

## Original Research Article

# A prospective study of postoperative outcome following splenectomy in immunocompromised thalassemia patient with special reference to CD4 count

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### ABSTRACT

**Background:** Thalassemia are inherited blood disorders that can result in the abnormal formation of hemoglobin. Splenectomy is indicated in the transfusion-dependent patient when hypersplenism increases blood transfusion requirement and prevents adequate control of body iron with chelation therapy. Ninety percent of recipients transfused with HIV antibody-positive blood are found to be HIV infected at follow-up. Prevailing literature on effects of splenectomy on CD4 count suggests that splenectomy causes an abrupt and prolonged increase in CD4 cell count. The aims and objectives this is an Institution based prospective observational study with the aim to observe postoperative outcome in immunocompromised thalassaemic patients following splenectomy, postoperative outcome following splenectomy in a patient with low CD4 count and to analyze the effect of CD 4 count if any on different patients in terms of wound infection, chest infection, urinary tract infection or infection at any other site.

**Methods:** The study included twenty immunocompromised thalassemia Patients attending in Pediatric Surgery OPD and admitted to Paediatric Surgery department of Medical college and hospital Kolkata with splenomegaly and HIV infection for splenectomy, between January 2015 to December 2016. Simple comparative analysis of gathered data was used to evaluate postoperative outcome and the preop and the post op CD4 count levels of splenectomised thalassaemic patients.

**Results:** Most patients in this study were in the (3-8) years age group and all are HIV positive patients with thalassemia. In this study author found there was increased CD4 count after splenectomy and postoperative period one patient developed postoperative oral candidiasis.

**Conclusions:** HIV-infected thalassaemic patients on ART can now safely undergo major splenectomy surgery with encouraging results and in patients with a low CD4 count, there is no relation of CD4 count and splenectomy outcome.

**Keywords:** CD4 count, Human immunodeficiency virus infection immunocompromised, Splenectomy, Thalassemia, Transfusion in thalassemia patients

### INTRODUCTION

The commonly adopted criteria for splenectomy in a thalassemia patient is a blood consumption greater than 50% above the mean requirement i.e. more than 200-250

ml/kg/year of pure red cells, to maintain a pre-transfusion Hb around 10 g/dL.<sup>1</sup> In addition splenectomy is now known to cause severe, sometimes lethal, infections and increase the risk of thrombosis. In the past, splenectomy was performed shortly after diagnosis because the spleen

soon became very large and severe hypersplenism may result.

Neutropenia, thrombocytopenia and mechanical encumbrance were not rare. The introduction of regular transfusions has resulted in a decrease in extramedullary erythropoiesis and has also decreased the number of nonfunctional red cells that needed to be destroyed in the splenic tissue.<sup>2</sup>

Splenectomy increases the hypercoagulability state, by permitting the circulation of greater numbers of altered membranes, and by increasing the number of platelets. Splenectomy has been reported to alter inconsistently the CD4 lymphocyte numbers in patients infected with the Human Immunodeficiency Virus (HIV).<sup>3,4</sup>

A recent observational study found that the rates of iron overload related organ damage in splenectomies patients were comparable with those who had not been splenectomised.<sup>5</sup> There is paucity of literature regarding CD4 count and post-operative outcome in HIV patient.

Prevailing literature on effects of splenectomy on CD4 count suggests that splenectomy causes an abrupt and prolonged increase in CD4 cell count.<sup>6,7</sup> However in this study the 3 patients who had splenectomy who were all HIV positive had a marked fall in CD4 count by 1<sup>st</sup> POD, with a small rise between 1<sup>st</sup> to 7<sup>th</sup> POD. This may be due to other stresses as all these patients required every five days interval blood transfusion. It could be also due to the fact that CD4% as opposed to CD4 cell count is more accurate in assessment of post splenectomy patients.

Splenectomy has been reported to alter inconsistently the CD4 lymphocyte numbers in patients infected with the Human Immunodeficiency Virus (HIV). There was a significant increase in the mean CD4 numbers following splenectomy. No significant difference was observed in the percentage CD4 lymphocytes. One patient developed oral candidiasis (CD4 960/microliters), and in one patient a 7 kg weight loss was associated with recurrent mouth ulcers (CD4 680/microliters). Author conclude that the total CD4 count increases significantly after splenectomy.

