Morbidity and mortality patterns in patients with thalassaemia during the COVID-19 pandemic in Sri Lanka; A single centre experience

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Abstract

Introduction: Patients with thalassaemia syndromes (TS) affected with COVID-19 attending a thalassaemia centre in Sri Lanka situated in the region most affected with COVID-19 were studied over a 16-month period.
Methods: To assess the collateral effects on overall thalassaemia care in the centre, data on transfusion, chelation and clinic attendance were analysed. Morbidity events and deaths recorded during the COVID-19 period and during a similar period before the beginning of COVID-19 infection in Sri Lanka were recorded in all clinic registrants.
Results: Seven patients (of 502) with TS had developed COVID-19 during the 16-month period; all were minimally symptomatic and had recovered without complications. Number of monthly clinic visits reduced from 338 pre-COVID to 268 during COVID (p=0.004). Iron chelator usage too reduced during the pandemic period (p<0.001). Though admissions related to morbidity reduced during the pandemic (58 vs 16, p<0.001) there were more non-COVID deaths (8 vs 4).
Conclusions: Numbers affected with COVID-19 were low and severity of infection was mild in this cohort of patients with TS. Collateral effect on the management of the unit and effects on mortality in this vulnerable population appears to have been substantial.

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Introduction

The first Sri Lankan patient infected with COVID-19 was detected on 27th January 2020. The country experienced the First Wave of the pandemic from January 2020 to October 2020, where there were 3396 cases and 13 deaths. (1) The Second Wave started as two clusters from the Western province and spread rapidly, infecting 92,341 persons and causing 591 deaths, from October 2020 to April 2021. By early April 2021, the number of cases were reducing. However, the Third Wave started in late April and spread across the country, affecting 213,102 persons and causing 3,837 deaths, as of 31st July 2021 (1). The largest number of persons affected by the disease in each Wave was in the Western Province of Sri Lanka (1).

Patients with thalassaemia are a particularly

vulnerable group with high risk of premature death due to infections and iron overload. There are over 2000 patients with thalassaemia in the country; 500 of them attend the only adult specialised centre in Ragama in the Western province. Thalassaemia care began to improve in Sri Lanka in the mid-1990s, but median survival of patients remained quite low, at only 13.2 years for those with beta thalassaemia major. (2). Blood is provided free of charge from the National Blood Transfusion Service (NBTS), which acquires blood from non-remunerated voluntary donors. There is usually an adequate supply of blood with the NBTS. For instance, in 2018 there were 412,154 blood packs used in the country and the total collection was 450,640 units (3). Chelator usage in the country is mostly Desferioxamine (DFX) and Deferasirox (DFO), at a ratio of 60:40 respectively. This too is provided free of charge from the state (2).

With the emergence of COVID-19, severe restrictions were placed on social activities, with lockdowns and travel restrictions. Most routine services in hospitals were cancelled, as screening and treatment of COVID-infected patients and infection control were prioritised. These changes to routine care greatly affected vulnerable groups, including patients with thalassaemia. Restriction of inter-provincial travel and frequent imposition of curfews severely limited the ability of patients to receive their routine care. Many patients decided to go to their nearest regional hospital to receive blood transfusions, instead of travelling to the main thalassaemia care centre.

We assessed the outcome in patients with thalassaemia who contracted COVID-19, the effect of the pandemic on regular care delivered by the Adult Thalassaemia Care Unit, Ragama and on the general life of uninfected patients.

Methods

The study was over a 16-month period from March 2020 to June 2021 (during COVID-19) and encompassed all patients with Thalassaemia registered to receive routine care at the Adult Thalassaemia Care Unit, Ragama, affiliated to the Colombo North Teaching Hospital, Ragama Sri Lanka. Patients with thalassaemia known to have become infected with COVID-19 were contacted by telephone and their baseline clinic data were assessed. Data on transfusion, chelation, hospital and clinic attendance, morbidity, and mortality of all patients with thalassaemia registered in the unit were assessed for the period under study. Similar information collected for a 16-month period prior to March 2020 (pre- COVID-19) was used for comparison. To calculate the transfusion load, pre-transfusion haemoglobin was compared in those who continued to attend the Unit for services and those who were compelled to attend peripheral hospitals of their choice due to government imposed inter-provincial travel restrictions, with 15 patients from each category randomly selected from the Unit register. Medians with interquartile ranges and numbers with percentages were presented and group comparisons were done with Wilcoxon Rank Sum test and Pearson Chi square test. A P value of 0.05 was considered as significant. Analysis was done with R programming language version 3.6.3.

