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Plasma fractionation, a useful means to improve national transfusion system and blood safety: Iran experience

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Summary. In 1974, the government of Iran established Iranian Blood Transfusion Organization (IBTO) as national and centralized transfusion system. Since then donations of blood may not be remunerated and therapy with blood and its components are free of charges for all Iranian patients. Donations are meticulously screened through interviewing donors and lab testing the donations using serological methods. Currently, Iranian donors donate 1 735 000 units of blood annually (donation index: 25/1000 population). Implementation of a highly efficient donor selection programme, including donors interview, establishment of confidential unit exclusion programme and laboratory screening of donated bloods by IBTO have led to seroprevalence rates of 0.41%, 0.12% and 0.004% for HBV, HCV and HIV in donated bloods respectively. Since 2004, IBTO has initiated a programme to enter into a contract fractionation agreement for the surplus of recovered plasma produced in its blood collecting centres. Although IBTO has used this project as a mean to improve national transfusion system through upgrading its quality assurance systems, IBTO fractionation project has played a major role in improving availability of plasma-derived medicines in Iran. During 2006–2007, this project furnished the Iran market with 44% and 14% of its needs to the intravenous immunoglobulin and albumin, respectively. Iranian experience showed that contract fractionation of plasma in countries with organized centralized transfusion system, which lack national plasma fractionation facility, in addition to substantial saving on national health resource and enhancing availability of plasma-derived medicines, could serve as a useful means to improve national blood safety profile.

Keywords: blood safety, centralized transfusion system, Iran, plasma fractionation

Introduction

Availability of safe blood and blood components is an essential part of the modern medicine and health care systems. Around the world, every year, millions of lives are saved or significantly improved by appropriate use of these products. It seems that at least for decades to come, reliable access to the safe blood and/or plasma-derived products would be an essential part of today's medicine. Therefore, it is quite clear that lack of access to sufficient quantities of these products whenever they are needed to treat patients will compromise the obvious right of patients to receive proper care. However, according to WHO, in many countries, people still die because of an inadequate supply of blood and blood products. This has a particular impact on women (as a consequence of pregnancy-related complications), children (malnutrition, malaria and severe life-threatening anaemia), patients with blood disorders such as thalessemia, trauma victims and especially, the poor and disadvantaged [1].

Like any other medical interventions and procedures, inherently, transfusion of blood and blood products is associated with some risks. Amongst those, acquiring disease associated with blood-borne pathogens, e.g. microbial and viral infections are the most important risks because of transfusion medicine. Presently, in many countries, even where blood

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is available, many recipients remain at risk of transfusion-transmissible infections (TTIs) as a result of poor blood donor recruitment and selection practices and the use of untested units of blood. The emergence of HIV in the 1980s highlighted the importance of ensuring the safety as well as the adequacy of national blood supplies. This emphasizes that every country has a common need not only to ensure availability of adequate supplies of blood and blood products and their accessibility to all patients requiring transfusion but also to improve safety of blood and blood products.

During the late 1970s and early 1980s, haemophilia patients began using revolutionary new products to treat their condition. Concentrates of clotting factors were heralded as the way forward in haemophilia treatment and some pharmaceutical industry, arguably, sourced their raw material to the cheapest possible source of plasma to make as much products as they could. This approach very soon created concerns about the safety of blood products and patients receiving such products. In 1980–90s, hundreds of thousands of patients became infected through transfusion of contaminated blood and blood products. Up to 64% of persons with haemophilia in some of the developed countries contracted HIV infection from transfusion of contaminated blood products [2]. Because of public concern about blood supply, as a result of decisions made in the 1980s, developed countries in the 1990s established reimbursement programmes for persons with transfusion-acquired viral infections from blood or blood products and held criminal jurisdictions of government officials and industry leaders accused of delaying implementation of potential blood safety measures. Meanwhile, several countries have established compensation programmes for persons infected with HIV as a result of HIV-contaminated blood products [2]. The transfusion of individuals with products infected with HIV and hepatitis C was the largest public health catastrophe in Canada's history. Estimates suggest that infected transfusions led to more than 1000 individuals acquiring HIV and up to 30000 acquiring hepatitis C [3].

Despite significant improvements in safety of blood and blood components in developing countries, blood safety continues to be a concern for developing countries as a majority of donations in some of these countries are not screened for HIV, HCV or HBV. It has been reported that significant numbers of AIDS patients in countries such as India and China contracted the diseases through transfusion of infected blood and blood products. A survey of blood banks performed in 2000 found that while 87% of respondents screened blood for HBV and 95% for HIV only 6% screened for HCV. It is estimated that up to 10% of HIV-infected persons in developing countries were infected by virally contaminated blood or blood products [2].

