REVIEW

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Plasma collection in Indonesia - a challenge to implement fractionation

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ABSTRACT

In recent years, the national usage of Plasma Derived Medicinal Products (PDMPs), particularly albumin and immunoglobulin, has expanded due to a rise in disease prevalence, as well as enhanced patient management practices and broader assurance coverage. Now, Indonesia is a country that imports all of its PDMPs, resulting in high pricing and market reliance; nevertheless, barely a third of recovered plasma gets transfused to patients. The plasma that has not been used should be discarded, at a cost. The government intended to begin meeting the needs of the PDMP by implementing the plasma fractionation program. The decision was taken to use contract fractionation for three years, after which a national fractionation manufacturer was anticipated. The potential utility of recovered plasma and the prospective requirement for plasmapheresis collection have been assessed. The Minister of Health has enacted legislation concerning plasma fractionation, including the potential of establishing plasmapheresis centers to facilitate plasma collections. The Food and Drug Administration of Indonesia has also initiated a certification scheme for blood establishments (BEs), and only certified BEs can provide plasma for fractionation. After the epidemic, the government restarted the fractionation program by modifying existing laws to allow private manufacturers to participate. The difficulty was obtaining plasma from uncompensated donors, recruiting plasma donors, increasing the number of qualified biological examiners, of which only 19 out of 469 have been certified, and increasing technology and personnel capacities. Other significant obstacles were the harmonization or consolidation of existing biological entities (BEs) and the expense of paying for recovered and source plasma. The government and other parties involved had to make substantial efforts and collaborate to overcome these problems.

Keywords: Blood Establishment, Plasma Fractionation, PMDPs.
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INTRODUCTION

Pharmaceutical firms utilize human plasma to manufacture plasma-derived medical products (PDMPs), including albumin, coagulation factors, and immunoglobulins. The World Health Organization included PDMPs on its list of essential medications.[1-3] These pharmaceuticals were life-saving treatments for various chronic and acute life-threatening illnesses, including bleeding crises, autoimmune disorders, and chronic ailments, including hemophilia, congenital and acquired immunodeficiencies, and other hereditary protein abnormalities. Increased access to medical care, new products and uses, and diagnostic advancements have led to a surge in demand for PDMPs on a global scale.[1] PDMPs must be imported due to the fact that plasma created in underdeveloped nations was typically unsuitable for fractionation and commonly discarded.[4]

Indonesia is the largest archipelago between the Pacific and Indian Oceans. Its population was 275 million with 13,000 Islands, 34 Provinces, 416 Districts, and 98 Municipalities.[2] In recent years, the usage of PDMPs in Indonesia, particularly albumin and immunoglobulin, has risen. This was not simply a result of an increased disease incidence but also of enhanced patient management practices and broader assurance coverage. Indonesia is a country that imports all of its PDMPs, resulting in high pricing and market reliance. However, barely 10–30% of plasma was transfused to patients. The plasma retrieved but not utilized must be discarded, and expenditures incurred. A budget of around 67 million USD was utilized yearly. The government intended to begin meeting national PDMP needs by implementing the plasma fractionation program. As the volume of plasma required will exceed two hundred thousand liters per year, the most important aspect of this program is the collection of sufficient plasma. From the description above, this study was conducted to review the challenges, situations, and efforts that Indonesia can take to implement plasma fractionation.

Blood Supply and National Fractionation Program

Worldwide, the collection of raw material (human plasma) for fractionation was managed both by public and private organizations. Plasma was typically derived from whole blood collected by transfusion services at public blood establishments to manufacture labile blood components; in this case, plasma was regarded as a by-product and, provided that a good quality system was in place in the blood establishments, then plasma can be fractionated by pharmaceutical industries.[5] In Indonesia, blood collection was performed by Blood Establishments (BEs) managed by MoH hospitals, local

governments or Indonesia Redcross. There were 469 BEs around the country, mostly in Java island, among them belonging to hospitals, local governments and Redcross were 231, 3 and 235, respectively. These BEs could collect and prepare recovered plasma, but recently only 19 BEs were certified by Indonesia FDA. Only the certified BEs were allowed to prepare plasma for fractionation.

