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ORIGINAL ARTICLE

Economic Evaluation of Nucleic Acid Testing for Screening of Blood Donations for Thalassemia Patients (ECONAT) in Western India

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Abstract

Background Transfusion Transmitted infections(TTI) are of significant concern for blood safety. The thalassemia patients who receive multiple transfusions are at an increased risk of TTIs and the Nucleic Acid Test (NAT) has been advocated for safe blood. Though NAT can reduce the window period compared to serology, cost is a constraint.

Methods The thalassemia patient and NAT yield data from the centralized NAT lab in AIIMS Jodhpur was evaluated for cost-effectiveness using the Markov model. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference between the cost for NAT and the cost of medical management of TTI-related complications by the product of the difference in utility value of a TTI health state with time and Gross National Income(GNI) per capita.

Results Out of the 48,762 samples tested by NAT, 43 samples were discriminated NAT yield all of which were reactive for Hepatitis B (NAT yield of 1:1134). There was no HCV and HIV NAT yield despite HCV being the most prevalent TTI in this population. The cost of this intervention was INR 5,85,14,400. The number of lifetime QALY saved was 1.38 years. The cost of medical management is INR 82,19,114. Therefore the ICER for intervention is INR 3,64,45,860 per QALY saved which is 274 times the GNI per capita of India.

Conclusions The provision of IDNAT-tested blood for thalassemia patients in Rajasthan state was not found to be cost-effective. Measures to bring down the cost or alternative options to increase blood safety should be explored.

Keywords Thalassemia · Nucleic acid test · NAT yield · Cost effectiveness analysis · Hepatitis B

Introduction

Patients with transfusion-dependent thalassemia are at a higher risk of Transfusion Transmitted infections (TTIs) like Hepatitis B, Hepatitis C and HIV than the general population. [1, 2] This can be attributed to the increased risk of TTIs in this population owing to the repeated transfusions. This has caused a lot of concern and repeated calls for improved screening techniques for blood donations for this population have been made.

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Blood Transfusion services in India are regulated by the Drugs and Cosmetics Act and the rules therein, which make it mandatory for serological screening for Hepatitis B Surface Antigen (HBsAg), and Hepatitis C virus antibody (HCV), Human Immunodeficiency Virus (HIV I and HIV II) antibody, Syphilis and Malaria. [3]

Available serological tests (Chemiluminescence, Radioimmunoassay, ELISA) vary in their sensitivity with the generation of technology and testing methodology. ELISA is the most commonly used testing platform in India. The 3rd generation assay which is currently recommended for Hepatitis B and Hepatitis C has a window period of 38 days and 60 days respectively.[4, 5] The 4th generation kits that are available for HCV and HIV can bring down the window period to 6 weeks and 15 days.[5, 6].

However, the long window period and problems of detecting immunosilent carriers, occult and mutant viral infections may require additional testing to improve the safety of blood.[7] Though not mandatory in India, the molecular diagnostic Nucleic Acid Test (NAT) is additionally added by some centres for screening donated blood. [8] NAT can be either done on the blood samples pooled together (MP-NAT) before testing or on individual samples (ID-NAT). ID-NAT [Procleix Ultrio plus® Assay (Grifols diagnostic)] claims to narrow the window period more than MP-NAT, with a window period of 14.9 days for HBV, 2.2 days for HCV and 4.7 days for HIV-1.[9] Earlier detection of viremia along with identification of occult infections and immune silent carriers helps in preventing transmission of Transfusion Transmitted Infections (TTIs). [10]

The high cost, unavailability of trained manpower, infrastructure, space and adequate blood collection for the sustainability of the model at the fragmented blood centres in India preclude the implementation of NAT in India.[7] Cost is particularly important in India where more than 80% of the population is dependent on the scant public health budget of 1 to 1.2% of GDP. The resultant 60–70% out-of-pocket healthcare expenses push people into poverty. [11, 12]

Rajasthan state which is the largest state in India has an estimated 2200 patients with transfusion-dependent thalassemia receiving transfusion from public-funded hospitals. Studies in thalassemia patients in Jodhpur, Rajasthan reported the prevalence of TTIs to be 2% for HBV, 40–45% for HCV and 1–3% for HIV. [1, 13] This has prompted repeated calls from the general public and courts of law to direct healthcare authorities to provide NAT-tested blood components for transfusion to thalassemia patients. [14, 15] National Health Mission (NHM) Rajasthan state has been providing support for the intervention for Thalassemia patients in Rajasthan state.

