

Convalescent Plasma and COVID-19: Meta-analysis of a Century-Old Technique

Meta-analysis

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ABSTRACT

Background: The coronavirus disease (2019) also known as COVID-19, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case of COVID-19 was detected in Pakistan on February 26, 2020. The current population of Pakistan is 221,856,736 as of December 18, 2020, and the number of total infected individuals tallies up to 304,386 (0.13%) along with deaths measuring up to 6,408 (2.1%). Convalescent plasma (CP) is a century-old technique that has been employed to manage emerging microbes. CP therapy has been observed to reduce morbidity and mortality through polyclonal neutralizing antibodies by reducing viremia.

Methods: PubMed and Cochrane databases were screened for randomized controlled trials (RCTs) and non-randomized studies on intervention effects (Non-Controlled NRSI) with keywords including "convalescent plasma," "plasma therapy," and "COVID-19." The primary objective was to assess for any benefits on the mortality outcomes of the intervention group. The secondary objective was to quantitatively analyze the patients discharged by the end of the study duration.

Results: We included 3 studies (RCT=1; NRSI=2) consisting of a total of 317 patients (CP n=96; SOC n=221). We found that patients in the CP group had lower odds of mortality as compared to the SOC group (OR=0.51, 95% CI=0.26-1.01, P value=0.05).

Conclusion: Convalescent plasma therapy may have some clinical benefits and can lead to a reduction in mortality. However, RCTs must assess the optimal time to administer convalescent plasma and ensure that the antibody titers in donated plasma are at an optimal level for efficacy.

Keywords: COVID-19, COVID19 serum therapy, SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the underlying etiological agent of the coronavirus disease (2019) also known as the

COVID-19 pandemic.[1] The disease was diagnosed in Wuhan, China on December 31, 2019, after many patients were reported to have pneumonia of unknown etiology.[2] After the outbreak increased in magnitude, the World Health Organization (WHO) noted it to be a Public Health Emergency of International Concern in the end of January, 2020. Nearly 2 months after COVID-19 was first diagnosed, it was announced as a pandemic on March 11, 2020.[3] As of March 17 2021 nearly a year after COVID-19 was declared a pandemic, 120,383,919 cases have been confirmed and 2,664,386 deaths have occurred. SARS-CoV-2 had been confirmed to enter Pakistan when two cases were confirmed in Karachi, Sindh, Pakistan on February 26, 2020.[4] The current population of Pakistan is 221,856,736 as of September 18, 2020, and the number of total infected individuals tallies up to 304,386 (0.13%) along with deaths measuring up to 6,408 (2.1%).[5]

Convalescent plasma (CP) is a century-old technique that has been employed to manage emerging microbes. CP therapy has been observed to reduce morbidity and mortality through polyclonal neutralizing antibodies by reducing viremia.[7] Convalescent plasma therapy requires blood donation from healthy donors who have already been infected with COVID-19. The U.S. Food and Drug Administration (USFDA) provided emergency use authorization (EUA) for COVID-19 patients.[8]

METHODS

PubMed and Cochrane databases were screened for randomized controlled trials (RCTs) and non-randomized



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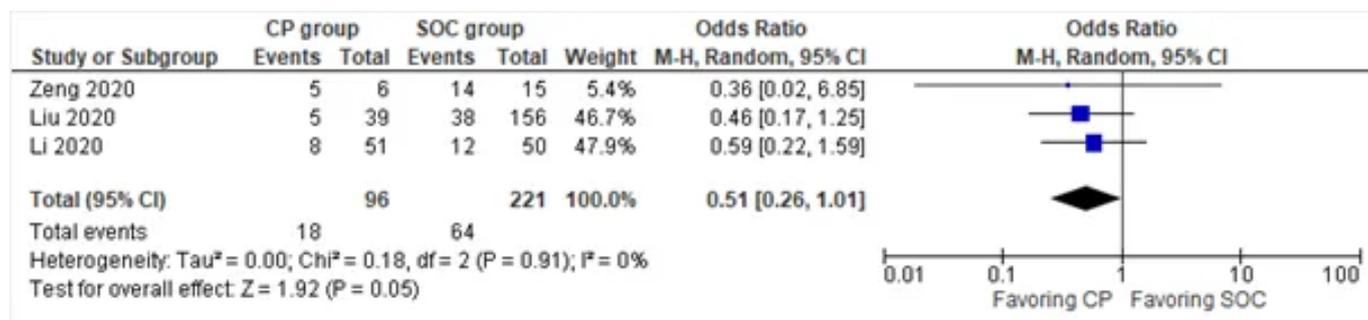


Figure 1: Forest plot of deaths in convalescent plasma and standard treatment groups.

