The Convalescent Plasma Craze! Where Does India Stand?

Arcot J Priyadarsini[1] Kumar Karan[1] Subramanian Arulselvi[2]

[1]Department of Transfusion Medicine, AIIMS, New Delhi, India
[2]Department of Laboratory Medicine & Blood Bank, Jai Prakash Narayan Apex Trauma Centre, New Delhi, India

Address for correspondence Arulselvi Subramanian, MD, Department of Laboratory Medicine & Blood Bank, Jai Prakash Narayan Apex Trauma Centre, New Delhi, India (e-mail: arulselvi.jpnatc@gmail.com).

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Abstract

India becomes the country with second highest number of coronavirus disease 2019 (COVID-19) cases (59,03,932) as of September 2020. As the world debates various treatment options, the current pandemic has led to the resurgence of an ancient technique, namely convalescent plasma therapy. Although it has been in use from the late 19th century, it is an uncharted territory for most developing nations. In this article, we have discussed the pros and cons of convalescent plasma transfusion in COVID-19 patients. Articles discussed in this review have been obtained from search engines, namely PubMed, Scopus, and Embase. We have also expressed our viewpoint on the feasibility and logistical challenges of convalescent plasma use in India.

Keywords
- COVID-19
- convalescent plasma
- India
- challenges

Key Message

The right and wrong regarding the usage of convalescent plasma are yet to be solved. Building enthusiasm must be dealt cautiously to prevent the promotion of paid donation in India.

Introduction

The current coronavirus disease 2019 (COVID-19) pandemic has been talked about for more than 8 months now. Highlights are the novelty of the virus and the unpreparedness of even the most developed nations. Viruses of the β-coronavirus genus commonly cause mild respiratory infection.[1] But the previous two pandemics caused by severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 were exceptions, as the strains became highly pathogenic and virulent on crossing the species barrier.[2] The SARS-CoV-2 genomically resembles SARS-CoV,[3] but differs in two aspects, namely better prognosis (except in older patients with comorbidities) and higher transmission rate.[4-6] Symptoms can be mild (fever, cough, myalgia, fatiguability, dyspnea) to severe (respiratory distress, multiorgan failure, immunomodulatory effects, coagulopathy) and sometimes even be fatal.[6-8] Although this is the third pandemic by coronavirus, there are no approved treatment options. From retrying pre-existing and native medicines to the development of newer-options/vaccines, mankind has left no stone unturned.[9,10] Convalescent plasma (CP) is one of the treatment options amply debated. CP refers to plasma obtained from a recently cured individual with an aim to harvest capable levels of antibodies directed against the causative agent. Theoretically, they can be used as treatment as it will prevent disease progression by offering short-term/passive immunity[11] or as prophylaxis.[12] Its role in active immunity has also been observed.[13] Along with neutralizing antibodies, other anti-inflammatory substances (defensins, non-neutralizing antibodies, etc.) provide further immunomodulatory benefits.[14] Antibody transfer dates back to 1890s when Emil von Behring used CP against bacterial toxins before the discovery of antimicrobials for which he received the Nobel Prize.[15] The current pandemic has led to resurgence of this ancient technique (►**Fig. 1**). In this review,

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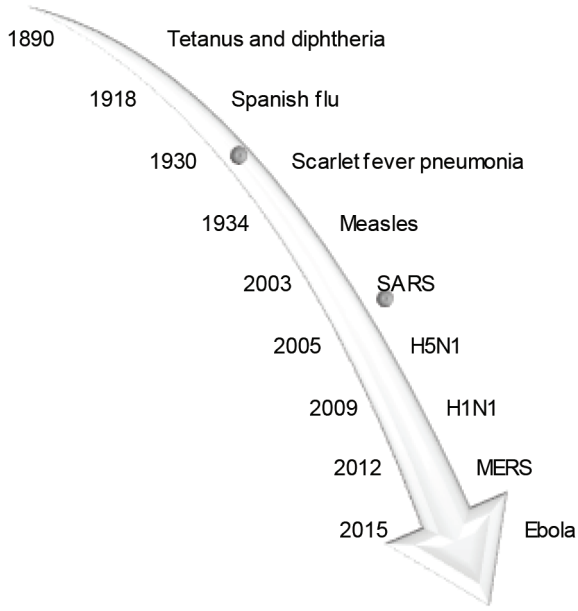

Fig. 1 Convalescent plasma—an ancient technique.

