Plasma Therapy: An Effective Treatment for Infections from Microbes with Special Reference to Coronavirus Disease 2019

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Sainani et al.: Effectiveness of Plasma Therapy

Infections hold a major place in the global disease burden. About thousands of different microbial species invade human body thereby leading to complications in the physiology of a particular system or the body as a whole. While the world has tried to combat the microbial infections through various natural and synthetic chemical constituents and certain additional medical aids, we still lack effective treatment against all kinds of microorganisms especially, the evolving new microbial species. Currently, as the world is suffering from a major pandemic spread of infection caused by severe acute respiratory syndrome coronavirus 2, scientists all over the world are trying to produce an effective prophylaxis as well as treatment to fight the viral attack. Amongst different trials going on, this review focuses on the effectiveness of plasma therapy, its mechanism and its applications in various infections so far and it’s possible role to treat coronavirus disease 2019.

Key words: Infections, microorganisms, severe acute respiratory syndrome coronavirus 2, plasma therapy, prophylaxis, coronavirus

Infections are sufferings caused by microorganisms. They occur when the microbes enter the body of the host and start disturbing the normal physiology in many ways. Their attack might be systemic or on a particular organ/organ system. Since ages, mankind has suffered from infections caused by innumerable microbes, bacteria, viruses, or fungi. They are considered foreign to the body since they are not normal residents and therefore not a part of normal physiological actions in the body.

This is the reason they cause serious problems, exaggerating symptoms that are sometimes tolerable while some others are quite dangerous. As known by all, there are millions of different species of microbes that lead to infections, hence we also have countless drugs that are used to either kill (microbial) or stop the growth (micro static) of these attackers. Researchers and Mother Nature have blessed us with so many synthetic and natural substances that act against the microorganisms. But unfortunately, there are certain infections where these substances are not effectively enough to nullify the infection thereby deteriorating the condition of the body or may be even causing death. Therefore, these infectious agents still pose a quite risk to mankind.

Apart from synthetic and natural chemical constituents used as therapy, there are proteins called antibodies synthesized by the immune system of the host body in response to the attacking microbe called as antigen. This is the reason human body is tolerable to certain kind of bacteria wherein the antibodies produced by the immune cells destroy them thereby eliminating the infection. Considering the usefulness of antibodies, one such therapy that is used to treat infectious diseases is the plasma therapy. It is a kind of treatment wherein the blood plasma of a person cured from the infection is transfused into a suffering patient.

This is because plasma of the cured person consists of specific antibodies against the causative agents which might also fight the antigen (microbe) in the body of plasma receiving patient. Therefore plasma therapy has served and can serve as an efficient treatment for various infections caused by bacteria, viruses and fungi. Infections from viruses originate from the proliferation of harmful viruses inside the body. Viruses require assistance of host to replicate themselves[11]. Viruses infect host cells by injecting their genetic material and

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by hijacking host’s internal cell machinery to make more viral particles by the process of replication[2]. There are so many viruses which can infect animals as well as human beings and can be life threatening. According to the structure and genetic makeup of viruses, researchers have developed better treatment options available to save the life of patients.

Infection from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has increased a global concern and challenges for the researchers to develop a better treatment option[3]. This infection starts with viral entry and recognition of host cell receptors which is mediated by corona virus spike (S) protein as shown in fig. 1. As it acts as a major binding site, it is a new valuable target for the researchers to develop effective therapy against SARS-CoV-2[4,5]. In case of corona virus family a receptor binding domain is poorly conserved, hence it is difficult to identify receptor binding domain for SARS-CoV-2[6].

In one study, Angiotensin-Converting-Enzyme-2 (ACE2) has been found as a receptor for SARS-CoV-2[7]. In normal individual, ACE2 is expressed in type I and II alveolar cells in the lungs. As compared to the females, males have more ACE2 expression in their alveolar cells. Damages to alveolar cells lead to series of systematic reactions, difficulties in breathing, lung injury and even death[8]. People infected with SARS-CoV-2 virus show fever and cough as most common symptoms followed by diarrhea and vomiting[9]. As of 30th April 2020, there is no vaccine available for Coronavirus Disease-19 (COVID-19) and prevention of this disease is an important step to decrease its rate of transmission[10]. Use of drugs like hydroxychloroquine and plasma therapy can give a ray of hope to fight against COVID-19[11].