There is now a general agreement that the full implementation of well-organized, nationally co-ordinated and sustainable blood programmes with appropriate regulatory systems that stress the role of 'voluntary, non-remunerated blood donors from low-risk populations'. Therefore the provision of blood, blood components and plasma derivatives from voluntary, non-remunerated donors should be the aim of all countries [1].

Iran blood safety profile

Because of establishment of Iranian Blood Transfusion Organization (IBTO) as a public and non-profit organization, transfusion system in Iran is very much centralized and under control of national health authorities [4,5]. Amongst other achievements, efforts of IBTO have resulted in improvement of blood donation index (25/1000 population). Currently, Iranian donors donate 1 735 000 units of blood annually, 98% of which is being processed into a variety of blood components for clinical use. Back in 1974, paid blood donation had been forbidden in Iran and since then the country's needs for blood components have been met through recruitment of mostly voluntary and sometimes family replacement donors. In 1995 and afterwards, IBTO enhanced its activities to promote non-remunerated voluntary blood donation (VNRBD) and elimination of replacement blood donation. Therefore, steady increase in number of voluntary donors in past decade finally resulted to 100% VNRBD in 2007. Both cultural and religious beliefs of Iranians who see blood donation as an altruistic and divine act created a unique opportunity for IBTO to invest on continuation of VNRBD. Presently, IBTO is much focused on increasing number of regular donors in the country. Currently, 40% of VNRBD in Iran are from regular donors who donate blood at least twice a year. However, the contribution of Iranian women to blood donation is low and only 9% of the total blood donations are currently contributed by Iranian women. Since 2007, to prevent any possible anaemia because of blood donation and as an incentive, IBTO initiated a free iron supplementation programme by distributing ferrous sulfate tablets for all female regular donors. According to a parliamentary law, since 2007, IBTO has started a medical insurance scheme to cover treatment of any possible medical

complication as a result of blood donation. The scheme also covers all blood and blood components receivers for any possible complication as a result of receipt of blood and blood components including TTI.

Despite absence of a published national survey regarding prevalence of HIV, HCV and HBV in general population in Iran, published reports estimated prevalence rates for hepatitis B, hepatitis C and HIV in general population as 3%, <1%, 0.1% respectively [6–8]. Despite limited resources available in developing countries and considerable costs of laboratory testing of blood samples, since 1973, IBTO screens all blood donations for HBsAg. However, screening donated blood for HIV and HCV was started in IBTO since 1989 and 1996 respectively. However, implementation of a highly efficient donor selection programme including meticulous donors interview, establishment of confidential unit exclusion programme and laboratory screening of donated bloods by IBTO have led to seroprevalence rates of 0.41%, 0.12% and 0.004% for HBV, HCV and HIV in donated bloods respectively. Prevalence of HBV has declined from 0.73% in 2004 to 0.41% in 2007. HIV prevalence also decreased from 0.005% in 2004 to 0.004% in 2007. Prevalence of HCV in 2007 (0.12%) also experienced a substantial decline from 0.13% in 2004.

Iran has a large number of thalessemic patients and currently about 18000 thalessemic patients depend on IBTO to receive their needed fresh-packed RBC. These patients like any other patients in need of blood components receive these products free of charges [9]. Therefore, ensuring availability of blood components to these patients who consume more than 25% of produced packed RBCs is one of the most important priorities of IBTO. To further reduce risk of TTI to the recipients, IBTO is now considering integration of a nucleic acid testing (NAT) system into its quality control system. However, the challenge the national blood system now faces is to find the appropriate balance between maximizing safety and ensuring affordability of the system. Despite the growing pressure from cost rises on IBTO, because of commitment of IBTO to safety of blood and blood components, cost will be a secondary concern.

Similar to some other countries, IBTO was also engaged in jurisdictional investigation regarding the possibility of infecting patients (e.g. haemophilic patients) through blood and blood components in past decades. Despite a two decade long court dispute, IBTO still faces legal challenges by the claims made by the haemophiliacs affected by HIV and hepatitis C. So far, some former officials of IBTO have received suspension sentences. By a court order, government of Iran has paid compensation to several hundred multitransfused patients claimed to acquire hepatitis C and HIV contamination through blood transfusion.