All donations in the country were based on voluntary bases, paid donors were prohibited. Because of the pandemic, Indonesia's total number of blood donors has decreased in comparison from 2016 to 2020. Blood was mostly collected from voluntary non-remunerated donors (VNRDs), but replacement donors (RDs) were also collected in some areas. In 2016 there were 2.99 million VNRDs and 261 thousand RDs, but in 2020 there were 1.6 VNRDs and 489 thousand RDs. The main cause of declining VNRDs was the COVID-19 situation. During this pandemic, blood collection must overcome the challenges of declining voluntary donors due to social restrictions and other health issues. Now, in line with the end of the pandemic, the number of VNRDs gradually returned to normal.

Since 1975, the WHO has passed resolutions urging the implementation of a blood supply system based on voluntary non-remunerated donation and the establishment of not-for-profit blood establishments with the goal of achieving self-sufficiency in blood supply.[5,6] This is the current basis for blood collection in nearly all European countries.[5] In addition to labile components, plasma-derived self-sufficiency can also be achieved through contributions from volunteer donors.[6] WHO stated that the voluntary unpaid blood donation rate should be between 10 and 30 percent to adequately satisfy a country's blood needs.

According to WHO data, only 55 of 171 reporting nations manufacture PDMPs by fractionating plasma obtained in the reporting nation. Ninety nations stated that all PDMPs were imported, sixteen countries claimed that none were utilized during the reporting period, and ten countries did not reply. About 25,6 million liters of plasma from 39 reporting nations was fractionated throughout the year to make PDMP. This includes around 47 percent of recovered plasma from whole blood donors.

Current Challenges of Plasma Collection

In order to achieve self-sufficiency, the World Health Assembly resolution WHA 63.12 urges member states to design, implement, and support nationally coordinated, effectively managed, and sustainable blood and plasma programs, based on the availability of resources. Individual countries were responsible for ensuring an adequate and fair supply of plasma-derived medical products (PDMPs): immunoglobulins and coagulation factors, which are necessary to prevent and cure a number of severe illnesses that occur globally.

In contrast to small-molecule medicines, the most difficult part of producing plasma-derived pharmaceuticals was the availability of plasma as the raw material. The majority of plasma used in pharmaceuticals was acquired from source plasma collection.[1] Therefore, the global challenge of plasma collection included the supply of medicine during turbulent times; clinical demand and market economy; political decision-making processes; national tenders for contract fractionation; political, legal and economic constraints; donor recruitment; local donor organizations based primarily on volunteers and geographical distribution of apheresis sites.

The United States was the world's greatest exporter of plasma, contributing the most to the worldwide source of plasma supply. This was made feasible by the combination of favorable regulatory conditions, the capacity to reward donors, an effective plasma-collecting infrastructure, and millions of donors. In 2019, almost 40 million liters of source plasma were collected in over 50 million collections in the United States. The majority of the global plasma supply comes from compensated American donors. European nations were around 60% reliant on American plasma goods, and the supply was not assured.[1,6] Only four European nations (Germany, Austria, the Czech Republic, and Hungary) permit the payment of plasma donors. In a similar fashion, China enables donor remuneration and gathers a substantial amount of the world plasma supply, which is then held in China.[1]

The volume of plasma collected varies on a variety of variables, including the number of plasma collections per donor, the number of donors (donor pool), the frequency of donations, the duration of active donor status, and the volume of plasma extracted in each collection. While a great deal of attention has been placed on the number of donors and the number of collections per donor, local restrictions have mostly determined the collection volume per donor. Donor recruiting was a primary priority for plasma collectors due to the relative scarcity of plasma donors. This included the creation of strategically positioned new centers, identification of possible new donors, and financial incentives. It was essential to maintain donors as active donors after they had been recruited. Local restrictions define the permitted frequency of donations (e.g., two times per week with two off-days in between in the United States), but donor satisfaction plays a crucial role in encouraging frequent donations and, more crucially, in retaining donors for longer durations.[1]

The whole plasma volume cannot be obtained from whole-blood donations alone, although space remains for improvement. In several European nations, plasma obtained from whole blood taken from VNRDs by non-profit blood institutions was discarded rather than fractionated because of a lack of volume, quality difficulties, and logistical and contractual obligations. Large plasma fractionation labs that are not-for-profit might use this plasma to create pharmaceuticals. The volume lost in this manner has not been measured. Given the declining need for whole-blood components, the modification of plasma for fractionation will necessitate the recruitment of apheresis donors and the establishment of specialized collection facilities.[6]

With the commencement of the COVID-19 pandemic, more strain has been placed on the system due to the rising demand for experimental COVID-19 treatments and the supply disruption.

