.

Mainstays of treatment consist of
1. Compensation of anemia by RBC transfusion
2. Removal of iron with an iron-chelating agent
3. Treatment of complications
4. Correction of hemopoiesis by bone marrow transplantation
5. Prevention of disease by antenatal diagnosis and genetic counseling
6. Pharmacological measures to increase gamma-chain synthesis
7. Gene replacement therapy
8. Immunization
9. Diet

Treatment of thalassemia places an immense burden on the family and society.

The mortality and morbidity are high in our country due to delay in initiation of treatment, non-compliance, non-availability and unaffordability of drugs and blood.

Development in the management of thalassemia can be summarized in decades.

1960s: Transfusion therapy to correct hypoxia
1970s: Chelation therapy to reduce iron overload
1980s: Bone marrow transplantation to cure disease

(A) **TRANSFUSIONS**

Aim of the therapy is to correct anemia and to suppress endogenous marked but ineffective erythropoiesis, thereby preventing marked skeletal changes or splenohepatomegaly.

The current recommendation is to maintain a mean Hb level of 12 g/dl. This can be achieved by not letting the Hb fall below 9.5-10 g/dl.

The following types of prepared blood are available in India:
Fresh whole blood
Stored whole blood
Packed red cells
Triple-washed packed cells
Frozen (re-constituted) red cells
Neocytes
Filtered blood

(B) IRON CHELATION

Although iron is vital to health, excessive amounts in the body are highly toxic. Iron overload is a feature of a number of pathological conditions; it is an inevitable and serious consequence of long-term transfusion therapy for anemia. Iron chelators complex with iron to reduce the labile iron pool or labile intracellular iron within cells, non-transferrin-bound iron outside cells and iron overload in the form of ferritin and hemosiderin deposits in different organs. They effectively prolong life of transfusion-dependent thalassemics and also improve the quality of life.

Iron overload occurs from two sources:
- Due to transfusion of blood
- Due to enhanced gastrointestinal absorption of iron

Each unit of packed red cells provides 200-250mg of iron and by the age of 10 years, about 20-30g of iron is deposited in the various organs of the body.

Following are the iron chelating agents shown to be effective clinically with acceptable toxicity.

IRON CHELATORS

As of today, there are 3 important chelators. Of these, one i.e., desferrioxamine is given subcutaneously or intravenously while the other two i.e., deferiprone and deferasirox are oral compounds.

Splenectomy should be delayed till the age of 5 year as there is a greater risk of sepsis. ¹⁴

All the thalassemic children needing splenectomy should receive pneumococcal vaccine, H. influenza vaccine and meningococcal vaccine 4 weeks prior to treatment.

Penicillin prophylaxis should be continued lifelong and any episode of infection should be treated as splenectomized patients are at an increased risk (200 times) of getting infection as compared to normal children.

Aspirin has been advocated to prevent pulmonary microemboli owing to platelet aggregation due to thrombocytosis after splenectomy.

METHOD OF SPLENECTOMY

OPEN SPLENECTOMY

Before splenectomy, bringing the patient to a relative normal status should pay better than an operation straight away.

Before operation, it is advisable to anticipate the blood loss and to prepare a cross-matched transfusion.

Before the operation is commenced, it is important to pass a nasogastric tube in all cases of splenectomy and to aspirate all contents present to ensure the stomach is empty and flaccid throughout the operation, as if the stomach is full, it will push the spleen into a very inaccessible position and render intraabdominal manipulation difficult, and this may be the cause of stomach injury during ligation of the upper portion of the gastroplenic omentum.

INCISIONS

The various types of incisions available for splenectomy are as follows:
- Left upper paramedian
- Midline epigastric
- Left subcostal
- Abdominothoracic
- Left vertical muscle splitting
PROCEDURE
As soon as the abdomen is opened, the main splenic artery is identified at the superior border of the pancreas.

The splenic artery is ligated so that the spleen becomes shrunken, blood loss is prevented and further handling will be easier.

The spleen is retracted medially and the splenocolic, lienorenal and splenophrenic ligaments are cut.

The gastroplenic ligament is identified, the short gastric vessels are ligated, and after retracting the stomach on right side, the gastroplenic ligament is cut with particular care to avoid injury to the greater curvature.

Both the splenic artery and splenic vein are ligated and transfixed flush to the splenic hilum with special care to avoid injury to the pancreatic tail.

The specimen is removed.

Hemostasis is achieved taking particular care at the splenic hilum, diaphragmatic surface and colonic surface.

An accessory spleen is searched for. The usual sites of accessory spleens include hilum of spleen, gastrocolic ligament, tail of pancreas, greater omentum, greater curvature of stomach, splenocolic ligament, small and large bowel mesentery and pancreaticosplenic ligament.