Fig. 1: Mechanism of plasma therapy
While the world is suffering from a serious pandemic spread of SARS-CoV-2 infection which damagingly affects the respiratory system of the host, this review attempts to explain the effectiveness of plasma therapy in general and to highlight its probable importance in COVID-19.

**BLOOD PLASMA: SOURCE OF FIGHTER IMMUNOGLOBULINS**

About 55% of blood is plasma which is a watery straw colored liquid consisting of 92% water, 8% of plasma proteins and trace amount of other constituents. Hence basically, blood is formed from 2 major components; blood cells and blood plasma. We already know how important blood (cells and plasma) is for survival of a human being. Each component has its own function, failure of which, leads to serious disorders. The blood cells include erythrocytes, leucocytes and platelets.

Talking about the composition of plasma, it includes various kinds of proteins, with variety of crucial functions; nutrients that are circulated throughout the body to reach different cells and waste products that should be removed through a proper route by a specific organ or medium.

Proteins present in plasma include fibrinogen and clotting factors which are vital for blood clotting mechanism; albumin is a carrier or transport protein, which is mainly responsible for maintenance of osmotic pressure of blood and for transfer of many substances from one region to the other. This occurs by binding of the substance (hormones, vitamins, enzymes, cations and drugs) to albumin. Due to this binding, albumin is also known to manage the levels of the substrate bound to it.

It is a major protein constituting about 50% of all plasma proteins. Plasma also consists of globulins which have an immune function to fight against the foreign bodies that damage the host cells. Apart from these constituents, there is a collection of regulatory substances in the plasma which includes exocrine and endocrine hormones that act on their specific targets; enzymes and co-factors which are crucial for all biochemical reactions occurring in the body; and electrolytes (salts, acids, bases, ions) which are important for maintaining physiological parameters like pH, osmotic pressure, electrolyte balance; contraction and relaxation, which is the basis of functioning of every organ system. Apart from these substances, plasma also contains nutrients absorbed from the intestine to reach various cells for Adenosine 5’-Triphosphate (ATP) production and waste products given by different cells to be eliminated out of the body through appropriate medium[12].

Of all the above mentioned components of blood plasma, we are concerned with globulins/ immunoglobulins in case of a bacterial or viral infection, since this review attempts to focus on the importance of immunoglobulins to get rid of an infection. Immunoglobulins, also called as antibodies, are specific glycoproteins produced by B cells[13]. Whenever an antigen (microbe) enters the body, it is taken inside a B cell where it is broken down into fragments which are combined with Major Histocompatibility Complex (MHC) proteins. This combination is identified by T cells to activate B cells[12]. On activation, B cells produce plasma cells and memory B cells. It is the plasma cell which proliferate and produce millions of antibodies that travel along the plasma to arrive at the site of infection[14].

Once they reach the required site, the antibodies fight the infection through various mechanisms like breaking up the bacterial toxins[15], preventing the attachment of virus to the plasma membrane of the cell[16], damaging the motility of microbe to limit its spread[17], cross-linking of microbes with each other rendering them inactive resulting in a clump or precipitate, by stimulating phagocytosis i.e engulfment and degradation of the pathogen and by activating complement system which is a collection of proteins produced by liver that functions to breakdown and engulf the foreign material as that of antibodies, but with different mechanism[18]. Also, the memory B cells store the information of the antigen so that if there are recurrent attacks by the same antigens, the cells can be immediately proliferated and specific antibodies can be synthesized[19].