Table 1 Modelled number of transfusions to thalassemia patients per year

Age group	Percentage of patients	Mean blood units transfused per year	Modelled number of thalassemia patients	Estimated number of transfusions to thalassemia patients
< 1	5%	4	110	440
1–5 years	15%	13.5	330	4455
5–10 years	30%	16.3	660	10,758
10–18 years	30%	27.5	660	18,150
18–40 years	20%	33.5	440	14,740
Total			2200	48,543

The present study aims to calculate the NAT yield and cost-effectiveness analysis of the intervention for thalassemia patients at the centralized NAT laboratory in All India Institute of Medical Sciences, Jodhpur, Rajasthan (AIIMS).

Methods

Baseline patient characteristics data

The thalassemia patient cohort was modelled based on the data available at the respective centres and the data from the thalassemia society. The approximate number of thalassemia patients receiving blood transfusions at the blood centres in Rajasthan was 2200. The age-wise distribution was modelled based on patient data from the thalassemia society and AIIMS Jodhpur. The calculation for the average number of transfusions required was estimated based on the previously published studies and the possible distribution of the 48,543 transfusions as shown in Table 1. [16] The patient population was divided into 2 groups, previously HCV reactive and HCV non-reactive. The probability of transfusion of HBV NAT yield units to different patient ages and previously HCV infected groups are taken to be uniform.

Setting

The ID-NAT lab at AIIMS has processed 48,762 samples from October 2017 to December 2021. A retrospective analysis of data from the ID-NAT reports at AIIMS Jodhpur and serological test reports was done by Enzyme-Linked Immunosorbent Assay (ELISA) or Chemiluminescent Immuno-Assay (CLIA) at the respective blood centres. Individual Donor Nucleic Acid testing using Procleix Panther System (Grifols International, Spain) was used for screening.

NAT yield was defined as a unit that was initially reactive by ID-NAT and repeat reactive at least in one of the three

Table 2 Probability of transition to different health states of Hepatitis B used in the study

HBV	Probability of transition to a health state [20]	Probability used for this study
Probability of infection after transfusion of infected unit		assumed to be 100%
Spontaneous sero clearance	1–3% per year	
Progression to chronic hepatitis, %	20–30% in children, < 1% in adults	25% for age 0 to 5 years 20% for age 5–18 years 5% for age 18–40 years
Progression to cirrhosis	8–20% every 5 years at mean age 41–52 years	18% for every 5 years after age of 20 years
Progression to hepatocellular carcinoma	1% for untreated without cirrhosis and 3–8% for untreated compensated cirrhosis	1% for untreated without cirrhosis and 5% for untreated compensated cirrhosis
Progression to decompensated cirrhosis	3.30% for 100 patient years in cirrhosis	3.30% for 100 patient years in cirrhosis

repeat tests while being negative by serology initially and on duplicate testing by the original serological technique. The NAT yields that were reactive in the discriminatory assay for HBV, HCV or HIV 1/2 were termed 'Discriminated NAT yield' and those that were not reactive in the discriminatory assay as 'Non- discriminated NAT yield'.

The health consequences of screening for HBV, HCV, and HIV infection with ID-NAT in combination with serological screening and serological screening alone were simulated for 48,543 transfusions to thalassemia patients. The transmission risk for HBV, HCV, or HIV infections for each screening strategy was estimated for each virus using the NAT yield model. In this model, the risk of infection after testing is estimated by multiplying the NAT yield with the total number of units tested. The disease progression model is based on the most likely estimate as per PERT analysis.

