Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience

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This is a preprint of an uncontrolled study examining the effect of transfusion of human convalescent plasma on mortality in hospitalised COVID-19 patients. The study aimed to answer two questions. 1. Is earlier treatment associated with reduced mortality compared to later treatment? and 2. Are higher antibody levels in the transfused convalescent plasma associated with reduced mortality?

QUESTION The study PICO is as follows;

P – hospitalised adults with SARS-CoV-2 infection who had (or were judged to be at high risk of) severe or life-threatening COVID-19
I – early (0-3 days after diagnosis) transfusion of at least 1 unit (200ml) of plasma harvested from patients convalescing from COVID-19; transfusion of plasma of high IgG content
C – late (4-10 days after diagnosis) transfusion of at least 1 unit (200ml) of plasma harvested from patients convalescing from COVID-19; transfusion of plasma with low IgG content
O – Death at 7 and 30 days

METHODS Convalescent plasma was administered to 35, 322 patients in the US via the government funded and Mayo Clinic initiated Expanded Access Program (EAP) for the treatment of COVID-19. The primary intention of the program was to provide access to convalescent plasma and to assess its safety. There was no untreated control group in this study. Comparator groups were created from within the exposed cohort according to whether the treatment was administered 0-3 days or 4+ days after diagnosis and whether high IgG plasma (>18.45 S/Co) or low IgG plasma were received (this was examined in approximately 10% of the study population). All hospitals, acute care facilities and licensed physicians were eligible to participate. Web-based standardised data reporting surveys were completed to assess the clinical status of participants. Antibody levels were unknown at the time of transfusion. Crude mortality estimates (number of deaths/number of persons at risk) were determined at 7 and 30 days follow-up and analysis stratified by potential confounders (age, ventilation, study period) was conducted.

RESULTS Characteristics of study participants are presented according to the time period of transfusion (before May 1, May 1-June 4, June 4- July 4). Participants transfused early in the study period were more critically ill, were more often concomitantly treated with hydroxychloroquine and azithromycin but had lower treatment with Remdesivir. Crude 7 day mortality was reduced in participants transfused within 3 days (8.7% 95%CI 8.3%-9.2%) of diagnosis compared to those transfused 4+ days after diagnosis (11.9%, 11.4%-12.3%). Similar results were seen for 30 day mortality (21.6% [21%-22.3%] vs 26.7% [26.1-27.3%] for administration 3 days or less and 4+ days after diagnosis respectively). 7 and 30 day adjusted mortality stratified by low, medium and high antibody groupings alone and for timing of transfusion are shown in Figure 1. These data suggest a dose dependent relationship with higher antibody levels.

COMMENTS The following points were discussed:

- The inaccurate reporting of the results of this study posted by the FDA. Figure 2 shows a tweet from the FDA stating '35% of individuals' benefited. The data in the figure is not consistent with this claim. The data appears to be suggesting an approximate 35% relative reduction in the comparison between high and low titers in a selected subgroup. We discussed the undermining of the process of critical appraisal when criticism of studies is made along political lines.

- While the intention of this study was to assess safety and to identify potential signals of efficacy among a population of people receiving convalescent plasma as part of a program to provide access to potentially beneficial treatments (while they are being studied in randomised trials), it was felt an important opportunity to conduct a pragmatic randomised trial in this large and varied population was missed.

- The emphasis on reporting 7 day mortality in this study is unclear. 30 day mortality seems the more clinically relevant.

- cut points for variables seem to have been made post hoc. IgG content was stratified at 20th and 80th centiles. Days between COVID-19 diagnosis and transfusion was dichotomized to 0-3 and 4+ days. but no justification for these cut-points were provided Sensitivity analyses to determine how results may vary with different cut-points would be helpful.

- Important confounders were identified and appear to have been included in the modelling however statisticians have criticized categorisation of some variables so that they do not provide sufficient resolution for analysis. Further, the time dependent nature of the treatment was not explicitly used in the analysis and appears to have been analysed as a baseline covariate.

- It was generally felt that while the study shows a signal of efficacy, the signal is not strong. The dose response data upon which the study hypothesis hangs is obtained from only 10% of the total population (though this is still approximately 3000 individuals).

- there has been extensive comment and criticism on this pre-print study. This form of open, living peer review provides enormous learning opportunities for readers, reanalysis of data and improved transparency of reporting.

OVERALL SUMMARY The primary intention of this program was to provide access to and assess safety of convalescent plasma and the investigators emphasise that the efficacy analysis is exploratory. The relationships between mortality and time to transfusion and antibodies provide a weak signal of efficacy but an effect that is consistent with previous studies of convalescent plasma treatment in influenza, SARS and MERS.

