Transfusion medicine in India: Expanding horizons

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Discovery of the ABO blood group system by Landsteiner in 1901 laid the foundation of immunohematology, blood transfusion and transplant biology.[1] Development of anticoagulant preservative solutions made it possible to store blood and hence separate the blood donation process from the recipient transfusion and establish "blood banks."[2] The first blood bank in the world was set up in Madrid in 1936, during Spanish Civil War. In India, the first blood bank was established in Kolkata in 1942 at the All India Institute of Hygiene and Public Health to meet war needs. It was later shifted to Kolkata Medical College in 1945, where it started functioning as the first civilian blood bank in the country.[3] The scope of the service today has far transcended the initial process of deposit, storage and withdrawal of blood units. It now involves complex laboratory technologies, community interface and patient care. The laboratory centered services includes serological aspects of blood, testing for transfusion transmitted infections (TTIs), preparation and improvement of blood components and research into various aspects of blood safety and development of blood substitutes. Patient care services are based on apheresis technology, cellular therapies and novel biomaterials. Blood donor motivation, recruitment and retention, rare donor registries and platelet/plasma/stem cell donors are equally challenging tasks. Blood banks today are evolving into Departments of Transfusion Medicine.

Immunohematology is the backbone of transfusion medicine. Presently, there are 33 blood group systems and 339 blood group antigens, though not all are clinically significant as evidenced by clinical manifestation of hemolytic transfusion reactions or hemolytic disease of the fetus and newborn.[4] Blood group antigens are traditionally tested through hemagglutination techniques, the tube technique being the gold standard for over a century. Advances in hemagglutination techniques to enhance sensitivity and adapt to automation have been made with an introduction of column agglutination methods, solid phase red cell adherence assays and magnetized erythrocyte technology. High throughput and multiple antigen/antibody testing platforms are available. Limitations of serology in recently transfused patients where both donor and patient red cells co-exist, or some typing reagents are not available in sufficient amounts has paved the way for molecular blood grouping. A variety of techniques ranging from low throughput polymerase chain reaction (PCR)-restriction fragment length polymorphism and allele-specific PCR to high throughput technologies like microarrays and mass spectrometry, which allow several single nucleotide polymorphisms to be simultaneously and rapidly tested are now available. Molecular typing is allowing the immunohematologists to make rapid strides in the manufacture of reagent red cell panel, identification of weak antigen phenotypes and mass screening for rare donors.

Immunohematology took roots in India due to the pioneering works of three great scientists: Dr. Y. M. Bhende, Dr. H. M. Bhatia and Lt. Col. C. W. G. Bird. Dr. Bhende and Dr. Bhatia discovered the Bombay blood group phenotype[5] and Lt. Col. Bird described the A1 lectin.[6] The Blood Group Reference Center was started in Mumbai as an Indian Council of Medical Research (ICMR) initiative, which has now been transformed to the National Institute of Immunohematology (NIIH). The NIIH continued its research in immunohematology with study of molecular characterization of ABO blood groups[7,8] and development of monoclonal antibodies against these blood group antigens,[9] D antigen variants,[10,11] platelet antigens polymorphisms, to name but a few. From hospital based Departments of Transfusion Medicine, data on red cell antigen frequencies in donors[12,13] and alloimmunization problems in recipients have been published in peer reviewed journals.[14-17]

Until early 1980s blood transfusion in India was largely whole blood, but the introduction of plastic blood bags in the country began to transform the blood processing techniques. Blood components become available. Innovations like pooling of platelet concentrates to yield an equivalent apheresis unit have been published from AIIMS, Delhi.[18] Multicomponent collection through cell separators yields high quality products and concurrent plasma/platelet collections are helpful for transplant recipients. Double unit red cell collections are possible and would be of immense help in the

collection of rare red cell units. Apheresis technology has helped the transfusion medicine specialist in direct patient care. In a large series of 125 patients with neurological disorders and atypical hemolytic uremic syndrome patients published from PGI, Chandigarh, therapeutic plasma exchange (TPE) was effective and less expensive as compared to intravenous immunoglobulins (IVIG).[19] It could serve as an alternate treatment modality when IVIG is not affordable by patients with various neurological disorders. The basis of TPE is to reduce the patients' load of pathologic substances and replace it with normal plasma. TPE has been helped in making ABO incompatible stem cell transplants and solid organ transplants possible through removal of the incompatible antibodies in recipients.