Female child showed a greater CD4 cell reduction than male child in this study unlike in a study by Wichmann where men suffered longer lasting depression of CD4 than women of about 5 days while the depression in the women the CD4 depression lasted only 2 days.<sup>8</sup>

In a study by Ramon, CD4 drop persisted for only two days after which there was a rise. This was independent of the type of operation done.<sup>9</sup> The reduction is said to be because stimulation and production of T-cells is reduced in the immediate post-operative period causing a CD4 drop. The rise in CD4 later occurs when stimulation and production increase.

The aim and objective were to observe Postoperative outcome in immuno compromised thalassemic patients following splenectomy, Postoperative outcome following splenectomy in a patient with low CD4 count and to analyze the effect of CD 4 count if any on different patients in terms of wound infection, chest infection, urinary tract infection or infection at any other site.

## METHODS

The study was carried out in Department of Pediatric Surgery Medical College and Hospital, Kolkata, in collaboration with institute of Hematology and Transfusion Medicine, Medical college Hospital, Kolkata. The study population comprised of immune compromised thalassemic Patients attending in Pediatric Surgery OPD and admitted to Pediatric Surgery department of MCH with splenomegaly and HIV infection for splenectomy, between January 2015 to December 2016. Twenty patients with immune comptonization and splenomegaly admitted to pediatric surgery Department of MCH were included. The inclusion criteria were all cases thalassemic immune compromised patients with splenomegaly undergoing splenectomy and the exclusion criteria included Thalassemia patient without immune compromise status, Hepatitis B and C virus infection, Abnormal PT, APTT, INR, unfit for Anaesthesia. This is an Institution based prospective observational study. The study Parameters included wound infection wound discharge, swelling and tenderness, drain site infection, chest infection, IV canula site infection, urinary tract infection, infection to any other site, Serum electrolytes, LFT, PT, APTT, complete hemogram, time taken for returning of the normal intestinal peristalsis sound.

The study tools used were informed consent from their guardians or patients, proforma for relevant history and clinical examination, weight machine, Measuring tape, BP machine, stethoscope, predetermined proforma for tabulation of data and statistical analytical tables

Simple comparative analysis of gathered data with known available English literature was done following standard statistical protocol, to evaluate postoperative outcome between normal and low CD4 count of the patient.

## RESULTS

A total of 20 patients and all were thalassemia and immunocompromised taken for this study. The observation period was over 18 months, and splenectomy was done in operation theatre (Table 1).

**Table 1: Gender wise distribution of study population.**

Gender	Number	Percentage %
Male	11	55
Female	9	45
Total	20	100

The mean age of the patients who underwent splenectomy was 3±8 years as shown in Table 2.

**Table 2: Age group wise distribution of the study population.**

Age group (years)	Number	Percentage %
3-4	9	45
4-6	8	40
6-8	3	15
Total	20	100

p value >0.05

Splenectomy improves anemia but does not reduce iron burden: more patients were found to be on regular iron chelation after splenectomy. Hematocrit and red blood cell indices were significantly increased after splenectomy, platelet count increased significantly. No overwhelming post splenectomy infection was reported in this series. Post splenectomy stitch line infection was reported in two patients with severe reduction of preoperative CD4 count.

In two patients, symptoms suggestive of impaired immune function developed post splenectomy, at a time when their CD4 lymphocyte numbers were markedly higher than their pre splenectomy values. One developed oral candidiasis (CD4 960/ML, PERCENTAGE CD4 32%), and in one patient a 7 kg weight loss was recorded and associated with recurrent mouth ulcers (CD4 680/milliliters, percentage CD4 7%)

Those two patients with CD4 cell count less than 200/mm<sup>3</sup> prior to surgery, 90.7% had moderately increased counts after surgery (95% Confidence Interval [CI] 32.9%, 81.6%), whereas 9.3% of patients had mildly increased CD4 counts after surgery (95% CI 14.2%, 61.7%).

The rate of thrombocytopenia in HIV infected patients in this study was 20%. There were no cases of thrombocytopenia among the females in this study. There was no significant difference in thrombocytopenia among the different age groups of this study. The rate of thrombocytopenia has been reported to be more common in older age groups. Important findings were that for patients with advanced immunosuppression severe thrombocytopenia was more frequent in those cases where CD4 count was less than 200.

Median hemoglobin level among patients studied was also almost similar 7-8 gm%. Between the pre-operative to 1st POD there was a general CD4 fall in all patients, with the highest fall for the patients who had more disease severity (-242 cells). Between the 1st and 7th POD there was a general rise in the CD4 cells as shown in table 3.