Results

The total number of patients with thalassaemia registered in the Unit was 502, and their ages ranged from 11-56 years [mean 33 (SD 7.64) years]. Fifty four percent (274/502) were males. The ethnic distribution was 450/502 (89.6%) Sinhala, 41/502 (8.1%) Moor and 11/502 (2.1%) Tamil. According to transfusion category, there were 211 (42%) beta thalassaemia major, 112 (22.1%) thalassaemia intermedia, 83 (16.5%) haemoglobin E beta thalassaemia, 24 (4.7%) sickle cell beta thalassaemia and 72 (14.3%) other variant patients attending the Unit.

During the study period a total of seven patients (5 males) contracted COVID-19. Their ages ranged from 16-48 years (Mean 27.5, SD 11.6) One contracted the infection during the first wave whilst three contracted the infection in the second and third waves respectively. Four patients had beta thalassaemia major whilst three had haemoglobin E beta thalassaemia. All patients had serum ferritin >1000ng/mL. During the preceding

year, the mean haemoglobin concentration in the patients with transfusion dependent thalassaemia (TDT) was 7.6g/dL while in those with E beta thalassaemia it was 8.1g/dL. One patient had diabetes mellitus but there were no major comorbidities in any of the others. Blood group was O + in 4 of them, B+ in two and A+ in the other. Four patients had undergone splenectomy, and none had been vaccinated against COVID-19 at the time of contracting the infection. Three patients had COVID-positive family members. Two patients remained completely asymptomatic during the infection whilst the others had only mild infection. None required oxygen or ventilator support. All patients were managed in hospitals as per national policy. Two patients received scheduled blood transfusions during their hospital stay.

Four of the seven patients who developed COVID-19 infection had persistent symptoms six months after recovery from the acute infection. The persistent symptoms included fatigability, 'brain fog', insomnia, dizziness, stomachache, loss of appetite and headache. There were no symptoms to suggest persistent anxiety or depression. However, as the infected number was small it is not possible to accurately define the more dominant post-infectious symptoms.

Effects of the pandemic on uninfected patients

We assessed the effects of the pandemic on the health of patients who did not develop COVID-19 infection, using direct and indirect parameters (Table 2).

Patients did not appear to be affected by lack of access to blood, since they received adequate blood transfusions from the Thalassaemia Care Centre or from peripheral hospitals. The mean haemoglobins of those who attended the Thalassaemia Care Centre and those who attended Peripheral Units because of difficulties in attending the main Centre due to travel restrictions, were similar at 8.1 g/dL and 8.4 g/dL respectively. However, the number of clinic visits and number of monthly admissions reduced during the pandemic, most probably due to travel restrictions. The use of Desferioxamine and

Table 1 - Comparison of parameters before and during the COVID-19 pandemic

Transfusion practice	Pre COVID-19	During COVID-19
Mean blood unit usage (SD) per patient	34.9 (10.3) units	35.6 (17.6) units
Mean Hb level (SD)(at Thalassaemia Care Centre)	8.1 (1.1) g/dL	8.2 (0.8) g/dL
Mean Hb level (SD)(at Peripheral Units)	8.4 (0.8) g/dL	8.5 (0.9) g/dL
Number of clinic visits	525	494
Number of admissions per month	338	268
Desferioxamine vial usage per month	3426	1699
Deferasirox tablet usage per month	18283	15280

Deferasirox was also significantly less during the pandemic period.

We compared morbidity and mortality in the 16 months up to March 2020, with the 16 months of the COVID-19 pandemic starting in March 2020 (Table 2). There were significantly less admissions due to morbidity during the pandemic (16 vs 58), but there were twice as many deaths (8 vs 4).

The causes of deaths and patient characteristics are listed in Table 3.

Table 2 - Comparison of Morbidity and Mortality Pre-COVID and during COVID

Morbidity and mortality	Before COVID-19	During COVID-19	P value
Number of deaths	N = 4 Septicemia (1) Hypoglycemia (1) Respiratory Arrest (1) Heart failure (1)	N= 8 Septicemia (4) Heart failure (3) Pneumonia (1)	0.248
Morbidity admissions	N = 58	N= 16	<0.001