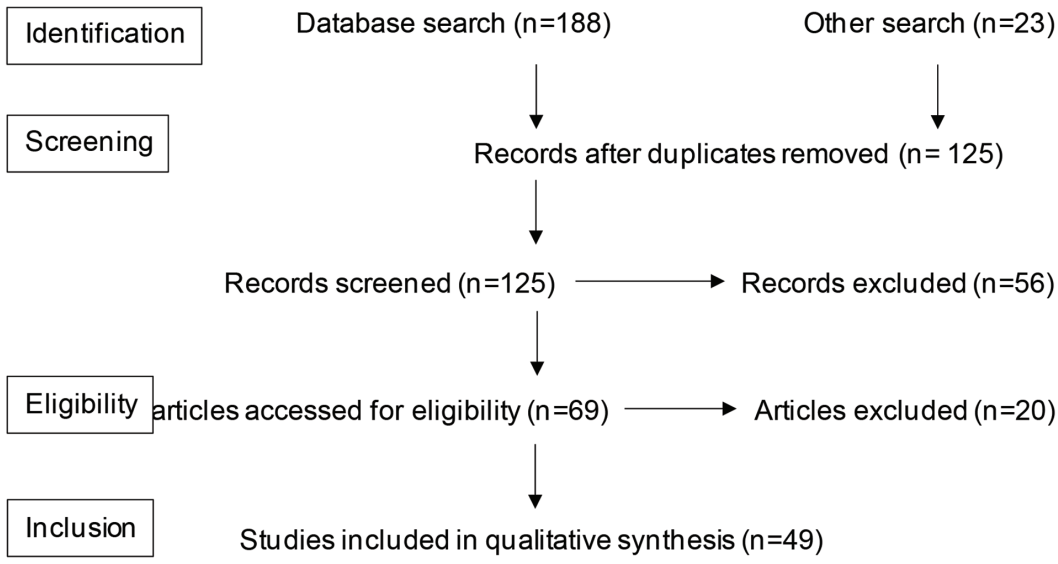

Fig. 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow for study inclusion.

we discuss the past and present experience with CP and the Indian challenges with respect to logistics and feasibility. Articles discussed in this review have been obtained from various search engines, namely PubMed, Scopus, and Embase till September 20, 2020 as shown in ►**Fig. 2**.

Previous Experience

Case reports and series have been published on the beneficial effect of CP in SARS-CoV-1, MERS-CoV emphasizing its use in the earlier phase of disease, lack of serious adverse effects, donor group to be targeted for harvest (recovered patients who were symptomatic during the time of illness), collection timing (antibody titer decreases as the time after recovery increases), and the most beneficial patient group (young patients with mild disease).[16-18] Quality research was not possible during the outbreak of Ebola as it mainly affected lower economic geography. However, an immediate decrease in viral load was observed in patients who received CP as an additional treatment.[19] Due to the devastating nature of the virus, the World Health Organization (WHO) went ahead and recommended the use of CP in treating ebola.[20] The use of CP was also studied in patients with influenza[21] and other viral hemorrhagic fevers.[22]

From previous experiences, two things are clear. First, there is evidence on the potential benefits of CP against various infectious diseases. Second, there is no literature about CP use from India. Hence, Indian setups are quite new to this territory that will give rise to newer challenges.