The CD4 changes with age were almost similar. As shown in table 3 between 1<sup>st</sup> and the 7<sup>th</sup> POD's all CD4 cells rises.

Between pre-operative to 7<sup>th</sup> POD the only small rise the patients were CD4 count less than 200 cells.

**Table 3: Pre and postoperative cd4 cell count level among the study population.**

Test	Mean	n	Standard deviation	t	df	p value
pre op cd 4 count	363.48	20	99.65511	22.86245	19	0
post op cd 4 count	510.58	20	116.70967	26.77503		

p value <0.05

Male patients had a greater CD4 reduction pre-operative to 1<sup>st</sup> POD (-55 cells). Female patients CD4 cells were reduced from pre-operative to 1<sup>st</sup> POD (-20 cells).

The median pre-operative CD4 counts in the HIV positive patients were above 200 cells/ml, the cut off below which HIV patients are considered to be at risk of developing AIDS, this signifies that the patients enrolled had good immunity and many hadn't developed AIDS.

Median CD4 reduction was greatest between the pre-operative and 1<sup>st</sup> POD in HIV positive patients.

As shown in table 3, there was also a general rise in CD4 levels between the preoperative level and the 7<sup>th</sup> post-operative days which was almost all patents. p-values was all over 0.05.

Taking HIV status as the exposure and CD4 fall as cases the median CD4 reduction was 64 cells. Cases were those with CD4 fall greater or equal to 64 and cases were those with CD4 fall less than 64.

Relative risk was 0.96 which is less than 1, thus HIV exposure wasn't a significant risk factor for CD4 reduction

Preoperative serum albumin was done in all patients, but no gross change was seen in postoperative period. That was statistically insignificant.

In two patients, symptoms suggestive of impaired immune function developed post-splenectomy, at a time when their CD4 lymphocyte numbers were markedly higher than their pre-splenectomy values. One developed oral candidiasis (CD4 960/microliters, percentage CD4 32%), and in one patient a 7 kg weight loss was associated with recurrent mouth ulcers (CD4 680/microliters, percentage CD4 7%). As shown in table 3, author conclude that the total CD4 count increases significantly after splenectomy while the percentage CD4 lymphocyte count and CD4:CD8 lymphocyte ratio do not. This data suggest that the CD4 lymphocyte count overestimates the immune function in these patients.

## DISCUSSION

The prevalence of HIV infection in thalassemia varies greatly worldwide, from <1% to >20%. Antiretroviral therapy should be administered to patients with thalassemia major based on the general guidelines used for other infected non-thalassemic individuals, side effects such as endocrine dysfunction and diabetes could be more significant.

The patient's iron status influences the outcome of HIV-1 infection. In HIV-infected patients with thalassemia major, the rate of progression of HIV was significantly faster in patients with low level of chelation with deferoxamine and higher serum ferritin concentrations.<sup>8</sup> Optimal control of iron overload with iron chelation is therefore recommended in HIV-positive patients with thalassemia and the choice of chelator should take into consideration. Because of an increased risk of neutropenia, deferiprone should be used with caution in such cases.

There is no direct evidence that splenectomy facilitates the progression of HIV infection, a decision to perform splenectomy in an HIV-positive patient with thalassemia should be made with extreme caution because removal of an important fraction of T cells and the potential for overwhelming infection in immuno-compromised patients.<sup>9</sup>

Splenectomy alters inconsistently the CD4 lymphocyte numbers in patients infected with the Human Immunodeficiency Virus (HIV). There was a significant increase in the mean CD4 numbers following splenectomy, no significant difference was observed in the percentage CD4 lymphocytes. In two patients, symptoms suggestive of impaired immune function developed post-splenectomy, at a time when their CD4 lymphocyte numbers were markedly higher than their pre-splenectomy values. One developed oral candidiasis (CD4 960/microliters, percentage CD4 32%), and in one patient a 7 kg weight loss was associated with recurrent mouth ulcers (CD4 680/microliters, percentage CD4 7%). Author conclude that the total CD4 count increases significantly after splenectomy while the percentage CD4 lymphocyte count do not. Splenectomy is warranted in patients with severe, persistent thrombocytopenia with thalassemia.