Laparoscopic Splenectomy
Laparoscopic splenectomy is indicated only in sickle-cell anemia, immune thrombocytopenic purpura and small- and medium-size hypersplenism.

In thalassemia major and hereditary spherocytosis with huge sized spleens, laparoscopic splenectomy is not indicated.

(D) BONE MARROW TRANSPLANTATION
(E) PERIPHERAL BLOOD STEM CELL TRANSPLANTATION
(F) CORD BLOOD STEM CELL TRANSPLANTATION
(G) GENE THERAPY
(H) STIMULATION OF FETAL HAEMOGLOBIN SYNTHESIS

OBSERVATION
The present series of 50 patients at GGH, Jamnagar, was observed to have the following details:

**Figure 3**
Table 1. Age-wise distribution

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>No. of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10</td>
<td>36</td>
<td>72%</td>
</tr>
<tr>
<td>11-15</td>
<td>10</td>
<td>20%</td>
</tr>
<tr>
<td>16-20</td>
<td>4</td>
<td>8%</td>
</tr>
</tbody>
</table>

The maximum number of patients was observed to be in the age group 5 to 10 years (72%). The youngest was 5 years old and the oldest was 18 years old.

**Figure 4**
Table 2. Sex-wise distribution

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34</td>
<td>68%</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>32%</td>
</tr>
</tbody>
</table>

There was a definite male preponderance in the above series (68% males).

**Figure 5**
Table 3. Symptom-wise distribution

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lump</td>
<td>50</td>
<td>100%</td>
</tr>
<tr>
<td>Pain</td>
<td>40</td>
<td>80%</td>
</tr>
<tr>
<td>Weakness</td>
<td>36</td>
<td>72%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>20</td>
<td>40%</td>
</tr>
</tbody>
</table>

The patients presented with a variety of symptoms which were meticulously studied.

A fixed combination of lump, pain, weakness and jaundice was noted here. A lump was present in 100% of our patients while there was pain in 80%.

**Figure 6**
Table 4. Distribution according to pre-operative Hb (g%) level

<table>
<thead>
<tr>
<th>Pre-operative Hb (g%)</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 - 8 gm%</td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td>8 - 10 gm%</td>
<td>28</td>
<td>50%</td>
</tr>
<tr>
<td>10 - 20 gm%</td>
<td>4</td>
<td>8%</td>
</tr>
</tbody>
</table>

Most of our patients (92%) had a preoperative Hb below
Most of our patients (88%) had a preoperative blood transfusion requirement of 250-300 ml/kg/year with an average of 279 ml/kg/year.

Per-operatively, the patients had no major complications because all of our patients had undergone elective surgery and meticulous care was taken regarding hemostasis.

Wound infection was the only post-operative complication and was found in 4 patients (8%).

Wound infection was rarer with left paramedian incision (5%). This is because muscles are generally split rather than cut. With subcostal incision, the muscles are cut and thereby time for opening and closure is prolonged. Hence the higher rate of infection.

Postoperatively, all the patients showed improvement in their Hb levels; all the patients had an Hb above 8%.
The average Hb postoperatively was 10g%; this improvement of postoperative Hb was sustained over the follow-up period (6 months to 2 years).

**Figure 12**
Table 10. Distribution according to post-operative hospital stay.

<table>
<thead>
<tr>
<th>Post-operative hospital stay</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 days</td>
<td>42</td>
<td>84%</td>
</tr>
<tr>
<td>10-15 days</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>15-20 days</td>
<td>6</td>
<td>12%</td>
</tr>
</tbody>
</table>

In our study, most of the patients (84%) were discharged within 5 to 10 days after the operation, with an average of 9 days.

**Figure 13**
Table 11. Distribution according to post-operative blood transfusion (packed cell) requirement.

<table>
<thead>
<tr>
<th>Post-operative Blood Transfusion (Packed Cell) Requirement (ml/kg/year)</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-150</td>
<td>48</td>
<td>96%</td>
</tr>
<tr>
<td>151-200</td>
<td>2</td>
<td>4%</td>
</tr>
</tbody>
</table>

Most of the patients had a decrease in blood transfusion (BT) requirement, with 96% of patients having a (BT) requirement below 150ml/kg/year.

The frequency of BT requirement was also decreased.

**Figure 14**
Table 12. Distribution according to complications on follow-up.

<table>
<thead>
<tr>
<th>Follow-up 6 months to 2 years</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent URTI</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td>OPSI</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Post-operative abscessions</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Six patients (12%) suffered from recurrent URTIs during follow-up. All of them were probably viral in origin and not bacterial; none of the patients suffered LRTI or pneumonia and none of our patients had overwhelming post-splenectomy infection (OPSI), thereby indicating the efficacy of pre-operative vaccination.