Although in 1980s, IBTO was involved in production of plasma-derived medicines [5], it is now known that imported concentrated clotting factors in 1980s are responsible for infection of haemophilia patients and not blood components prepared by IBTO. Administration of the imported clotting factors has apparently led to the HIV infection of about 200 haemophiliacs in whom the appearance of infectious symptoms in 1996 brought legal claims against Ministry of Health and IBTO as the defendant parties vs. Iran Hemophilia Association as the plaintiff. It was claimed that previous IBTO's fractionation plant was not equipped with an updated virus inactivation system. This caused confusion in Iran's judiciary system regarding the case of patients infected with HIV. The judiciary system intended to track back the source of infection to imported or locally produced plasma-derived medicines. However, later, the results of studies conducted by Pasteur Institute of Iran indicated that Iranian haemophilia patients are affected by HIV type B, whereas the HIV patients in general population of Iran were affected by type A virus [10]. Therefore, it may be concluded that the HIV-affected haemophiliacs in Iran were infected by imported clotting factors. However, HCV infection in patients can be attributed to both imported and locally prepared products. According to published results, prevalence rates of HBV and HCV in Iranian thalassemic patients who are mostly affected before 1996 are 1% and 22.4% respectively. Vaccination of most of the thalassemics at infancy or early childhood during past two decades contributed to the low rate of HBV contamination amongst thalassemic patients [11,12]. Vaccination against hepatitis B in Iran is part of national vaccination programme and all newborns including multitransfused patients received the vaccine thereby being at low risk for residual risk of HBV infection. However, there are few sporadic reports of HCV incidence in under 11-year-old multitransfused patients in Iran with indeterminate causes. Amongst many other causes, possibility of transferring infection to the blood recipients through blood donated by seropositive donors in window period without NAT testing is a valid concern. Although currently IBTO is evaluating implementation of a NAT system, it is evident that implementation of an efficient look-back and haemovigilance

systems which are high in IBTO agenda could shed light on the above cases.

IBTO plasma fractionation project

In recent decades, role of plasma-derived medicines in managing several disabling and/or life threatening diseases in clinical medicine has been substantially increased to the degree that treating specific diseases without these medicines would be very difficult or even impossible. However, because of some reasons including reduction of raw material supply and sharp increase in consumption of these products especially in newly emerging markets, world pharmaceutical market has frequently experienced shortage of plasma-derived medicines. Shortage of plasma supply worldwide has created a fragile situation in supply-demand balance of these products. As a result, international market has experienced substantial rise in price of these medicines which ultimately has limited access to these medicines in some instances and has compromised well being of patients, especially those living in resource-limited countries. This situation through possible introduction of plasma-derived medicines resulted from plasma with compromised safety may endanger safety of patients receiving such products.

This is evident that a national blood service plays crucial role in providing safe and adequate plasma to be fractionated to the very important medicines including clotting factors, albumin and immunoglobulins. Today many countries have developed a national policy to improve and secure availability of safe and affordable plasma-derived medicines. Although importing these medicines might be a prompt approach to meet national market's needs, worldwide shortage of these medicines and limited resources available in low resourced countries' health care system make this approach far from ideal. Therefore, an alternative would be to either manufacture these medicines locally or use contract fractionation approach. Although contract fractionation of locally produced plasma is a practical approach to respond to the needs of patients and physicians to these medicines, steady production of sufficient quantities of plasma either through plasmapheresis or donated bloods is an essential prerequisite for successful contract fractionation projects. This might be easily available in countries with accountable national blood services. Such organizations which receive sufficient blood donation through non-remunerated donors could provide substantial quantity of safe plasma to be fractionated to its derivatives [13].

In Iran, blood transfusion system has evolved as a result of direct involvement of government in health care system. Collecting of sufficient blood from VNRBD is the underlying policy of IBTO to cover needs for blood and freshly prepared blood components. Inevitably, with the implementation of component therapy instead of whole blood use, plasma recovered from donated whole blood is generated and could be used for fractionation. IBTO which receives over 1.7 millions donations from VNRBD is able to produce about 300 000 L of plasma annually. After responding to the needs for fresh plasma, each year at least 150 000 L could be reserved for fractionation. Despite presence of a viable national pharmaceutical industry in Iran [14], production of plasma-derived medicines has not been an area of interest for Iranian pharmaceutical industry. Therefore, plasma fractionation has developed as an adjunct of blood transfusion system and is mainly based on fractionation of plasma recovered from the whole blood donations. Iran as a country with increasing demand for plasma-derived medicines has successfully implemented a contract fractionation project in past years to improve availability of these medicines [5]. Since its establishment, IBTO implemented strict guidelines to minimize the risk of TTI. These strategies have greatly improved blood safety profile of the country and as it was already discussed in the previous section that the prevalence of viral markers has significantly reduced.

