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Nucleic Acid Test Versus ELISA for Detection Of Hepatitis B Infection Among Blood Donors : A Mini Review.

Neha Honnalli[1]*, and Desy TM[2].

[1]Research Scholar, Central Research Laboratory, K S Hegde Medical Academy, Nitte–DU, Mangalore, Karnataka, India
[2]Research Scholar, Central Research Laboratory, K S Hegde Medical Academy, Nitte–DU, Mangalore, Karnataka, India

ABSTRACT

Objective of the study is to compare two techniques, routinely used ELISA (HBsAg) versus nucleic acid test (NAT), in terms of their sensitivity and specificity as screening tests in detecting hepatitis B infection among blood donors. The primary benefit of NAT is the ability to reduce residual risk of infectious window period donations. The major constraint for implementing NAT as a routine screening technique in India appears to be its high cost per test. There is a need to evaluate the technique and its cost-effectiveness as compared to routine screening test,ELISA in Indian setting as there is a scarcity of literature in this area.

Keywords: NAT, ELISA, blood donors, screening test

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Corresponding author

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BACKGROUND

Hepatitis B is an infectious disease caused by hepatitis B virus(HBV) that affects liver. The virus is transmitted through exposure to infective blood and other body fluids of an infected person.It can cause both acute and chronic infection.

Global Prevalence of Hepatitis B

Hepatitis B virus (HBV) infection is one of thesignificant global health problems. World Health Organization (WHO) estimates suggest that more than 2 billion people worldwide have been infected with HBV. Of these, approximately 240 million individuals have chronic liver infectionsand at risk of serious illness and death, mainly from liver cirrhosis and hepatocellular carcinom. More than 780 000 people die every year due to the acute or chronic consequences of hepatitis B[1-4].

Different areas of the world are classified as having high (8%), intermediate (2–7%) or low (<2%) HBV endemicity, based on the prevalence of Hepatitis B surface Antigen (HBsAg) . South-East Asia, China, most of Africa, most of Pacific Islands, the Amazon basin and parts of the Middle East have high endemicity. South Asia, Eastern and Southern Europe, Russia and Centraland South Americahave intermediateendemicity. United States, Western Europe andAustraliahave lowendemicity[5].

Prevalence of Hepatitis B in India

As India has one-fifth of the world's population, itaccounts for a large proportion of the worldwide HBV burden. India harbors 10–15% of the entire pool of HBV carriers of the world[6]. It has been estimated that India has around 40 million HBV carriers. About 15–25% of HBsAg carriers are likely to suffer from cirrhosis and liver cancer and may die prematurely. Infections occurring during infancy and childhood have the greatest risk of becoming chronic. Of the 2.6 Crore (26 million) infants born every year in India, approximately 10 Lakhs (1 million) run the life-time risk of developing chronic HBV infection.The overall rate ofHBsAg positivity has been reportedto range between 2% and 8% in most studies [7-10].Many of these studies were based ondata from blood bank donors, including professionalblood donors who are known to have a higher prevalenceof HBV infection. Results of a systematic review by Lodha et al concluded that the true prevalence of hepatitis B in India was 1–2%[11].Many of the blood banks show HBsAgprevalence was0.2–4%, most of which have prevalence much lower thanthat of the commonly quoted prevalence data[12-16].

Transfusion of Blood & Blood Productsand Need for a sensitive screening technique

Transfusion-transmitted infection is a major challenge tothe transfusion services. The prevalence of HBV infectionreported by various authors from India ranges from 2 to69.2%[17-20].An earlier report of 1995 had shown that69.2% of thalassemic patients had HBV infection[17].However,subsequent reports have however shown a lower prevalenceof HBV infection in thalassemics. Vidja et alhave shown that only 2% of 200 multi-transfused patientsof beta thalassemia major had HBV infection[20]. The decreasein seropositivity may be because of implementation ofmeasures such as donor education, strict standardsfor donor selection criteria, improved serologicalscreening protocols and improved blood collectionand transfusion techniques.

A survey of blood transfusion practices in India showedthat screening for transfusion-transmitted infections isunsatisfactory, often poorly regulated, and enforcementof existing guidelines is poor[21].A strict audit of bloodbanking practices is required to prevent transmission ofthe disease.Use of nucleic acid testing (NAT) has been proposed forpreventing transmission of HBV as well as other bloodbornepathogens in Indian blood donors[22,23].Whilesuch a strategy would make the blood transfusions safer,this would add to the cost of blood screening and istherefore not routinely recommended.

Nucleic acid testing (NAT) as a screening technique during blood transfusion

Nucleic acid testing is a molecular technique for screening blood donations.This technique reduces the risk of transfusion transmitted infections (TTIs) in the recipients.Thus it provides an additional layer of blood safety. It was introduced in the developed countries in the late 1990s and early 2000s and presently around 33 countries in the world have implemented NAT for human immunodeficiency virus (HIV) and around

27 countries for hepatitis B virus (HBV)[24]. NAT technique is highly sensitive and specific for viral nucleic acids. It is based on amplification of targeted regions of viral ribonucleic acid or deoxyribonucleic acid (DNA) and detects them earlier than the other screening methods thus, narrowing the window period of HIV, HBV and hepatitis C virus (HCV) infections. NAT also adds the benefit of resolving false reactive donations on serological methods which is very important for donor notification and counseling. In a Malaysian study[25] 1388 donor samples were tested by serology as well as NAT, authors found 1.37% samples reactive on standard serology methods but non-reactive by NAT. These samples were confirmed to be "false reactive" on confirmatory serological tests.