Hence antibodies are outstanding fighters of our immune system which show their action through various ways to throw out the micro-organism from the body. There are millions of bacteria and viruses against which our body produces antibodies and we are saved from a rigorous damage to the tissues and organs. The effects of an infection may be mild to moderate which are manageable but sometimes it might be quite severe and non-curable. If there is a new variety of antigen attacking the body, until our immune system designs antibody against it, there is a lot of damage either systemically or on a specific organ system, especially in case of viruses. This damage is so rigorous that it
might permanently affect functions of vital organs such as respiration, pumping of heart, control of organs by brain, digestion and metabolism, fluid and electrolyte balance and excretion of wastes or it may also be fatal.

To treat infections by bacteria, viruses and fungi, researchers and scientists have discovered innumerable drugs like antibiotics, antivirals, antifungals, natural oils etc. which may be synthetic or natural\[20\]. But unfortunately, these agents are not efficient against certain type of pathogens. In addition to drugs used to kill the microbes, use of immunomodulators\[21\], operative drainage and plasma therapy\[22-24\] have also been found to tackle the infectious diseases.

**USE OF BLOOD PLASMA AGAINST INFECTION: PLASMA THERAPY**

Plasma therapy is an approach to treat infectious diseases by the use of plasma, serum or antibodies from an infection survived individual. An attempt to study this approach was first made in animals in the early 20th century considering the fact that 26 patients were cured of poliomyelitis infection when they were infused with serum of poliomyelitis survivors. Cure of an infection due to serum from disease survivors indicates that there are immune rich contents in the serum which might destroy the pathogen.

One of the pathogen fighting substances produced by immune system are antibodies that breakdown the infectious agent. These antibodies were found to circulate in the blood plasma and became the basis of plasma therapy wherein the plasma from a patient who has survived from the infection is used as a source of antibodies in the suffering patient. Once, transfused into a new patient, the antibodies present in the donor’s plasma will fight against the antigen present in the receiver’s body as shown in fig. 1. It might also trigger the synthesis of the antibodies by the receiver’s immune system.

Apart from transfusion of plasma, sometimes, particular antibodies might be isolated and injected into the patient. Hence plasma therapy serves as an efficient approach to fight infectious diseases provided the donor’s antibodies are found to be active and efficacious inside the receiver’s body and if they are stable while isolation, transfusion and other steps performed in the therapy.

**APPLICATIONS OF PLASMA THERAPY TILL DATE**

Probably, an immunoglobulin in the form of diphtheria antitoxins is the first therapeutic product developed from plasma. It was also observed that fresh plasma is also responsible to correct clotting time in hemophilia patients\[25\]. Therapeutically useful immunoglobulins and fibrinogen can be extracted from plasma which can be useful in treatment of various infectious disease conditions. As the blood plasma of patient recovered from any infection has developed immunity against it, the immunoglobulins present in that plasma can be therapeutically effective for treatment in other infected individuals.

During pandemic infection of H1N1 Virus in 2009, a cohort study was conducted in which significant reduction in respiratory tract viral load, serum cytokine response and relative risk of mortality were observed in the patients treated with convalescent plasma\[26\]. In subgroup analysis reduction in the viral load was observed in Intensive Care Unit (ICU). No adverse effects were found in patient treated with plasma therapy\[27\]. Antibodies from convalescent plasma might be suppressing viraemia. Schoofs and colleagues reported that 3BNC117-mediated immunotherapy, a broad neutralizing antibody to Human Immunodeficiency Virus-1 (HIV-1) enhances immunity of host as well as it helps in blocking new infection and clearing infected cells\[27\].