Due to COVID-19 infections or the risk of exposure to COVID-19 in a collection facility, the number of collections per donor has decreased, as has the donor pool. As the situation progressed, collection centers placed a significant focus on safety and swiftly introduced social distancing and other safety measures (e.g., usage of face masks, and better cleanliness standards). Consequently, the collecting capacity at the center level was diminished. Currently, multicomponent collection machines for plasmapheresis are used almost exclusively in blood centers and hospital-based transfusion medicine departments to collect convalescent plasma for transfusion. In the absence of a vaccination or other specialized medications, plasma-derived pharmaceuticals have been recommended for the treatment of this novel illness.[1] In Indonesia, this situation made some BEs become confident in collecting plasma using the apheresis method, therefore increasing the possibility of collecting source plasma in the fractionation program.

The potential for the pandemic to spread is a cause for concern at blood centers, particularly for blood donors. Social distancing minimizes donor mobilization, which further leads to donor shortage.[7,8] Donors felt uncertain about donating blood in a blood center located within a hospital of COVID-19-treated patients. In this circumstance, transfusion professionals require innovative strategies to limit the impact of blood donor availability, both to encourage blood donation and draw the potential donor's interest. Transfusion professionals not only need to promote proactively but also need a strategy that could encounter the deepest motive of the donors. Some critical roles that play the greatest intentions to donate blood are approval from others, self-efficacy, appraisals, and organizational trust. Maintaining trust with potential donors was also very important.[9] In some blood centers, community promotion was performed in fixed donor sites.[8] A comprehensive approach based on blood donor motivations such as psychology, economics, biology, philosophy, and sociology of altruism is also needed to maintain the trust of potential donors.[10] The sifting characteristics of blood donors inform us that maintaining regular donors was very important, despite recruiting new potential donors. The new donor was very usual in hospital-based blood establishment compared to regular's ones. The new donor is usually a one-time donor, they came to the hospital for some reason and then suddenly donated their blood. There were two forms of this donor, i.e., those who spontaneously donate at blood collection sites (so-called random donors) and who donate blood for their family, friends, or relatives (so-called family donors). It was vital to note that the primary reason for our blood donors was social altruism, however, there were additional motivations such as spontaneity, being inspired by a friend/relative/colleague who was a blood donor, or because one of their family members, friends, or acquaintances had previously had a blood transfusion. With the campaign, it also tends to change family donors became random regular donors, and later possibly became plasma donors.

Blood establishment was crucial for both the donor's health and the plasma's quality.[11] Ongoing efforts of donor recruitment and retention need to be intensified. Continued donor recruiting and retention efforts must be strengthened. Countries that now prohibit the payment of plasma donors should reconsider this policy in order to increase the worldwide supply. In the middle of the epidemic, protocols were crucial to ensure donors regarding the safety of collection locations and the collection procedure. Improve donor satisfaction to enhance contribution frequency and length of active donor status. Lastly, it will be essential to maximize the collection from each contributor. Several solutions were already in place, such as the technology to securely collect the maximum permissible collection volume (without anticoagulant) and the technology to decrease waste in the disposable collection sets. In addition, clinical investigations, including increased donation strategies, indicated the possibility of collecting more plasma from individual donors in a safe manner.[1] Local synthesis of plasma using BEs (recovered plasma) and/or plasmapheresis (source plasma) makes it possible to produce PDMPs locally.[3]

Plasma for the production of PDMPs is collected from two sources: recovered plasma and plasma obtained by plasmapheresis(apheresis plasma or source plasma). The commercial plasma sector produces the majority of source plasma. Even as whole blood collections and the quantity of recovered plasma suitable for fractionation declined, the global demand for PDMPs grew. While whole blood donations decreased in rich countries, they increased in low- and middle-income countries. Sadly, the majority of the growth in whole blood collections will not translate into additional recovered plasma and PDMPs; the majority of the plasma, frequently prepared from donors who were not adequately screened and in facilities that lacked Good Manufacturing Practices and plasma freezing and storage capacity, did not meet fractionation quality criteria and was discarded.[4] Based on a similar situation in Indonesia, the centralization of BEs for component preparation and infectious screening must be considered. Using this program more plasma for fractionation could be collected with a complement to GMP requirements.