The outcomes were calculated using life expectancy, quality of life, and health care costs for the cohort. The 50% survival by 26.9 years of age was noted in earlier studies on the life expectancy of thalassemia children in India.[17] The life expectancy in this study for all thalassemia patients was considered to be 40 years based on the expected increase in survival after the increase in ease of availability of iron chelating agents and better management of complications of thalassemia.[18] The modelling for health consequences of the infections of Hepatitis B was modelled with age 20 as the start of hepatitis-related complications. The probability of transition to various health states is given in Table 2.

Table 3 Utility scores and cost of management of various health states in Hepatitis B

Condition	Utility score [21, 22]	Median cost of management for HBV only [19]	Median cost of management for HBV + HCV[19]
Patient of thalassemia having no complication	0.93		
Noncirrhotic chronic hepatitis B	0.92	64,550	1,67,000
Compensated cirrhosis	0.88	84,150	94,200
Decompensated cirrhosis	0.73	202,700	202,700
Hepatocellular carcinoma	0.81	202,700	202,700

Calculation of costs

The cost of ID-NAT screening was obtained from the agreement for screening at our institute which is INR 1200 per test. The costs of reagents included the cost of NAT machine, reagents, operational costs including manpower and overhead expenses including the cost for transport of samples from the site of collection to the site of testing. Treatment costs for HBV, HCV, and HIV infection were obtained from the study by Balasundaram et al. with missing information being supplemented by unpublished estimates from treating physicians.[19].

Quality-adjusted life-year (QALY) was estimated by multiplying the utility value associated with a given health state by the probable years lived in that state. The utility states and median cost of management are given in Table 3. [20–22] The gross national income per capita was obtained from the data provided by World Bank for the year 2020 which is INR1,33,000 (USD 1900) (Table 4).

Cost-effectiveness analysis

The 2 strategies compared here are the cost of screening by 'Serology' alone (Strategy 1) and screening for TTIs by 'IDNAT and serology' (Strategy 2). Since the cost of serological testing is constant in both the strategies, it was discounted in calculation and only the additional cost of IDNAT testing and the cost of medications for the treatment of infection-related complications was considered for cost evaluation.

The incremental cost-effectiveness ratio (ICER)—was calculated by the formula.

[Cost of IDNAT + Serological screening]- [Cost of serological screening + Cost of management of complications of Hepatitis B in possibly infected patients]/ [QALY gained * GNI].

Table 4 Patient years, cost of management and QALYs lost for different health states of Hepatitis B in patients of thalassemia who receive transfusion without IDNAT test

	Patient years (HBV + HCV)	Cost of management HBV + HCV(in thousands)	Patient years (HBV only)	Cost of management HBV only(in thousands)	QALYs lost
Total patient years asymptomatic chronic	28.62	4780.20	42.94	2771.52	0.78 years
Total patient years decompensated cirrhosis	0.98	198.41	1.47	297.62	0.5 years
Total patient years HCC	0.34	68.54	0.51	102.81	0.096 years

The estimated ICER was compared with the per capita gross national income (GNI) for India according to the WHO Choosing Interventions that are Cost Effective (CHOICE) program.[23] Strategies that yield a cost-effective ratio (CER) below the per capita GNI are regarded as cost-effective, whereas strategies with a CER above three times the per capita GNI are regarded as not cost-effective.

Results

Out of the total of 48,762 samples that were tested, 86 were found to be initially reactive by ID-NAT, but non-reactive on serology. 43 NAT reactive samples were discriminated NAT yields and all were reactive to HBV in the discriminatory assay. 42 samples were initially reactive by NAT and non-reactive on repeat testing, 8 samples were reactive in initial and repeat testing but were non-reactive on discriminatory testing. There was one sample which was non-reactive initially by NAT but was reactive by ELISA and repeat testing by NAT was reactive. Therefore, the risk of transmission of Hepatitis B averted by NAT was calculated to be 8.8 per 10,000 transfusions (1: 1134). There was no HCV or HIV NAT yield in our centre.

The addition of ID-NAT to the donor screening for TTIs likely prevented the transmission of HBV to 43 thalassemia patients. The cost of medical management of these patients is given in Table 4.