Table 3 - Mortality details: Pre-COVID patients 1-4, During COVID patients 5-12

Patient Number	Diagnosis	Age (years)	Last ferritin (ng/mL)	Mean Hb (g/dL)	Splenectomy done/not done	Cause of Death
1	thalassaemia intermedia	24	9520	7.5	done (8 years ago)	Septicemia
2	beta thalassaemia major	37	2200	8.1	done (8 years ago)	Hypoglycemia in a diabetic patient
3	beta thalassaemia major	33	2310	8.6	not done	Respiratory Arrest
4	thalassaemia intermedia	34	1590	6.3	not done	Heart failure
5	beta thalassaemia major	26	4360	11.4	not done	Septicemia
6	beta thalassaemia major	52	2680	8.7	not done	Septicemia
7	beta thalassaemia major	25	1650	7.7	not done	Septicemia
8	beta thalassaemia major	48	5210	9.3	not done	Septicemia
9	beta thalassaemia major	28	1300	10.4	not done	Heart failure
10	beta thalassaemia major	16	1300	6.3	not done	Heart failure
11	beta thalassaemia major	28	5230	7.9	not done	Heart failure
12	beta thalassaemia major	37	1285	8.8	done (8 years ago)	Pneumonia (non-COVID)

Discussion

We found only a few published studies and one systematic review which looked at the effects of COVID-19 in thalassaemia syndromes (TS). Studies originating from Italy and Iran had only a few patients with COVID-19 among patients with thalassaemia, despite large caseloads of COVID-19 in the society (4,5). In Iran, of 18,350 patients with TS in the country there were only 15 confirmed cases of COVID-19. In Northern Italy only 11 COVID-19 cases were reported from a total of 6,900 patients with TS (4). In the Italian study all the patients had mild to moderate disease with no mortality, while in the Iranian study of 15 infected patients 4 (26.6%) died. The disproportionately high mortality rate in thalassaemia patients in the Iranian study was ascribed to the high comorbidities in the deceased (4,5). Likewise, in a study from Lebanon only 40 cases were reported among the thalassaemia patient population during a period of over 12 months from a large centre and 90% of these patients had asymptomatic to moderate disease. Only one patient in the Lebanese cohort needed oxygen support and there were no deaths. (6)

Our study, though limited to a single centre, was conducted in the Western province which had the largest case load of COVID-19 in the country. It was also conducted in the centre responsible for the care for over 25% of all the patients with TS in the country and the only centre dedicated for adult TS patients in Sri Lanka.

The eight patients with thalassaemia who developed COVID-19 infection in our study had mild symptoms. None had clinical deterioration of their COVID status while in hospital. Symptoms were more in the immediate aftermath rather than during the period of infection. Whether these symptoms are part of the so-called 'Long COVID post-infection syndrome' is not clear at this stage and it is hard to know if the symptoms described by the patients could justifiably account for this clinical classification (7).

The bigger effect seems to have been on the day-to-day administration of the Thalassaemia Unit, with a significant reduction in clinic attendance and patient admission during the 16 months of the pandemic, compared to a similar time immediately preceding the start of the pandemic. The effects of this on the overall health of the patients appear variable as most had managed to access blood transfusion adequately at local hospitals without coming to the main Thalassaemia Centre. This speaks favourably of the organisation of the national and regional transfusion services which managed to collect sufficient blood stocks to keep this high-demand sector well supplied during a time when blood stocks tended to run low.

The biggest challenge during this time was the reduced availability of desferrioxamine (DFO), which about a third of patients use exclusively or in combination with deferasirox. These chelators are provided by the government. Inadequate stocks are available in the private sector. Intermittent shortages of chelators due to poor coordination in the supply chain are well known in Sri Lanka. The prolonged shortage of DFO during the second and third waves of the COVID-19 pandemic in the country may be indirectly linked to the outbreak itself, as most efforts of the government supply chain were directed towards COVID-related activities.

Most distressing was the doubling of mortality figures when compared to a similar period pre-COVID. The average number of deaths in the Adult Thalassaemia Unit at Ragama is 3.7 deaths per year (range 1-6) from 2011-2019. Analysis of the eight deaths during the COVID pandemic showed that in 3 patients serum ferritin was dangerously high (with values over >2500ng/mL), while in 5 patients, sepsis and non-COVID pneumonia were responsible for death. Delays in access to health care was a major problem during the pandemic and this may have contributed to these deaths. As postmortems were not undertaken, accurate assessments were not possible about the deaths due to heart failure and respiratory arrest. Sepsis is found to be the commonest cause of death in patients with thalassaemia in Sri Lanka and across Asia, as opposed to the direct effects of iron overload on the heart or malignancies as seen in the Mediterranean countries (8). The significance of infection as a cause of death during the COVID

era is more pronounced when the four deaths during the pre-COVID period are compared; only one was directly attributed to infection.

Conclusions

The indirect collateral effects of COVID-19 seem to be far worse than the direct effect on the lives of patients with thalassaemia at the Adult Treatment Centre. The breakdown of administration and other health services due to the prolonged pandemic situation could have a severe impact on the lives of vulnerable thalassaemic patients.

Article Information

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Conflicts of interest: none

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