CP in COVID-19 Pandemic

Typically, during the earlier phase of the disease, antispike antibodies (inducing apoptosis) are produced. Only during the later phase, antinucleocapsid antibodies (neutralization) are produced. Most of the published case series,[23,24] randomized,[25] and matched-controlled trials[26] have had good outcomes (symptomatic/radiological resolution, lymphocyte count, viremia) with minimal side effects emphasizing its use in the earlier phase of the disease. But few have questioned its actual role in reducing disease mortality.[27] Also, the routine use of CP may suppress the patient's humoral immunity[28] and may lead antibody-dependent enhancement of the disease[29] that should be kept in mind.

The side effects of CP are similar to routine plasma transfusion. A susceptible-exposed-infected-removed model-based risk–benefit analysis was used to compare the benefit of CP and its transfusion-associated risk from the available literature. In simple words, the authors concluded that the mortality due to the disease is more than the mortality due to CP administration.[30]

Finally, the Cochrane Library of reviews that compared the efficacy and safety of CP versus hyperimmune immunoglobulin (HIIG) concluded the uncertainty of CP's effect due to low-quality evidence till date and is waiting for results comparing the two from ongoing studies.[31] Based on the available evidence, it is only clear that CP does not cause any serious side effects. Hence, CP was approved as an emergency investigational new drug by the United States' Food and Drug Administration (FDA) on August 23, 2020 and later three types of access to CP were established, namely compassionate use (for life-threatening illness), clinical trials, and expanded access.[32] FDA does not allow its use for prophylaxis. It calls for further high-quality studies. A comparison of the three major guidelines, namely American, European, and International Society of Blood Transfusion (ISBT) is shown in ►**Table 1**.

Studies Till Now

Till now studies have had different objective/s, population type (mild/ moderate/severely ill-patients/mixture), timing of administration (prophylactic/earlier/later), and with/without a control group (exclusive benefit). The control group can receive random donor plasma or standard care. Aspects such as wastage of plasma, transfusion-related side effects, and beneficial effects of routine plasma must not be forgotten.

The ultimate end point measured will depend on population type. For instance, symptomatic/radiological improvement and pulmonary function status will be the end point in hospitalized noncritically ill patients. But for ventilated/patients admitted in intensive care unit (ICU), death will be the end point. Secondary end points shall range from duration of hospital/ICU stay, cost incurred, antibody titers, viral load, and end-organ failure. With unlimited number of published material and ongoing studies, it is becoming difficult to conclude on the role of CP. Broadly, the studies can be divided into three types.

1. Role of CP in postexposure prophylaxis: Study subjects are those exposed to virus but yet to develop symptoms. End point will be "patients testing positive." Such studies will show the effect of CP as post-exposure prophylaxis in high-risk groups (health-care workers, elderly with comorbidities). No studies of this type have been published till date.
2. Role of CP in halting disease progression: The effect of CP when transfused in patients with mild (end point—hospital stay/disease progression/oxygen requirement) or moderate disease (end point—progression to critical disease/intubation). Encouraging results have been obtained in mild-to-moderate illness.[33]
3. Role of CP as a last/rescue option: Results are unreliable due to several confounding factors (received/receiving other treatment/already developed antibody). End point will be death. Although studies have proved the safety and beneficial effect of CP in severe/critically ill patients,[34,35] some have shown that the benefit is obtained only when the CP is administered during the earlier phase of illness.[36,37]