The addition of ID-NAT to the current serological screening strategy resulted in an incremental cost of INR 5,85,14,400. The number of patient years spent in the asymptomatic chronic phase of Hepatitis B was 72 years, 0.8 years in Hepatocellular carcinoma and 2.5 years in decompensated cirrhosis. The QALYs gained by IDNAT testing in the thalassemia population is 7.07 years. When adjusted for the utility value for thalassemia, the QALYs gained is 1.38 years. The cost of medication and medical management of these patients saved is INR 82,19,114. Therefore the ICER for implementation of IDNAT screening in thalassemia patients is INR 3,64,45,860 per QALY gained which is 274 times the GNI per capita of India.

Discussion

The discriminated NAT yield in our study was 43 out of 48,762 samples tested, that is 0.088% (1 in 1134 samples tested. Our NAT yield is comparable to the NAT yield reported in other studies in India which varied from 1:476 to 1:4403 with a cumulative 286 NAT yield from 3,89,367 units tested in various studies (1:1361).[8] All the discriminated NAT yields in our study were reactive to Hepatitis B. Many other studies on NAT yield in India have also reported HBV-only NAT yields with a range of 1:686 to 1: 2972 units tested.[24–27] HIV NAT yield has been reported from studies in DMC Ludhiana, AIIMS Delhi and Medanta hospital, New Delhi with a yield of 1:24,220 to 1: 73,898.[9, 28, 29] HCV NAT yield was also reported from these three centres with a NAT yield of 1: 2537, 1: 1997 and 1: 24,220 respectively.

The earlier studies regarding Transfusion Transmitted among thalassemia patients reported a high prevalence, especially of HCV. This decreased gradually since 2001 when a mandatory HCV antibody test was introduced.[2] However, this is still a cause of concern as the high prevalence of HCV is still reported in a few centres in their thalassemia patients.[1, 30, 31].

The benefit for detecting window period infections is the highest for HCV infections given the long window period for HCV antibody detection by ELISA (60 days) compared to ID-NAT (2.2 days).[9, 32] This leads to the assumption that the NAT yield for HCV should be considerable. However, our study as well as other studies in India, have failed to show the advantage of NAT in the detection of HCV. Also, the 2 NAT yield HCV cases have not demonstrated seroconversion in the study by Pandey et al. [28]

NAT is reportedly most useful in detecting window period infections and occult Hepatitis B infections. This is due to the doubling time of HBV (2.56 days in a mouse model) being more compared to Hepatitis C (11 h) and HIV-1(18 h).[33] However, the transmissibility of occult Hepatitis B or window period infections through blood transfusion is very low.[34] Pandey et al. have determined that only 4 out of the 7 (57%) initial NAT yields for HBV to be true.[28] Therefore, the transmissibility of Hepatitis

B NAT yield is questionable. The addition of Hepatitis B vaccination to the universal immunization programme has considerably brought down the Hepatitis B carrier rate in India.[35] The patients who have received the vaccine may also have reduced transmissibility of Hepatitis B through these units.[36].

NAT yield for HIV is considered significant both in terms of the patient outcome as well as the inherent social stigma associated with it. However, in our study, as in other studies across India, there has been a very low to absent HIV NAT yield. This could be due to the stringent donor screening measures deferring donors with high-risk behaviour and the use of 4th generation ELISA kits for screening for HIV I and II.[6].

Ghosh et al. in 2017 reported that of the 2,550 blood banks in India, only 58 blood banks (2%) are doing NAT testing, resulting in the testing of 7% of the units collected in the country.[8] The problems with NAT implementation include high cost, non-availability of trained manpower and equipment, dedicated infrastructure and emphasis on cost-effectiveness in Indian public healthcare expenditure.[7] The Transfusion services in India are fragmented and small blood centres neither have the infrastructure and capital to establish NAT labs nor do they have adequate samples to frequently test with high throughput NAT testing platforms. Centralizing NAT services with a hub and spoke model, where samples from nearby blood centres are brought to the central NAT lab for testing, brings down the costs while also ensuring adequate utilization of the resources and provision of timely results. Centralization also helps in testing samples promptly as a batch and assures timely availability of blood components for release.