Plasmapheresis utilizes centrifugation to separate plasma while returning blood cells to the donor. A unit of recovered plasma spans from 100 to 260 ml (WHO) and can be used to create fresh frozen plasma (FFP), convalescent plasma treatment (CPT) for COVID-19, or PDMPs. Whole blood donors were often limited to donating every three months to prevent anemia. Plasmapheresis (source plasma) produces more plasma (450–880 ml, depending on the country's collection rules). In comparison to recovered plasma, plasmapheresis permits the collection of substantially greater yearly plasma volumes for fractionation due to a combination of increased donation frequency and bigger volumes for each donation.[11]

Plasma meets the criteria for a strategic resource. There was a need for a more balanced and equitable international plasma supply in order to lessen the possibility of supply shortages worldwide. We recommend that blood and plasma be regarded as strategic resources equivalent to electricity, water, and other products

and services deemed essential to national or regional autonomy. The objective was to emphasize the significance of balanced and diversified collection and preparation and to limit the danger of plasma and life-saving PDMP shortages. Governments or regulatory organizations should take steps to limit the present danger of reliance on plasma supplies from a particular country or area.[4] The optimal use of blood products was of the utmost importance in the field of transfusion. Hence, the clinical use of the products must be controlled (either by regulatory agencies or by scientific societies) by means of programs of appropriate use, attaining self-sufficiency from national plasma for the approved indications of use and possibly leaving to the market supply the fluctuation in use due to indications still under investigation. However, once the additional indications have been adopted into recognized clinical practice, patient product availability must be ensured and the national plasma collection program must be changed accordingly.[5] The Indonesia FDA (BPOM) and the Ministry of Health (MoH) were responsible for this initiative. The Ministry of Health has enacted legislation addressing plasma fractionation, including the potential of establishing a plasmapheresis center to facilitate plasma collections. The Food and Drug Administration of Indonesia has also initiated a certification scheme for blood establishments (BEs), and only certified BEs can provide plasma for fractionation.

In countries with legislation restricting plasma collection to VNRDs (as is the case in the majority of European countries), the priorities of plasma fractionation policies differ from the perspectives of the global market; the amount of plasma to be fractionated to reach or maintain self-sufficiency must be clearly linked exclusively to the requirements for appropriate uses of plasma products. Indeed, the correct use of national plasma resources, the ethical use of donations, the proper clinical use of plasma products, the adequate provision of PDMPs, and the cost-effectiveness of the national plasma program all require a precise definition of the term "self-sufficiency." In this regard, the application of WHO definitions of self-sufficiency to plasma and plasma products in Europe could be expressed as "the capability to systematically guarantee to patients the prompt and continuous availability of a defined set of essential MPD, aligned with patients' specific needs."[6]

However, due to the exorbitant cost of plasma-derived medications, these therapeutically valuable instruments were out of reach for the vast majority of patients in impoverished nations. There were several approaches for ensuring the availability of these medications. Locally produced plasma may be manufactured locally, imported, or fractionated under contract. However, local production of plasma-derived medicines and/or importation of these medicines may be a practical way to meet the demand for these medicines. In recent years, a number of nations have utilized contract fractionation of locally produced plasma as a highly effective method for increasing the availability and affordability of plasma-derived medicines on their national market.[3]

Therefore, a combination approach comprising national production through contract fractionation and importation (either plasma source or synthesized proteins) would be the most practicable method for facilitating access to plasma-derived pharmaceuticals. To ensure proper utilization of nationally collected plasma, appropriate clinical use of plasma products, ethical use of the donations, the cost-effectiveness of the national plasma program, and adequate provision of medicinal products to patients, the concept of self-sufficiency must be more precisely defined.[5]

Contract fractionation/toll fractionation of locally produced plasma, primarily for their national transfusion services, was another effective method employed by several nations in rich and emerging economies to provide PDMPs. Plasma contract fractionation was a scheme in which local plasma was supplied to the fractionator and final products were returned to the plasma supplier's country. This program has a number of advantages, such as improving the national blood and/or plasma collection system by enforcing the standards required for plasma production to be suitable for fractionation, the source of the plasma and its quality level were known; the surplus of the recovered plasma produced in the national transfusion system will not be wasted; it offers relatively quick access to the PDMPs; and it offers a relatively secure method for gaining access to PDMPs even during global pandemics.[3]