Indian Scenario

Although the second interim guidelines by National Blood Transfusion Council (NBTC) did not recommend the routine use of CP,[38] the recent advisory by Central Drugs Standard Control Organization has indicated CP as off-label therapy in patients not improving with steroids.[39] As of now, 12 registered clinical trials on CP are ongoing.[40] Indian Council of Medical Research (ICMR) in collaboration with other health centers conducted the PLACID (open label phase II multicentre randomized controlled) trial.[41] Although this is the largest study in the country involving 46 centers, it represents the finding of real-time setups with limited resources. The primary objective was to assess the safety and efficacy of CP in moderately ill patients with primary end points being progression to severe acute respiratory distress syndrome, all-cause mortality at 28 days and secondary end points being symptomatic-radiologic–clinical resolution, hospital stay, viral load, antibody titer, and biomarker levels (C-reactive protein, interleukin-6, ferritin). Control group received standard care (symptomatic treatment, antiretrovirals, immunomodulators, anticoagulants, etc.). Although there was symptomatic improvement and seronegative conversion, reduction in 28-day mortality was not achieved.[42] Studies with longer duration of follow-up (3 months), on different study population (critically ill), survey-based study on the knowledge/practices concerning CP usage are all ongoing[40] and published results are expected soon. Delhi developed the first plasma bank in the country on June 2, 2020 followed by the second one on July 14, 2020 in two major COVID-19 hospitals.[43,44] Maharashtra has launched Project PLATINA, involving 21 centers to enroll 5,000 critically ill patients.[45]

Indian Challenges

Although CP is considered a cheaper/quicker alternative to other options, it is still dear and fancy for developing countries. India has a long way to go due to challenges ranging from lack of guidelines, apheresis centers, and testing kits.[46] The major challenges are discussed in the following text.

Lack of Guidelines

As of date, India has no guidelines regarding collection, testing, storage, and use of CP. Addressing the importance of research, the ICMR—Bioethics unit released a guideline for undertaking quick research without compromising validity and ethics.[47] This document highlights the importance of prioritizing COVID-19-related research, patient/donor confidentiality (circulating pictures might create nuisance due to stigma associated with disease), consent (CP is an experimental drug), equitable patient enrolment, nonremuneration, coverage for research-related injuries, accessibility of research findings, and biosafety precautions.

Donor Recruitment

The success of CP depends on number of donors coming forward to donate. In the current setup where inventory is already dipping,[46] it is sad to observe when blood banks repeatedly call donors to receive no response in return. Hence, counselling must start at in-patient level, emphasizing their moral responsibility to donate CP post-recovery. A dedicated team should tie up with COVID-19 centers to recruit potential donors. Use of social media can have huge impact. Robust mass tracking/tracing for donors should be considered after weighing the public health need versus privacy issues. Guideline for transfer of CP from one blood bank if established can ease the availability of CP to peripheral centers.

Donor Selection

CP obtained in India is majorly through directed or replacement donation who may not completely reveal the history under pressure to help the patient. This is riskier compared with voluntary donation due to higher risk of transmitting infections to the recipient (especially without nucleic acid testing) and health care workers (respiratory shedding of SARS-CoV-2). Hence, it is better not just to rely on the donor claiming to be asymptomatic.

Female donor parity is again a topic of controversy. Although the FDA and European guidelines recommend CP collection from parous females only if they are negative for human leukocyte antigen antibodies, such testing facilities are not available in Indian blood banks. Hence, the decision to defer parous female donors must be weighed considering the rare incidence of transfusion-associated lung injury) versus CP availability.

Donor Testing

Although studies have observed respiratory shedding of virus from 13 to 29 days of symptom recovery,[48] no one exactly knows when the shedding stops. Most countries follow a policy of recruiting donors after 14 days of recovery. But with regard to testing, some countries recommend a negative nucleic acid test before donating, sometimes even two negative results obtained 24 hours apart (prevent exposure to health-care workers) and some allow donation after 28 days even without testing (►**Table 1**). Longer duration post-recovery ensures complete resolution and adequate dose of antibody.

