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TRANSFUSION

Upper age limits for convalescent plasma donation and treatment of COVID-19 patients: A further marker of ageism

To the Editor,

With millions of people experiencing COVID-19, older subjects have a higher risk of severe clinical manifestations of COVID-19, including mortality. Besides drugs and monoclonal antibodies proposed for COVID-19 treatment, a possible therapeutic option, especially early in the course of disease, is convalescent plasma (CP).[1] Given ample evidence of ageism in clinical trials,[2] we investigated whether trials of CP in COVID-19 restricted either donors or recipients on the basis of age.

We searched the WHO International Clinical Trials Registry Platform (WHO-ICTRP) on August 25, 2020 for clinical trials of CP for the treatment of COVID-19 illness (https://www.who.int/ictrp/en/). The following keywords were used: "COVID" as condition and "plasma" as intervention. We identified the most relevant data from the study protocol of each trial, adapting the methodology previously used in the PREDICT study.[3] We evaluated trial design, contacting by email the researchers when information was not available. When the age limit for plasma donors was not specified and there was no response from the authors, the information was obtained consulting national regulations. Logistic regression models were used to identify variables associated with upper age limits on the basis of χ^2 Wald statistics.

After the exclusion of observational studies (105), interventional studies not using COVID-19 CP as treatment (151), expanded access studies (10) and studies on pediatric subjects (5), 157 studies were included (95 RCTs and 62 non-RCTs). We found that 64% of the studies had an upper age limit for plasma donors, and 33% for receiving patients. Moreover, 26% had upper age limits both for donors and recipients. In at least 18 studies, donor's age limits were set independently of the national regulations, which would have allowed higher limits. In the logistic regression, geographical area was the only characteristic related with upper age limits.

Abbreviations: CP, convalscent plasma; PREDICT, Increasing the PaRticipation of the ElDerly in Clinical Trials; RCT, randomized controlled trial; WHO ICTRP, WHO clinical trial registration platform.

No scientific reason can justify exclusion of patients for treatment on the basis of age and the Food and Drug Administration and the European Medical Agency strongly recommend against it. In the context of the COVID-19 pandemic, which presents a more severe disease with increasing age, the exclusion of older subjects from trials supporting an emergency therapy has a clear relevance. The main reason explaining the age limitation for donors are the criteria used for blood donation in each country, often based on past practice rather than on scientific evidence. WHO guidelines indicate an upper age limit of 65 years, with discretion after 65 for regular donors based on individual evaluation. In North America, upper age limits for donors have been abolished. Europe is generally aligned with WHO. The presence of an upper age limit for blood and plasma donation is scientifically unfounded.[4] Donation does not pose safety issues to older adults: on the contrary, donation-related moderate and severe reactions, including vasovagal reactions and loss of consciousness, are less common in older donors, and there is no evidence that blood or plasma donated by older people produces negative consequences in recipients. Although part of the CP donors could be first-time donors and therefore at higher risk of adverse events, in the context of the pandemic emergency and in clinical trials it would have been possible and appropriate to consider a higher age limit for plasma donation.

Upper age limits in blood and plasma donation are unnecessary and should be revised. In the context of COVID-19 pandemic, they reduce the number of older people who can provide their plasma and of those who can benefit from it,[5] a particular irony for a condition whose most serious consequences occur among older people.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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Storage of cryoprecipitate: Role of blood storage

Thompson et al.[1] provide useful data supporting the extension of the storage period for thawed cryoprecipitate beyond the regulatory requirements for this blood component applicable in Australia, which comprise the European Directorate's "Guide to the preparation, use and quality assurance of blood components"[2] ("the Guide"). Further details on the preparation of the cryoprecipitates which they studied could shed light on their observation regarding the deterioration of functional Von Willebrand Factor (VWF) during post-thaw storage of cryoprecipitate. According to the Guide, fresh-frozen plasma (FFP) used as a raw material for cryoprecipitate production may be generated through separation from whole blood units within 6 h of collection or from blood held at between 20 and 24°C, followed by buffy coat separation for platelet concentrate production and harvesting of the residual plasma. These two routes to FFP both do not include the removal of leucocytes from blood prior to the production and freezing of the plasma, and the possibility of degradation of leucocytes with the release of proteases into the plasma cannot be discounted, particularly with prolonged storage of the blood prior to processing. We have previously shown that VWF degrades rapidly in banked blood donations not subjected to leucocyte depletion,[3] possibly through proteases released from granulocytes. Degradation of granulocytes and release of these proteases is enhanced at low temperatures,[4] and we note that the loss of functional VWF reported by Thomson et al is enhanced at 4°C compared to room temperature. We suggest that precipitation of cold-insoluble proteins during 4°C cryoprecipitate storage could concentrate insoluble VWF, with subsequent degradation of the higher molecular weight forms of this protein by proteases released by granulocyte debris sedimented by gravity over the storage period studied. Thomson et al. prudently warmed the samples they harvested for analysis, recognizing that 4°C storage would precipitate proteins of interest, but this would not obviate the degradation of precipitated VWF prior to resolution by warming.

We propose that the loss of functional VWF during the conditions of storage proposed by Thomson et al should induce caution in prolonging the storage period. While supplementation of VWF for inherited and acquired disorders of this protein in the established economies is best achieved with concentrates of VWF, these products are not available in emerging countries where blood bank components, including FFP and cryoprecipitate, are still used in the treatment of bleeding disorders.[5] Hence, we encourage the development and publication of fully detailed manufacturing protocols for these components, which include adequate assessment of their fitness of purpose for the different therapeutic application which may be required. Further characterization of these products in specific clinical situations is also desirable before manufacturing methods can deviate from established standards.

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The authors have disclosed no conflicts of interest.