Toll plasma fractionation was thought to refer to a system in which a licensed pharmaceutical corporation transforms human plasma obtained by blood facilities into pharmaceuticals for usage inside a country. This was the sole option in Italy to fractionate plasma collected and tested from VNRDs by Italian transfusion agencies, who were prohibited by law from selling plasma to fractionators into medical goods. One area manages the contract on behalf of numerous others, necessitating the formation of a partnership in order to fractionate enough amounts of plasma. As required by national law, this was completed at the point of national self-sufficiency for blood products.[12] Many countries also implement this scenario to use local plasma for fulfilling PDMPs needs. In Indonesia, toll fractionation can be implemented as the first phase, in line with the development of its own national manufacturing.

Contract manufacturing programs must, of course, advocate the technology with the highest yield, primarily in the driving product, in order to produce the largest quantity of driver product with the smallest volume of plasma necessary. When risk-benefit, cost-effectiveness, and/or health technology analyses indicate that products generated from sources other than human plasma are preferable, they must be utilized instead. Given that the collection of plasma for any driving product will inevitably generate significant quantities of other products (e.g., coagulation proteins), programs must be in place to ensure the availability of these latter products in countries where insufficient therapeutic products were delivered to patients, while recovering manufacturing costs as permitted by Italian law.[4]

In Italy, for instance, domestic plasma toll fractionation was conducted by only one business until 2014, limiting access to diverse technologies and products

and pricing competition. In 2017, four businesses competed to fractionate 827,720 kg of plasma as toll fractionators. Competition among companies resulted in higher yields of albumin and immunoglobulin, decreasing their level of market dependence, an expansion of the portfolio of medicines, and a 20–30% price reduction due to fractionation, thereby enhancing the outlook for the national program for self-sufficiency in plasma-derived medicinal products.[12]

The geographic disparity in the collection of plasma in the United States raises worries that local interruptions of plasma supply may lead to regional and worldwide shortages of key PDMPs.[4] Indonesia is the largest archipelago making the distribution and coordination even harder. As a result of the outbreak in Indonesia, more BEs were able to collect plasma. The government has provided more than sixty new apheresis machines to BEs and hospitals for use in plasma collection.

The Indonesia fractionation program has been delayed because of the epidemic. The government expected to begin meeting PDMP's needs by implementing the plasma fractionation program. The decision was taken to use contract fractionation within three years, after which the government firm intended to operate a national fractionation factory. It has been determined if plasma received from whole blood donations may be utilized and whether plasmapheresis treatments may be necessary. Currently, the government is resuming implementation of the fractionation program and modifying current restrictions, such as the prospect of allowing private manufacturers to participate. The present obstacles include how to meet plasma supply from uncompensated donors, initiate plasma donors, increase BE certification, since only 19 of 420 BEs are now qualified, and increase technological and human resource capabilities. Other significant obstacles in Indonesia included the harmonization or centralization of existing BEs, which were controlled by the government and the Indonesian red cross, and the expense of paying for retrieved and source plasma collected. In addition, there were factors such as meeting internationally recognized standards for donor eligibility, laboratory testing and Good Manufacturing Practices (GMP) in product processing to ensure that the quality of recovered plasma was acceptable for fractionation, inadequate cold chain and supply chain logistics to ensure that appropriate standards were met, and absence of regulatory oversight to ensure that appropriate GMP standards were met. These challenges were overcome with some strategies, including nationally coordinated blood collection centers, networking between BEs, centralization for blood screening and component processing, policies & guidelines for blood donation still need to be improved, national campaigns & advocations were maintained, benchmarking and cooperation with other countries in the region.

The authors are very aware that this study has limitations, there are not many domestic references related to this manuscript so several technical factors are taken from experience in other countries/ centers. The next study will elaborate on the stages of implementation in Indonesia, along with the problems in the field and how the results of the follow-up carried out by the Indonesian government.

CONCLUSION

Indonesia's national self-sufficiency in plasma necessitated colossal efforts and partnerships from the government and other stakeholders.

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AUTHOR CONTRIBUTION

TT: drafting ideas, writing and editing manuscripts; HF: references, writes and edits manuscripts.

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CONFLICT OF INTEREST

None.

ETHICAL CONSIDERATION

Not applicable.

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