Patients who were proposed for splenectomy had higher baseline CD4 cell counts only two patients were CD4 count less than 200. With a one and half year follow-up and after adjusting on the CD4 cell count, splenectomy did not influence the progression to AIDS or to death. However, splenectomy increases the risk for severe, sometimes fulminant, sepsis, especially because of encapsulated pathogens such as *S pneumoniae*. Author recommend both pre splenectomy vaccination and postoperative oral antibiotic prophylaxis.<sup>9</sup>

Splenectomy led to a twofold increment of the lymphocyte count and to a significant increase in the absolute CD4 cell count. In these patients, the decisions regarding antiretroviral therapy and especially prophylaxis of opportunistic infections should take these constitutions into account and focus on the percentage of CD4 cells.<sup>10</sup>

CD 4 count in this subject were quite low to normal and lowest CD 4 counts were seen in patients with extensive disease.

The findings of lymphadenopathy (size >15 mm) and hypoechoic/necrotic echotexture, hepatosplenomegaly in HIV infected patients with fever and low CD 4 counts. However, if the CD 4 count is very low, or there are manifestations of advanced immunodeficiency, the best choice is to start the antiretroviral regimen as soon as possible.<sup>11</sup>

This study set out to investigate the outcome of splenectomy surgery on CD4 count among HIV positive patients. Author found that splenectomy did not significantly reduce CD4 count, even after splenectomy CD4 count found slightly increased.<sup>12</sup>

The exact mechanism of CD4 reduction is said to be due to several factors; cell lysis, autoimmune mechanism, energy, effect of super antigens, apoptosis and virus specific immune responses.<sup>13</sup>

Molecules causing them to be refractory to further stimulation and destruction by HIV. Super antigens are microbial or viral antigens capable of activation of many T-cells, in HIV infection; they render T-cells more susceptible to HIV. All these factors are worsened by stress which is caused by surgical trauma. Other factors like infection and use of steroids can also trigger these factors. The CD4 cell counts were generally lower in the HIV infected group than in the HIV uninfected group.

The high values of the CD4 count even in the HIV positive i.e. higher than 200 cells/ml the AIDS defining level of CD4 by WHO, can explain the finding that surgery had no statistically significant effect of reduction in CD4 as the pre-operative CD4 levels were high (347 cells/ml).<sup>14</sup>

The blood for CD4 test was taken between 7 pm and 11 pm to cater for the diurnal variation. The CD4 reduction was transient in this study with CD4 levels rising to above pre-operative values on the 7<sup>th</sup> POD in the HIV positive patients. This was similar to previous study by Rahal, where it lasted 8 days.<sup>15</sup> Surgery and anesthesia cause T-cell apoptosis which is said to be only transient lasting up to 5 days.

In this study splenectomy surgery caused transient reduction in CD4 because within seven days the levels had risen to above pre-operative values. In this study, the



children had a better rise in CD4 count on 7<sup>th</sup> POD. The CD4 reductions after surgery were highest in the HIV positives on 1st POD which was unexpected as the HIV infection itself reduces the CD4 count. CD4 levels are said to vary by about 25% even in HIV positive patients.

Available information suggests that HIV positive patients should have a higher reduction in CD4 count because of the effect of the disease itself in addition to the other factors affecting CD4 count.<sup>14</sup> CD4 rise was more in the HIV positive patients in this study between 1<sup>st</sup> and the 7<sup>th</sup> POD and pre-operative to 7<sup>th</sup> POD as expected. In comparison, a study by Rahal also showed that surgery does not affect immune function adversely in HIV-infected patients, as judged by CD4 cell counts or viral titers which were also done in their study.<sup>15</sup> There are no relation of low CD4 count with chest infection and urinary tract infection.

### CONCLUSION

This is a prospective study with thalassemia HIV-infected patients on ART with different CD4 counts. The primary outcomes considered were mortality and complication rates after splenectomy surgery. Author emphasised on the value of CD4 as a predictor of outcome. Author included 20 patients. The majority of patients were operated on as an elective procedure and the indications were similar in all patients.

The overall and the septic complication rates were higher in the patients with a low CD4 count. This resulted in a significantly longer admission period but did not result in a higher mortality rate. HIV-infected patients on ART can now safely undergo major splenectomy surgery with encouraging results. CD4 count remains a significant predictor of outcome and in patients with a low CD4 count, there is no relation of CD4 count and splenectomy outcome. CD4 count increased after splenectomy and there is no relation with chest infection, wound infection and urinary tract infection.

With long-term follow-up after splenectomy for treatment of thalassemia major, thrombocytosis and the risk of thromboembolic event persist. Splenectomy improves anaemia but does not reduce iron burden or the requirement for blood transfusion. Proper preoperative vaccination can reduce the risk of overwhelming post splenectomy infection.

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