As in many other countries, in Iran plasma-derived products are regarded as medicinal products and their marketing authorization, which involves the official approval of the production process and quality assurance system used as well as product efficacy, is the responsibility of the National Regulatory Authority (NRA) in Ministry of Health. Therefore, it is expected that this procedure will contribute to improving safety profile of these products. This should allow plasma for fractionation to meet the quality and safety criteria necessary as a source material for the production of plasma products, complying with the requirements of the fractionator and of the national regulatory authorities involved. Therefore, as a prerequisite of plasma contact fractionation, Iranian NRA inspected and approved contractor site and currently evaluated all batch release documents before issuing marketing authorization for produced plasma-derived medicines. This is a prerequisite for releasing such products into Iranian market.

According to WHO guidelines, appropriate selection of blood/plasma donors, testing of blood/plasma donations, epidemiological surveillance of the donor

population, strict adherence to Good Manufacturing Practices (GMP) and implementation of a postdonation information system are amongst the most important measures to minimize the probability of transmission of TTI to the recipients of plasma-derived medicines [15]. Plasma for fractionation should be obtained from carefully selected healthy donors who after review of the medical history (the donor questionnaire), medical examination and laboratory blood tests, including approved tests for HBsAg, HIV and HCV, would be considered not to present an increased risk for transmission of infectious agents by plasma-derived products. Establishment of a continuous epidemiological surveillance system to collect data and monitor the prevalence and incidence and their respective trends of infectious markers that are relevant to the safety of plasma-derived medicines ensures long-term safety of such products and blood resources [15].

Therefore, IBTO has considered plasma fractionation as a mean to further improve national transfusion system. Plasma as a raw material for fractionation has safety and quality requirements which are unique and, in some aspects, distinct from those needed for plasma for transfusion [13]. However, establishing a domestic plasma fractionation facility is a resource-intensive exercise and for the time being, IBTO has chosen to enter into a contract fractionation agreement with an established and regulated manufacturer to improve access to plasma-derived medicines from its own domestic supply.

Since 2004, IBTO initiated a programme to enter a contract fractionation agreement for the surplus of recovered plasma produced in its blood collecting centers. Although this activity would obviously meet some of the needs of domestic market to these products, one of the main objectives of IBTO was to improve the national transfusion system and the profile of blood safety in the country. For this reason, IBTO has chosen to work with European fractionators and therefore it was necessary to obtain authorization of the relevant European regulatory authorities for processing the produced plasma in a European country. Between 2004 and 2007, details of quality control system and cold chain system of blood collecting centers of IBTO have been inspected by the auditors of European regulatory authorities and Paul-Erlich Institute (PEI), before receiving authorization for exporting plasma to Europe. Iran has an established centralized transfusion system, since four decades ago, with a reliable quality assurance system in place [5,16]. Therefore, IBTO did not receive any comments indicating critical or major defaults or deviation from GMP rules as consequences of inspections by inspectors of regulatory authorities and/or fractionators. However, most noticeable comments were in the field of documentation and traceability. Therefore, these audits and their feedback reports contribute to improvement of IBTO quality assurance system, especially in automation, cold chain, documentation and traceability areas. For example, IBTO has changed its method of plasma freezing from alcohol tank to blast freezer. IBTO has also planned to improve its automation using internationally recognized automation software, and in 2008, its first phase of this project was implemented in Tehran (Iran's capital) blood center.

Obviously, IBTO fractionation project is also a major importance in improving availability of plasma-derived medicines in Iran. As it is shown in Fig. 1, during 2006–2007, this project furnished the Iran market with 44% and 14% of its need of the intravenous immunoglobulin and albumin respectively. However, its role in providing Factor VIII (FVIII) was not substantial. Although the fractionation yield for FVIII was in acceptable range (160 IU L^{-1} of plasma), because of fairly high consumption of FVIII (1.7 IU per capita) [5], the amount of FVIII produced through fractionation project did not play a major role in responding to the needs to FVIII. Therefore, as depicted in Fig. 1, Iranian market is still very much dependent on the imported plasma-derived medicines and it is evident that as long as Iran relies on importation of plasma-derived medicines from abroad, Iran's blood safety policy will be heavily influenced by those of exporting countries.