In 2014, use of convalescent plasma collected from patient recovered from Ebola virus disease was suggested by World Health Organization (WHO) as a treatment\[28\]. Convalescent plasma from recovered patients helps in viral clearance on one hand and increased sustainability of protective neutralizing antibodies on the other hand, when used in infected patients. Also plan was made to prepare IV immunoglobins which can be utilized in treatment of further new cases\[29\]. In another case treatment of Argentine hemorrhagic fever, caused by an arenavirus (Junin virus), in which patients were shown to be benefited from immune serum administered within 1 w after symptoms began\[30\]. In patients infected from Chikungunya Virus (CHIKV), it was observed that administration of CHIKV immunoglobins extracted from plasma of recovered patients show safety as well as prevention of infection in individuals who are at risk of severe infection\[31\].
In case of measles, it was observed that the adults who had got infected in childhood have developed immunity in them but the concentration was low. The immunity can be transferred from the mother to child through plasma transfusion which can protect the child from many infections. The use of convalescent serum from the patients who recovered from the infection showed significantly effective results. It can be used to develop passive immunity if injected after 3 to 5 d of exposure to the pathogen. With the increasing disease exposure, larger dose had to be used to develop immunity.

In 2015, protocol was established stating use of convalescent plasma therapy in patients suffering from infection caused by Middle East Respiratory Syndrome (MERS) related corona virus (EMC/2012). In order to evaluate the efficacy of convalescent plasma therapy in the treatment of patients with SARS, administration of plasma on 14th d of infection had shown a positive response and on 22nd d of infection many patients were discharged from the hospital after the therapy.

The result from 10 adult cases showed that 200 ml dose of convalescent plasma was well tolerated and maintained the neutralizing power of antibodies at high level leading to improvement in symptoms within 3 d and cure of infection within 7 d of treatment. From above studies we can conclude that convalescent plasma therapy has shown positive response to cure various infectious diseases.

**PLASMA THERAPY IN COVID-19**

According to WHO, no specific treatment is recommended for COVID-19 disease because of lack of evidences. But some evidence shows that convalescent plasma from the patient recovered from viral infections can be utilized for treatment without occurrence of any adverse effect. The novel corona virus (“SARS-Cov-2”) outbreak has created a sense of global panic and to treat the COVID-19, currently no specific antiviral drug is approved. The increasing mortality rate challenges researchers to investigate new antiviral drug to save the lives of people across the globe. The search for the effective treatment is underway with multiple investigations across the globe. However various studies conducted in China reported that plasma therapy in COVID-19 can benefit the infected patients. When infected patient receives plasma from the survivors of illness, it benefits patients by producing protective antibodies. Though plasma exchange is not a novel treatment but therapeutic plasma exchange can be a possible treatment for COVID-19.

Plasma therapy is a classic immunotherapy and has been used for the prevention and treatment of various infectious diseases for more than a century. According to the researchers, from past two decades it has been used for the treatment of MERS, SARS and H1N1 pandemic with satisfactory safety and efficacy reports. A meta-analysis was carried out in which 32 patients infected from SARS-CoV-2 receiving plasma therapy were studied and statistically significant reduction in mortality rate was observed. As, SARS and MERS show similar clinical and virological characteristics, plasma therapy might be a promising treatment option for COVID-19 rescue.

A pilot study was conducted to explore feasibility of plasma therapy on 10 severe COVID-19 patients from 3 different hospitals receiving one dose of 200 ml plasma transfusion. The dose was well tolerated by the patients with significant improvement in clinical symptoms. Also, the increase in oxyhaemoglobin saturation accompanied by rapid neutralization of viremia and decreased lymphocyte count in peripheral blood were reported. In addition, plasma therapy is reported to be effective in temperature normalization, relief of dyspnoea, normalization in oxygen saturation and radiological improvement in the patients. In New Delhi, India, a 49 y old male patient who was treated with plasma therapy has shown positive result and also weaned off ventilator support on 4 d of plasma transfusion. And also the two consecutive tests were found negative for infection.