Reverse transcription polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA), and rapid diagnostic test (RDT) are the common tests used to detect the presence of viral antigen. Apart from nasopharyngeal swab (preferred sample), others include oropharyngeal swab, bronchoalveolar lavage, tracheal aspirate, sputum, lung tissue (autopsy), blood, urine, and stool.[39] ICMR has advised the use of FDA-approved in-vitro-diagnostic-kits.[49] Since RT-PCR is restricted to higher level centers, has longer turnover time, and is costlier, the use of RDTs have been approved.[50] The availability and affordability of these testing kits have improved.[51] It is important to mention the test-seeking behaviors of anxious individuals who may/may not have contracted the infection.[52] Having said that, the reliability of donor information on infection resolution is questionable. Hence, the decision on whether or not to test donors and if yes, which test to be done (rapid/nucleic-acid-based) and the number of tests required should be decided accordingly. For example, donor recruited from the same hospital/with reliable documented test result can directly go through the donation process. The chance of false positives/negatives must also be kept in mind before deciding on the testing modality. Routine testing (blood grouping, infectious markers) and quality-checks have to be adhered to.

Antibody Titration

Various controversies on minimal titer, time of collection, and type of antibody/isotype/subclass to be measured exist. Till date studies claim that titers increase from day 10 to 15 and become steady after.[53] The minimal titer requirement varies from country-to-country (►**Table 1**). Although neutralizing antibodies are the focus, their titers are variable (especially after mild symptoms).[54,55] Another theory suggests that high titer of immunoglobulin (IgM) might not be safe, as it indicates recent/current infection. Hence, it is safe to measure both IgM and IgG levels. Other hurdles include availability of testing equipment and lack of standardization. The gold standard test, namely plaque-reduction-neutralization-assay requires biosafety level-3 setup, has a longer turnaround time and requires expertise to perform. Hence, developing countries predominantly use ELISA. But there are challenges in the availability and procurement of these testing kits. Addressing all these barriers, none of the guidelines have made it mandatory to test for antibody titer before transfusion, although they suggest sample storage for later testing that will help in correlating the therapeutic effect (►**Table 1**). In other words, the sole purpose of CP transfusion in itself need not be confirmed before transfusion. This might lead to unwanted side effects with no benefit probably.

Table 1 A comparison of major guidelines

Criteria	US-FDA[32]	European[70]	ISBT[71]
Donor-selection	1. Routine donor eligibility[72] 2. 14 days following recovery 3. Documented positive diagnostic test (nasopharyngeal swab) at the time of illness or positive serological test after recovery 4. Female donors who have been tested as negative for HLA antibodies since their last pregnancy	1. Routine donor selection guidelines[73] Direct recruitment from National COVID-19 registry and not restricted to social media/calls 2. Documented prior RT-PCR positive or current antibody-positive irrespective of previous symptoms 3. 28 days following recovery or 14 days if there is use of pathogen-reduction-techniques, negative RT-PCR from upper-respiratory-tract sample and positive serology in donors who never developed symptoms/never had RT-PCR done 4. No history of blood transfusion and female donors who have been tested as negative for HLA antibodies since their last pregnancy 5. Donors donating more than once should test for antibody titers	1. Local regulations in line with donor selection during pandemic[74] 2. Confirm recovery by physical examination and testing Documented and traceable history, symptoms, treatment, and date of resolution 3. 28 days following recovery (2 negative test result by nucleic-acid-testing on nasopharyngeal swabs 24 hours apart) 4. Preferably female donors who have never been pregnant (including abortions) 5. Repeat donations complying local regulations
Antibody-titer	1. If available 2. Minimal titer 1:160 recommended, 1:80 acceptable 3. If not, store sample for later testing	1. Strongly recommended to measure antibody titers before/after donation/after processing 2. No robust cutoff > 160 recommended by Italian Society[60] If no antibody detected, divert for routine transfusion/fractionation 3. Additional sample saving (irrespective of testing) 4. For repeat donation, donors with higher antibody titer preferred	1. If feasible 2. Samples stored at –80°C for testing later
Collection	1. Licensed centers 2. Label mentioning "Caution: New Drug–Limited by Federal law to investigational use," along with ISBT-128 labeling	1. Apheresis whenever possible; whole blood can also be collected; notify serious donor reactions 2. Labeled as COVID-19 convalescent plasma/blood 3. Final product split to 200 mL units 4. Pathogen reduction need not be applied in specific to CP alone	1. Certified establishments with approved collection equipment and trained staff 2. Clearly labeled 3. 200–600 mL (without anticoagulant) 4. Pathogen inactivation preferred
Storage	Stored within 8 hours of collection at –18°C or colder (1-year expiry)	Routine guidelines of storage in dedicated location[72]	Freeze as soon as possible (–20°C or colder)
Patient-selection	1. Clinical trials 2. Expanded access 3. Emergency treatment	1. Laboratory confirmed positive in-patients 2. Preferable to enroll in trial and share coded data 3. Transfused within 7 to 14 days of symptom onset[60]	Preferably through organized research studies only
Transfusion	As per trial protocols	1. Aim to transfuse CP with highest antibody titer 2. Transfuse 8–10 mL/kg, maximum 600 mL/day and up to 3 consecutive days[60] 3. Absolute contraindication: IgA-deficiency; record all side effects[60]	1. Hospital plasma transfusion protocol 2. Initial dose of 200 mL followed by additional (one or two) 200 mL doses according to tolerance and disease severity 3. ABO compatible 4. Preferable to transfuse CP of 2 different donors 5. Strict hemovigilance of recipient (pre- and post-transfusion sample to be stored)