There has been a decrease in the prevalence of TTI in thalassemia patients which seems to follow the generalised decrease in seroprevalence of TTIs among donors over the years noted by various centres in India. [10, 37, 38] The stringent donor selection criteria, the extensive screening procedure, increase in voluntary donors and quality control measures taken up by various centres across the country along with the decreasing prevalence of HIV, universal vaccination against Hepatitis B in the general population have likely resulted in decreased TTI prevalence. The use of fourth-generation ELISA has further reduced the window period for detecting TTIs. In such a scenario the utility of NAT to increase blood safety is further reduced.

Another important question regarding the implementation of NAT is the cost-effectiveness of the intervention. An approximate cost of Rupees 5.85 crore was spent on NAT tests. This has prevented transfusion of PRBC at risk for transmission of Hepatitis B to a maximum of 43 thalassemia patients. The ICER for the intervention was INR 3.64 crore per QALY saved, which is 274 times the GNI (PPP) of India. Any health intervention is cost-effective if its ICER is less than 3 times the GNI. Therefore, even though the NAT can increase the sensitivity of screening tests to detect TTIs, it is not a cost-effective intervention.

Numerous cost-effectiveness analyses in various developed and developing countries have also found that the implementation of NAT for screening blood components is inefficient.[39–43] This is particularly important in India where the union public health budget is only around 0.34% of GDP. With competing priorities, cost-effective alternatives wherever available must be implemented. Blood components are provided free of cost to a majority of the population by the union and state governments. The near doubling of costs of blood components on implementation of NAT can hamper the availability of blood products for all as mandated by the National Blood Policy, India and the WHO due to the already stretched public health budget.

As this analysis is for patients of thalassemia alone, who receive PRBC for transfusion, the risk of transmissibility through other blood components(RDPC, FFP etc.) has not been taken into account. This is the first study on the cost-effectiveness of NAT screening of blood donations in India. This is also the first study on the cost-effectiveness of this intervention specifically for thalassemia patients. This study aims to answer the query for this particular patient population which is generally raised in India. The limitations of this study are that it is based on experience and costs based on single-centre data and discounting of cost and effectiveness has not been done. The strength of this study is that it draws patient and NAT yield data from different centres in Rajasthan served by NAT lab of AIIMS Jodhpur and base populations of the region which are catered to by these centres. The cost calculations have been made using the premise that all NAT yield units would have transmitted hepatitis B. Even though the model overestimates the costs, this analysis also shows the intervention to be cost-ineffective.

As the analysis of this data shows that this intervention is cost-ineffective in our setting, preventive approaches for thalassemia like carrier screening, counselling, and prenatal diagnosis, therapeutic intervention like hematopoietic stem cell transplantation etc may be considered for better utilization of funds for this population.[44] An analysis by Joseph John et al. in India has previously shown that hematopoietic stem cell transplant(HSCT) was highly cost-effective compared to transfusion chelation therapy.[45] The use of other alternatives like compulsory vaccination with Hepatitis B vaccination along with booster doses, stringent blood donor selection and increased voluntary blood donation, strengthening of the serological testing methodology by incorporation of 4th generation testing wherever available may help to improve blood safety without entailing higher costs. The cost of Hepatitis B vaccination is Rs 135 to INR

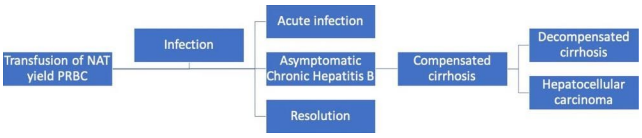

Fig. 1 Natural history and health states of Hepatitis B

750 per person. Immunization of all thalassemia patients in Rajasthan would cost a maximum of Rs 15 Lakhs. And this would have likely resulted in a similar outcome. Development of in-house RTPCR-based techniques or other measures to bring down the cost of tests may be used for cost-effectiveness.

Conclusions

Nucleic acid testing has been advocated to decrease the transmission of transfusion-transmitted infections. However, the high cost and cost ineffectiveness, especially for a developing country with limited public healthcare resources, do not support its implementation. Stringent donor screening measures, strengthening of serological testing methods and Hepatitis B vaccination could be a more effective alternatives to prevent TTIs while other interventions like prenatal carrier screening, early HSCT etc. can be done to better manage thalassemia patients.

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