The discovery of causative agents of TTIs led to the development of diagnostic tests and subsequent screening of donor blood became mandatory as per Government of India notifications. This widened the scope and range of pretransfusion testing and blood transfusion services entered into the realm of ELISA technology, donor counseling and epidemiology. The realization that window period transfusion was occurring by antigen/antibody screening alone, nucleic acid amplification testing (NAT) was evaluated in India in a multicentric trial and the combined NAT yield for the three viruses (hepatitis C viruses, hepatitis B viruses, human immunodeficiency virus-I) was 1 in 1528.[20] NAT is presently being added as an additional layer of blood safety in some centers where resources are available.[21]

Cellular therapies are progressively becoming an accepted treatment modality for a large number of inherited and acquired disorders. Sources of stem cells include bone marrow, peripheral blood and cord blood. Stem cell collections from peripheral blood by leukapheresis are generally easier than bone marrow collections and postcollection processing is less from peripheral blood stem cell (PBSC) products. Human leukocyte antigen matched sibling donors are available in not more than 40% of the cases and there has been a steady increase in the number of registered volunteer unrelated donors. Since stem cell mobilization through granulocte colony stimulating factors is required in PBSC donors, stem cell donation is not without adverse effects. Stem cell donor management and follow-up has emerged as a major activity in transfusion centers supporting stem cell transplant programs.[22] Cord blood is an alternate, readily available source of hematopoietic stem cells and in the public sector almost 600,000 cord blood units are presently stored worldwide.[23] In the private sector the numbers of units may be 1,000,000. The first reports of collection and cryopreservation of cord blood stem cells were published from AFMC, Pune.[24] However, a financially viable model of public cord blood bank (CBB) in India is still not feasible. Few private CBBs have come up; the regulatory authorities have also notified the rules for setting up CBBs. A major concern with allogeneic hematopoietic stem cell transplant is still the risk of recurrence of the primary disease. Pharmacological and immunological approaches are being explored. Donor lymphocyte infusions, NK cells, co-transplantation with mesenchymal stem cells and CD-8 depleted T cell preparations are all under evaluation. Stem cell therapies in regenerative medicine[25,26] and tissue engineering are gaining root in the country, the expertise is being drawn from the disciplines of hematology/transfusion medicine/basic sciences and concerned clinical services. Draft guidelines on stem cell research and therapy have been put up on the ICMR website.

Blood derived biomaterials — fibrin sealant, platelet gel, and platelet-fibrin glue are used in many surgical specialties. They have distinct advantages over synthetic products as they are physiologically compatible, do not cause necrosis, are readily colonized by cells and are totally biodegradable. Fibrin sealant can also be prepared on a commercial scale and is available in India from Reliance Life Sciences as ReliSeal. Platelet gel — prepared from platelet rich plasma has a high concentration of growth factors which help in tissue healing and repair. It is being evaluated in orthopedic and maxillo-facial surgery, bone reconstruction, sports medicine, cosmetic and dental implant surgery.[27] Pooled human platelet lysate supports mesenchymal stem cell cultures. The first double-blind randomized trial of use of platelet rich plasma in osteoarthritis knee from India was published from PGIMER, Chandigarh.[28]

Since transfusion medicine services provide biological products, cells and plasma for patient therapy, quality system implementation akin to the manufacturing industry have been adapted to blood centers. The concept and model of Total Quality Management which aims at continuous improvement and customer satisfaction implies implementation of Quality System Essentials and assigns a managerial role to the transfusion medicine specialists. Standards for accreditation of blood banks have been developed by the National Accreditation Board for Healthcare providers.

Clinical transfusion is becoming more evidence based. Transfusion audits and hemovigilance are taking center stage for optimum patient transfusion requirements. In India, a national program on recipient hemovigilance has been launched since December 2012, as a joint venture between the National Institute of Biologicals and Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India.[29]

Cutting edge research worldwide continues for generation of "universal red cells." Inadvertent mismatching of red cells for ABO antigens can cause a near fatal or fatal transfusion reaction. Laboratory attempts to convert A and B red cells to O red cells by using bacterial galactosidases have been successful more for B than A cells.[30] *In vitro* erythrocyte cultures from CD34+ hematopoietic stem cells leading to a massive expansion of stem cells and their terminal differentiation up to stage of red blood cells has been achieved. The potential of induced pluripotent stem cells to generate large amounts of red cells is also being explored. Translation from "bench to bedside" is awaited.[31,32]

Considering the leaps and bounds by which the specialty has grown in the last 2-3 decades, the need for trained personnel became essential. Objective six of the action plan of blood safety reads as "to strengthen manpower through human resource development." In recognition of this need, the Medical Council of India granted approval to conduct MD immunohematology and blood transfusion (transfusion medicine) course and the National Board in Immunohaematology and Transfusion Medicine. For technologists, a postgraduate diploma and MSc Medical Laboratory Technology in Transfusion Medicine are being conducted. Staff already working in blood centers usually found it difficult to acquire new degree/diploma. The Blood Safety Division of National AIDS Control Organization (NACO), Ministry of Health and Family Welfare Government of India initiated in-service induction and refresher training for medical officers, laboratory technologists

and staff nurses already working in blood centers. 17 nodal training centers are conducting the training program. Sensitization and training of bedside transfusion staff is still a major challenge.

Blood banking traditionally is a more pharmaceutical like activity involving screening of donors, blood collection, component preparation and blood testing. Since blood and blood products are classified as "drugs" the blood banking activities are regulated by the drug control authorities. Transfusion medicine includes research and active involvement of specialists in patient management with cellular therapies and therapeutic apheresis. However, somatic cell therapies are considered biological products and are now subject to licensing regulations to ensure products safety, purity and potency in many countries in the world. The challenge is to amalgamate the production of high quality cellular and noncellular blood components with development of need based research and clinical involvement by the specialists of transfusion medicine.

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