Abbreviations: COVID-19, coronavirus disease 2019; CP, convalescent plasma; HLA, human leukocyte antigen; IgA, immunoglobulin A; ISBT-128, International Society of Blood Transfusion; RT-PCR, reverse transcription polymerase chain reaction; US-FDA, U.S. Food and Drug Administration.

Match Donor with Patients

Ensuring selection of right donor, harvesting product at right time, allotting to right patient, and transfusing at right time are a cumbersome task. Use of health information technology will help simplify this process. A team of informatics experts from Malaysia and Iraq has come up with a fully automated-computing-solution-framework,[56] which shall compile the national recommendation for CP, donor parameters (blood group, viral marker status, antibody titer, etc.) and patient parameters (serology, blood group, disease severity). By multi-criteria-decision-making software, which will weigh and outweigh various combinations of donor-patient, a said product will be allotted to a said patient by subjective-objective-decision-by-opinion-score-method just by the click of a mouse. Such programmed software can help in simplifying the work of doctors.

Harvest

Only licensed blood centers with trained staff should collect CP following good manufacturing practices (►**Table 1**). India is still at a toddler level, as even the tertiary centers (government funded) in many states do not have a functional apheresis unit due to higher cost and required expertise.[57,58] Procuring cell-separators and training of staff had to be fastened to enroll more blood banks to participate in trials. The ISBT-working-group-on-convalescent-plasma has suggested to keep the CP collection to a restricted area of blood center. Mobile collections to be done in areas only where a significant number of individuals have been cured.[52] Preliminary telephonic screening will prevent unnecessary exposure of health-care workers. Plasma from whole blood collection can be considered in resource-poor setups (►**Table 1**). There is no national guideline till date on collection volume for which other guidelines are to be followed (►**Table 1**).

Pathogen-Reduction Technologies

SARS-CoV-2 is a large (120 nm) lipid-enveloped virus, which makes it susceptible to pathogen-reduction-technologies (PRT) (solvent-detergent, pasteurization, dry-heat, nanofiltration). Studies on the effect of PRT on SARS-CoV-2 have promised results.[59] There is enough evidence that SARS-CoV-2 is not transmitted by blood. Hence, the unavailability of these techniques will not pose any increased risk of transfusion-transmitted infections.