**DISCUSSION**

The clinical study was undertaken at GGH, Jamnagar a total number of 50 patients were considered who were admitted in GGH with thalassemia major with various complains and operated (splenectomy) during the years 2007-2009.

In our series, the patients were aged between 5 to 18 years with an average of 9 years. In a similar study conducted by Chaudhary et al., the age range was 2 to 6 years with an average of 5 years. The reasons for the older age of our patients probably include delayed referral for splenectomy and unwillingness of patients for major surgery.

In our series, the male-to-female ratio was approximately 7:3, a finding similar to Bhattacharya who had a ratio of 6:4. Definite male preponderance has been noted by various other authors.

In our series, abdominal lump and pain were the most common presenting symptoms. A similar finding was noted by Bhattacharya who reported lumps in almost 90% of cases.

The major indication for splenectomy in our patients is higher blood transfusion requirement. In our series, the minimum pre-operative blood transfusion requirement was 250ml/kg/year and the maximum was 320ml/kg/year, with an average of 279ml/kg/year. In a similar study by Chaudhary et al., the blood transfusion requirement was 180-200ml/kg/year. The frequency of blood transfusion in our study was more than 1 unit (300 ml) in 15 days whereas in the study by Chaudhary et al. it was 1 unit in 1 month. Both of these findings were probably due to delayed referral and unwillingness of parents for major surgery.

A left paramedian incision was most commonly used in our study (80%); this is the safest and most effective incision considering good exposure and easy closure. Good exposure allows for easy and early identification of the splenic artery and better space for mobilization of the spleen and it also helps to prevent injury to surrounding organs. The time taken for closure is also reduced and so overall wound complications are reduced. Schwartz et al. have advocated thoraco-abdominal incision, but opening of two cavities definitely increases mortality. So recent literature has advocated left paramedian incision.

Overall, approximately 8% of patients suffered wound infections; none of our patients had septicemia or other
infective complications. This finding is similar to that by Chaudhary et al. who had no cases of septicemia or meningitis.

After splenectomy, our patients were followed up for a period ranging from 6 months to 2 year. The patients were followed up at 15-day intervals for one month, then at monthly intervals for six months and then six-monthly. All patients had CBC on follow-up. All patients showed an improvement in the Hb levels from an average of 8.7g% preoperatively to 10g% postoperatively. These findings were similar to those of Sedwick et al.\(^\text{18}\)

A longer follow-up is required for a still better evaluation of the long-term efficacy and late complications after splenectomy.

**CONCLUSION AND SUMMARY**

This was a study of 50 patients having thalassemia major operated for splenectomy between June 07 and September 09.

From this study we concluded that

**Figure 15**

Fig. 3. Result of splenectomy!! (courtesy: www.the hindu.com)

Thalassemia major is a quite common condition affecting mainly pediatric age group patients. It can affect males as well as females.

Thalassemia patients do suffer from splenomegaly because of extramedullary haematopoiesis, increased RBC destruction, repeated blood transfusions and iron overload.

Splenectomy is indicated if there is increasing blood transfusion requirement, gross splenomegaly causing hypersplenism or if there are pressure symptoms on surrounding organs.

Left-paramedian incision offers good exposure and is easy to close with minimum chances of wound infection.

Splenectomy definitely reduced blood requirements from 279 ml/kg/year preoperatively to less than 150 ml/kg/year and improved Hb levels. These improvements are sustained over a prolonged period of time.

Preoperative vaccination definitely needs to prevent postoperative OPSI and other infective complications.

Although strong clinical evidence is lacking, routine use of penicillin also helps to reduce postoperative infective complications.

Thalassemia intermedia and thalassemia minor are generally more benign conditions and splenectomy is rarely required.

Quality of life improved after splenectomy because of improved hemoglobin. Patients felt less fatigue and were able to carry out their daily activity in a better way. Decreasing blood transfusion requirement helped them reduce the hospital visits. The cost of iron chelation therapy was also reduced. Most patients had improved school attendance and better academic performance. Their family members also benefited due to decreased hospitalization. Overall, quality of life of entire family improved.

So, we strongly recommend that, as splenectomy improves quality of life, surgery should not be withheld if indicated.

This research work also conveys a very clear message to the thalassemia society, that the society should encourage the members to know the advantages of splenectomy in patients with thalassemia major and awareness should be raised that splenectomy at proper time with proper indication and with proper preparation drastically improves the quality of life of the patient as well as the family, reduces the disease-specific economic burden over the family, improves physical, mental and social aspects of quality of life of the patients and thus
improves significantly the emotional attachment of the patient with his life. It boosts the ‘NEVER SAY DIE’ spirit of the parents and the patient with thalassemia major. In nutshell, the thalassemia society should develop the ‘TOMORROW NEVER DIES’ attitude to gain a positive vision in thalassemia-struck families for splenectomy to improve the future prospects of the precious life of the patient and his family.

References

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