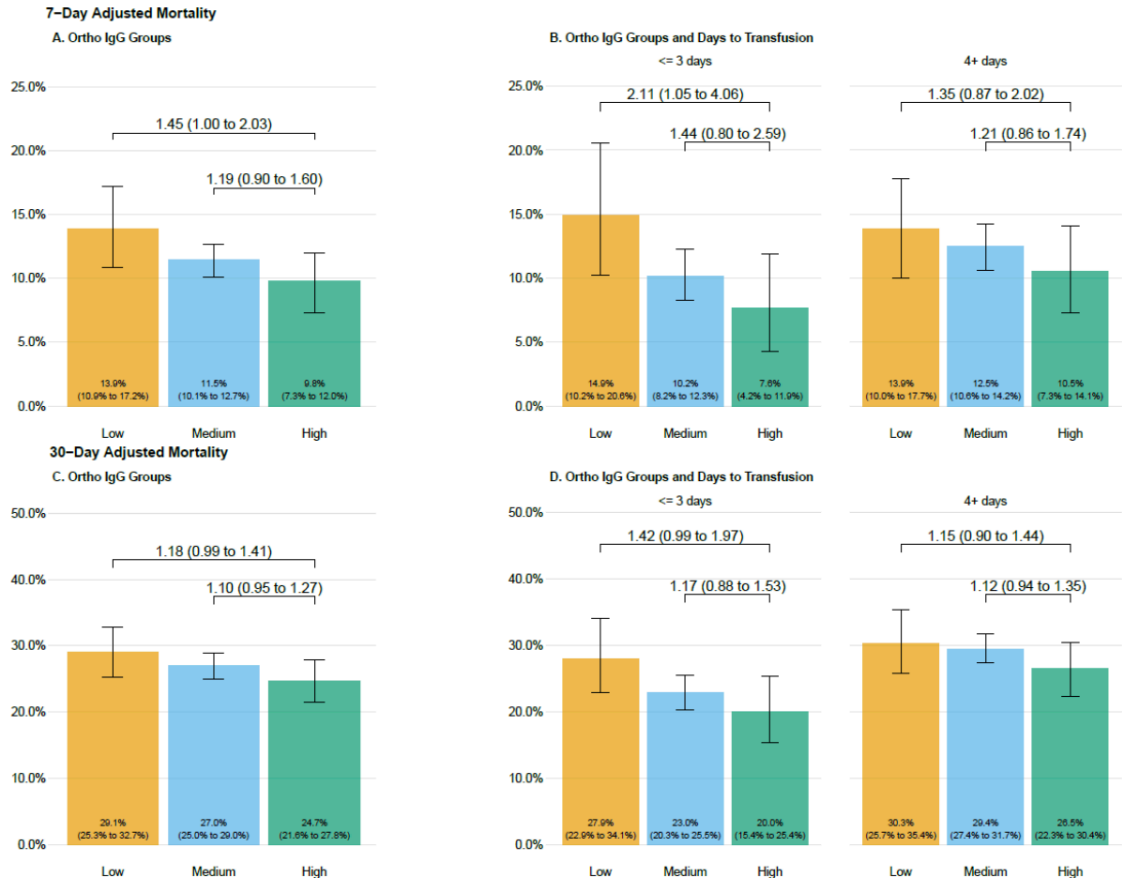

Figure 1. 30 day adjusted mortality stratified by antibody groupings in patients transfused with COVID-19 convalescent plasma. Vertical axis is adjusted mortality rate. Values within the boxes are the estimated adjusted mortality rates. Values connecting various categories (overbraces) are bootstrapped estimates of relative risk and 95% bootstrap confidence intervals.

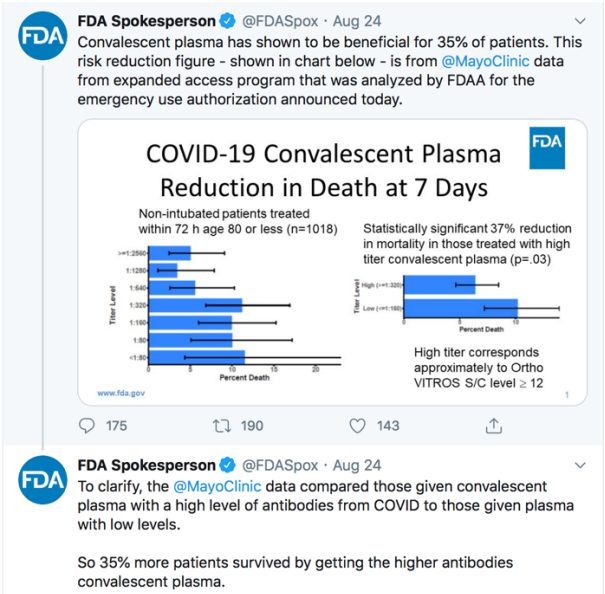

Figure 2.