Recipient Monitoring

No strict guidelines on the volume to be transfused exist. Italian society suggests transfusion of 8 to 10 mL/kg once a day up to 3 days consecutively.[60] ISBT working party suggests a minimum of 200 mL.[52] Actual dosage can only be calculated after knowing the bioavailability of the transfused product. Studies to conclude the optimal dose and best therapeutic window are ongoing.

No concerning side effects were observed till date apart from those associated with routine plasma transfusion (febrile reactions, allergic episodes) that can easily be resolved by symptomatic management and slowing of transfusion rate. Although in theory patients with pre-existing lung injury can have more severe transfusion-related respiratory side effects and vice versa,[61] such findings have not yet been found in COVID-19 patients. Blood group matching is of critical importance in blood transfusion, but it is not the case in plasma. The occurrence of a hemolytic transfusion reaction is estimated to be approximately 1 in 2,000 to 9,000 (anti-A, B IgM titers >100 can cause hemolysis).[62] But, the national guidelines on the use of CP as an off-label drug recommend ABO compatible usage only.[39] This hugely impacts the CP availability in relatively rarer blood groups.

Other risks such as aggravation of hyperimmune attacks exist,[63] emphasizing the importance of timing of administration. The exact timing of administration of CP still remains controversial. Transfusing CP in the earlier phase of disease (when the body has not produced antibody) will reduce repeated immune system stimulation, thereby preventing cytokine storm. On the other hand, transfusing at later phase of the disease might have a better effect as the patient will have a higher viral load. Although transfusion from two different donors might be beneficial, there exists a risk of multiple exposures to immunogenic antibodies and blood transmitted infections. Strict surveillance and reporting on adverse effects following transfusion, clinical, laboratory, and radiologic changes are necessary to obtain conclusive data. But in India, only 368 out of 3,108 blood banks have enrolled in the National Hemovigilance Program.[64]

Privatization and Misuse

In India, selling or donating blood in exchange of money is illegal under the NBTC Services Act 2007. Those convicted may face 3 months sentencing to jail with fine.[65] Although centers are intolerant toward paid/professional donation, a crisis such as the current situation will be misused by opportunists.[66] Such behavior can only be prevented by having a voluntary plasma bank.

In absolute contrast to the Act,[65] the Karnataka government has announced Rs. 5,000 incentive for CP donors. Paid donation is a transparent and lawful practice in the West. But, in a country like India, paid donation leads to high rate of transfusion-transmitted infections, repeat donation before 3 months, and looting of the patient's family. Such monetary promotions may be beneficial in the short term, but in the long term may be unwelcome.[67]

Immunoglobulin Preparation

Diversion of CP to produce HIIG by pooling and fractionation can be done. Studies comparing CP with HIIG are ongoing.[31] There are advantages (concentrated product, lower chance of transfusion reactions, ABO nonspecific transfusion) and disadvantages (costly, longer preparation time) of HIIG as compared with CP.[11,68] With an annual collection of 10 to 11 million units annually, India has only four fractionation centers, with importing majority of the fractional products.[58,69] Also, the availability of CP is just enough to fulfil the patient requirement. There is a long way to go before India can divert excess CP for HIIG manufacturing.

Conclusion

The right and wrong debate in the use of CP is yet to be solved and generalization of published evidence is not advisable. The low incidence/severity of CP-related adverse events and lack of evidence on other therapies have promoted the use of CP as an off-label drug. But its widespread use must await high-quality evidence. Despite the ocean of published and ongoing research on CP, it is still alien to many parts of the developing countries. Although in the right path, the building enthusiasm must be dealt cautiously to prevent the promotion of professional/paid donation.

Authors' Contributions

P.J.A. contributed to developing the concept and design of the review, definition of intellectual content, literature search, and manuscript preparation, editing, and review. K.K. contributed to developing the concept of the review, definition of intellectual content, literature search, and manuscript editing, and review. A.S. contributed to developing the concept of the review, literature research, and manuscript editing, and review. He is also the guarantor of the article.

Conflict of Interest

Nil.

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