As plasma therapy is an effective treatment for various infectious diseases, with safety and efficacy studies, it can be a better treatment option for COVID-19. The various research challenges in the development of specific anti-viral drug or vaccine for COVID-19 and gradually increasing mortality rates lead to increased global panic. But administration of plasma therapy is not only found to be useful in reducing clinical symptoms but also decreased the duration of hospitalization of patients. Table 1 highlight some of the important works where convalescent plasma transfusion was used as treatment option in COVID-19 patients and results of certain works indicate that plasma therapy can be an effective treatment in reducing the suffering period and saving the life of patient in COVID-19 pandemic.
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Title</th>
<th>Country</th>
<th>Authors</th>
<th>Dosage</th>
<th>No. of patients in the study</th>
<th>Patient details (age, gender, co-morbid conditions, etc.)</th>
<th>Adverse effects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Treatment with convalescent plasma for COVID-19 patients in Wuhan, China (^{[41]})</td>
<td>China</td>
<td>Mingxiang Ye _ et al.</td>
<td>200 ml</td>
<td>6</td>
<td>Age: 28-75 y</td>
<td>Nil</td>
<td>Resolution of Ground Glass Opacities (CGOs) in 5 patients.</td>
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<td></td>
<td></td>
<td></td>
<td>Gender: 3 males, 3 females</td>
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<td>Immediate increase in anti-SARS-CoV-2 antibodies in 2 patients</td>
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<td></td>
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<td></td>
<td></td>
<td>All patients had chest abnormalities confirmed from CT scan</td>
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</tr>
<tr>
<td>2</td>
<td>Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial (^{[42]})</td>
<td>China</td>
<td>Ling Li _ et al.</td>
<td>4-13 ml/kg body weight</td>
<td>103</td>
<td>Median age: 70</td>
<td>2 patients showed severe transfusion related adverse events</td>
<td>The plasma therapy along with standard treatment was compared to standard treatment alone in this study.</td>
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<tr>
<td></td>
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<td>Gender: 60 subjects were male and 43 were female</td>
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<td></td>
<td>Patients with conditions like hypertension, diabetes, cardiovascular disease, cancer etc were included</td>
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<td>All patients showed symptoms suggesting severe or life-threatening COVID-19 disease</td>
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<td></td>
<td>All patients showed pneumonia confirmed by chest imaging</td>
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</tr>
</tbody>
</table>

\(^{[41]}\) Source:Ye et al. (2020)
\(^{[42]}\) Source:Li et al. (2020)
Convalescent plasma therapy in patients with COVID-19\textsuperscript{[43]}  
Turkey  
Fevzi Altuntas et al.  
(age: 60 y)  
(\text{gender: 1250 male and 526 females})  
(\text{age: 30-70 y})  
(\text{age: 19-77 y})  
\text{Reduction in ICU stays period}

Treatment of 5 critically ill patients with COVID-19 with convalescent plasma\textsuperscript{[44]}.  
China  
Chenguang Shen et al.  
(\text{age: 30-70 y})  
(\text{gender: 3 male and 2 females})  
\text{Plasma therapy showed improvement in clinical status of patients but the subjects were also on other medications}

Treatment of COVID-19 patients with convalescent plasma in Houston, Texas\textsuperscript{[45]}  
Texas, US  
Eric Salazar et al.  
(\text{age: 30-70 y})  
(\text{gender: 11 male and 14 female})  
\text{76 \% of patients showed improvement in clinical status and 44 \% of patients were discharged after 14 d of plasma transfusion indicating plasma therapy as a safe treatment option in severely ill COVID-19 patients}
Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients\textsuperscript{[46]}

**China**

Qing Lei Zeng et al.

300 ml

21 (only 6 of them received plasma due to availability and compatibility) All patients were critically ill and showed symptoms like fever, cough, shortness of breath and fatigue. They were also confirmed of having pneumonia. All patients had respiratory failure.

Age: Around 60 y

Gender: 5 male, 1 female

Convalescent plasma therapy decreased viral load and contributed to longer survival duration in COVID-19 patients with respiratory failure.

It did not reduce mortality in critically end-stage patients.

Improvement in recovery rate

Early discharge from hospital

Convalescent plasma with neutralizing antibody titer of more than 1:160 showed complete recovery and decreased mortality.

Good clinical improvement in all patients with moderate disease and 2 patients with severe disease.

Convalescent plasma therapy in the management of COVID-19 patients-The newer dimensions\textsuperscript{[47]}

**India**

Mahapatra S et al.