Economic aspects of plasma fractionation projects were also reported previously in other countries [17]. In addition to substantial direct effect of this project

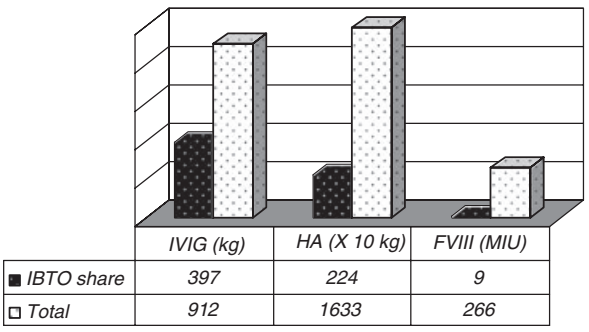

Fig. 1. Share of plasma derived medicines produced through IBTO contract fractionation project in Iran market (2006–2007). IVIG, intravenous immunoglobulin; HA, human albumin; FVIII, Factor VIII.

on saving of resources allocated for importation of these medicines, indirect effect of the IBTO project on reducing costs of imported medicines should be considered. Availability of medicines produced from plasma collected by IBTO in the market has convinced the international pharmaceutical companies to offer more reasonable prices for their products to hold their share in Iran market.

Since the main objective of IBTO for plasma fractionation is to improve the national transfusion system and furnishing the Iran market with plasma-derived medicines is its secondary objective, IBTO has no intention to increase the amount of plasma produced by increasing unnecessary blood collections. However, setting up plasmapheresis centers might be considered in future. However, Ministry of Health currently issues permits for plasma pheresis centres in Iran. Although these centres will operate outside of IBTO, this may eventually increase the volume of plasma produced inside the country.

Ensuring the traceability of plasma between blood donations and final plasma products is also a key element for blood safety. Following successful implementation of plasma contract fractionation with European fractionators and due to importance of following any possible postdonation infections, an effective communication system between IBTO and the fractionator has been established. Therefore, any significant postdonation events, especially any evidence for the presence of TTI in a donor whose plasma was sent for fractionation, may be immediately transmitted to the fractionator. This is mainly due to the presence of a national registry of donors in IBTO which allows proper evaluation of seroconversion rates. Most importantly, IBTO has implemented a look back procedure which enables it to track back all donations from a given donor with rejection in his next donation due to reactive viral marker or other risks related to TTI. IBTO transmits such information to the fractionator in order to exclude the donated plasma units from fractionation procedure. IBTO also notifies donor for counselling purposes intended for both donor health and safety of the blood supply. According to the fractionation agreement, the fractionator should perform NAT on plasma exported for fractionation for the HCV, HBV, HIV, HAV and parvovirus B19 viruses. To facilitate this test, IBTO developed a system to collect and provide labelled samples suitable for the test. Meanwhile, the fractionator is also obliged to notify IBTO of any positive or indeterminate NAT results performed on plasma units received for fractionation. These notifications will be promptly be followed by IBTO look-back system for proper actions including calling donor for further confirmatory tests and medical follow-up and recalling all relevant blood components from storage and distribution chain.

Conclusions

IBTO as a national centralized transfusion system, to ensure the provision of safe, high quality blood and blood products that are accessible to all patients and to provide adequate and timely supplies of safe blood for all patients in need, restricted its activities to collect blood only from voluntary unpaid blood donors at low risk of acquiring TTI, through stringent blood donor selection criteria and screening all donated blood. Through these policies IBTO was able to establish a sustainable supply of acceptable safe blood and blood components. IBTO produces substantial amount of recovered plasma from blood donations which exceeds the country's need to fresh plasma. On other hand, Iran's health sector is under pressure from increasing demand for plasma-derived medicines, and local production of these medicines would significantly improve access to these medicines. Therefore, for further improving national transfusion system and enhancing availability of plasma-derived medicines, since 2004 IBTO has initiated a contract fractionation project for surplus of recovered plasma from donated blood. Iran's experience showed that contract fractionation of plasma in countries with well-organized centralized transfusion system which lack national plasma fractionation facility, in addition to substantial saving on national health resource and enhancing the availability of plasma-derived medicines, could serve as a useful mean to improve national transfusion system and blood safety.

Disclosures

Authors are working for IBTO.

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