In India, mandatory blood screening for HBV, HIV and HCV is done by serological tests for HBsAg and antibodies to HIV 1/2 and HCV. The screened seronegative donations are still at risk for TTIs because of false negative results. Thus there is a need for a sensitive screening test to reduce this residual risk. It has been reported that risk of TTIs have been reduced significantly over the last two to three decades in western countries where NAT has been implemented. NAT testing has been started in few centers in India, but it is not a mandatory screening test for TTIs as per Drug and Cosmetics Act, 1940 and the rules therein[26]. Major barriers in implementing routine NAT testing in India is its high cost and lack of technical expertise in most of the blood centers.

In India blood centers are gradually introducing NAT to provide safe blood to their patients. First multicenteric study was done by Makroo*et al*.[27] where a total of 12,224 samples along with their serological results were obtained from eight blood banks in India and were tested individually manually by procleixultrio assay for HIV 1, HCV and HBV. They observed eight NAT yield cases. According to a study from the western part of India combined NAT yield (NAT reactive/seronegative) for HIV, HCV and HBV was 0.034% (1 in 2972 donations)[28] which is high when compared to studies from developed countries. In another study conducted in north India, 18,354 donors were tested by both ID-NAT and fourth generation enzyme-linked immunosorbent assay (ELISA), 7 were found to be NAT-positive but ELISA-negative (NAT yield) for HBV and HCV. The prevalence of NAT yield cases among routine donors was 1 in2622 donations tested (0.038%)[29] . This high yield of NAT is due to the high prevalence of TTIs in India, further highlighting the need for NAT in India. In another study from a tertiary care center from north India ID NAT results were compared to serological method for 73,898 samples, 1.49% were reactive by NAT, HIV-1 (0.09%), HCV (0.25%), 1.05% were reactive for HBV only and around 0.08% were HBV-HCV co-infections with a combined yield of 1 in 610 donations (total 121 NAT yields)[30].

NAT is a highly sensitive and advanced technique which has reduced the window period of HBV to 10.34 days[31] but it is highly technically demanding, involving issues of high costs, dedicated infrastructure facility, equipments, consumables and technical expertise. The need for NAT depends on the prevalence and incidence rate of infections in blood donor population, available resources and the evidence of benefit added with serology tests.

Cost effectiveness analysis

Cost-effectiveness analysis is an important tool to assist clinicians, scientists and policymakers in determining the efficiency of healthcare interventions, guiding societal decision-making on the financing of healthcare services and establishing research priorities. Diverse approaches to synthesize evidence have been considered in biomedical research [32-35], including economic evaluations of healthcare interventions [36-43]. At the same time, decision-making in health care requires an understanding of the state of economic evaluation at a national level, where the completeness of the reporting is generally less well understood but where specific priorities are often set. Cost effectiveness analysis (CEA) compares two diagnostic tests, where the costs are identified in monetary terms and the outcomes in non-monetary terms.

Measurement of cost effectiveness could be made in two different ways:

- ACER – Average Cost Effectiveness Ratio
- ICER – Incremental Cost Effectiveness Ratio

It helps a decision maker to compare one treatment/diagnostic test to other thereby quantifying the opportunity cost of decisions.

Quality adjusted life years (QALY) is used in economic evaluation to assess the value for money which of two medical interventions/diagnostic tests. It is a measure of disease burden which include both quality and quantity of life lived. One QALY equates to one year of perfect health and QALY of a dead person will be zero. QALY can be used to evaluate different intervention, programs and to set priorities for future programs(44).

Future Research Perspectives

A research study can be plnned to compare sensitivity , specificity and yield of two screening tests, HBsAg by ELISA and nucleic acid testing (NAT) in the detection of hepatitis B infection among blood donors. In addition, cost effectiveness of the two screening techniques, NAT versus ELISA can be compared by calculating incremental cost effectiveness ratio(ICER),average cost effectiveness ratio(ACER),quality adjusted life year (QALY)

Applicability and outcome of such endeavor:

Economic assessments of diagnostic tests are inherently difficult than assessments of therapeutic interventions because of uncertainty about the relation between diagnosis and end result or outcomes of care. Towards the end, this study would evaluate the economic feasibility of introduction of NAT as a screening test for hepatitis B. The economic evaluation of the cost effectiveness of NAT using QALY and Yield of the NAT test vis-à-vis the conventional ELISA test would have profound implications with respect to policy making and utility of the test for screening individuals for Hepatitis B. If the Hepatitis B detection rate in NAT were to be proven to shorten the period for diagnosis of Hepatitis B, it would pave new roads for early diagnosis of the disease by providing scientific evidence for possibly implementing this test as a useful screening test. This study would help in planning out further strategies for the effective management and treatment of individuals detected by the test. It would also dive into newer research areas to establish the subsequent decrease the morbidity and mortality associated with Hepatitis B given appropriate facilities for early treatment after detection would be mandated at policy level. The prevalence of hepatitis B infection among blood donors in Karnataka would also be determined.

National relevance

The Implications of such study from the patient's perspective would mean early diagnosis which forms the tenet of control of the disease by increasing the yield. Early diagnosis at community level would translate into application of efficient prevention mechanisms to spread the infection especially among blood donors. The cost effectiveness analysis would provide scientific basis for adoption of the best test for screening given the economic feasibility of the study. Early diagnosis will aid the clinician in providing timely treatment by reducing the morbidity and mortality due to hepatitis B infection. From the policy point of view it will aid WHO's *Global Health Sector Strategy on viral hepatitis* which aims to test 90% and treat 80% of people with HBV by 2030.

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