200-250 ml

2432 (Test: 1189, control: 1243)

959 subjects were grouped under pre-critical group

230 subjects were grouped under critical group among the test subjects.

Age: 18-85 y

Gender: 813 males and 196 females

Convalescent plasma therapy decreased viral load and contributed to longer survival duration in COVID-19 patients with respiratory failure.

It did not reduce mortality in critically end-stage patients.

Improvement in recovery rate

Early discharge from hospital

Convalescent plasma with neutralizing antibody titer of more than 1:160 showed complete recovery and decreased mortality.

Good clinical improvement in all patients with moderate disease and 2 patients with severe disease.

Convalescent plasma therapy in patients with moderate-to-severe COVID-19: A study from Indonesia for clinical research in low- and middle-income countries\textsuperscript{[48]}

**Indonesia**

Marliana S. Rejeki et al.

3 doses of 3 ml/kg

10

5 subjects were moderately ill while the other 5 suffered from severe COVID-19

3 subjects were diabetic and 1 was reported to have hypertension.
<table>
<thead>
<tr>
<th>Country</th>
<th>Study Title</th>
<th>Authors</th>
<th>Age Range</th>
<th>Male:Female Ratio</th>
<th>Site of Illness</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuwait</td>
<td>COVID-19 convalescent plasma treatment of moderate and severe cases of SARS-CoV-2 infection: A multicenter interventional study</td>
<td>Sondas Alsharidah et al.</td>
<td>45-60 y</td>
<td>105:35</td>
<td>Moderate (symptoms and pneumonia) or severely (Oxygen saturation less than 90, more than 30 breath/minute, admitted to ICU) ill</td>
<td>200-400 ml</td>
<td>High rate of clinical improvement</td>
</tr>
<tr>
<td>India</td>
<td>Effectiveness of convalescent plasma in Indian patients with COVID-19</td>
<td>Sandeep Budhiraja et al.</td>
<td>40-75 y</td>
<td>3:1</td>
<td>Severe (Oxygen saturation less than 90, more than 30 breath/minute, admitted to ICU) ill</td>
<td>-</td>
<td>Reduced mortality rate</td>
</tr>
<tr>
<td>India</td>
<td>Effectiveness of convalescent plasma in Indian patients with COVID-19</td>
<td>Sandeep Budhiraja et al.</td>
<td>40-75 y</td>
<td>3:1</td>
<td>Severe (Oxygen saturation less than 90, more than 30 breath/minute, admitted to ICU) ill</td>
<td>-</td>
<td>Oxygen saturation improved within 3 d of transfusion</td>
</tr>
</tbody>
</table>

All subjects were either moderately (symptoms and pneumonia) or severely (Oxygen saturation less than 90, more than 30 breath/minute, admitted to ICU) ill.

Around 45% of patients were diabetic and hypertensive.

385 patients were moderately ill while 694 were severely ill.

All patients who were severely ill had one or more co-morbid conditions like hypertension, diabetes, Coronary Artery Disease (CAD) and were admitted to ICU.

Convalescent plasma transfusion showed significant reduction in mortality in patients admitted to ICU, particularly in females and especially in patients with one co-morbid condition.
CONCLUSION

The SARS-CoV-2 infection affects one of the most vital systems of the body, i.e., the respiratory system. Its incursion on the respiratory cells (alveoli) leads to difficulty in breathing and insufficient supply of oxygen to the body. This in turn leads to serious complications like multiple organ failure and death if there is no timely cure of the infection. Therefore, targeting the foreign body itself would serve the purpose. Antibodies are the major fighters produced by the immune system to degenerate and eliminate the microbes from the body. But if the immune system fails to produce appropriate and adequate antibodies against the virus, plasma therapy, involving transfusion of plasma containing antibodies from a disease survived patient can be a ray of hope. Considering this phenomenon, the trials of plasma therapy in COVID-19 patients have been started. Hence, plasma therapy can be an effective treatment to cure people from COVID-19.

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Conflict of interest:

The authors declare that there is no conflict of interest in the present study.

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