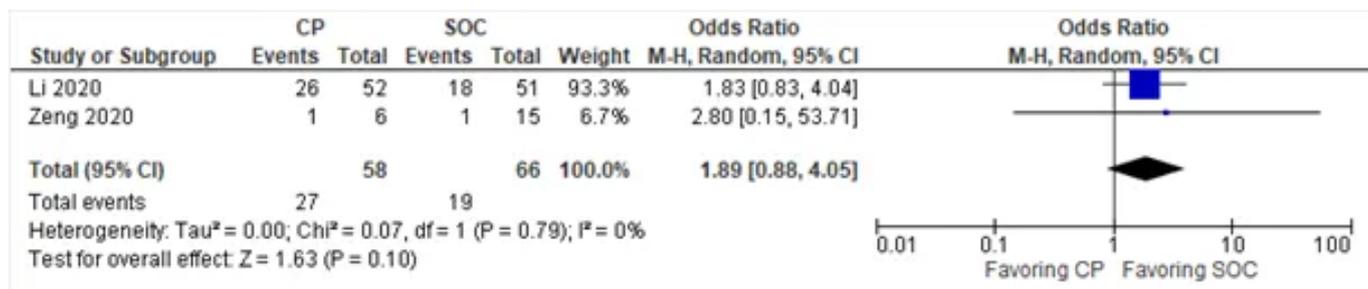


Figure 2: Forest plot of patients discharged in convalescent plasma and standard treatment groups.

studies on intervention effects (Non-Controlled NRSI) with keywords including “convalescent plasma,” “plasma therapy,” and “COVID-19.” The inclusion criteria included studies that enrolled patients from all age groups with diagnosed SARS-CoV-2 infection, with control and intervention groups, and underwent plasma therapy. The exclusion criteria were studies with no control groups comprising of case reports, or case series with no standard of care (SOC) group. The primary objective was to assess for any benefits on the mortality outcomes of the intervention group. The secondary objective was to quantitatively analyze the patients discharged by the end of the study duration. Unadjusted odds ratios using a random-effects model with 95% confidence intervals, and a significant p-value of less than 0.1 utilizing Review Manager V 5.4 was assessed by calculating the I² index.

RESULTS

We included 3 studies (RCT=1; NRSI=2) consisting of a total of 317 patients (CP n=96; SOC n=221).[9-11] Overall, one study was conducted in the United States, whereas two were led in China. Three of the 3 studies in our analysis presented mortality data. We found that patients in the CP group had lower odds of mortality as compared to the SOC group (OR=0.51, 95% CI=0.26-1.01, P value=0.05). There was no heterogeneity in the included studies (I²=0%) (Figure 1). Two of the 3 included studies also provided evidence of the effect of CP on the number of patients discharged by the end of the intervention. We found that the CP group had higher odds of being discharged post-treatment as compared to the SOC group (OR=1.89, 95% CI=0.88-4.05, P-value=0.1). No

heterogeneity was found in the included studies (I²=0%) (Figure 2). As the number of studies was below 10, we did not assess for publication bias. Moderately high or high methodological studies were identified in the studies we analyzed.

DISCUSSION

As of 15th September, 2020, only one RCT has been conducted in India studying the survival and mortality benefits.[12] There are over 20 RCTs currently recruiting patients in the United States, but none have insofar been completed.[13] While there is a lack of survival benefit in the recently published RCT, there were a few positive aspects of convalescent plasma therapy from the trial.[12] There were improvements witnessed in the symptoms, oxygenation, and the viral clearance in patients in the CP intervention arm as compared to the SOC arm.[12] Our study finds that patients are likely to benefit from intervention with CP by demonstrating a reduction in mortality and a higher likelihood of discharge from the hospital.

When obtaining convalescent plasma from donors, it is essential to assess their neutralizing antibody titers, using an enzyme linked immunosorbent assay (ELISA). [14] It is viable to obtain the donor samples from the same vicinity as there may be mutations of the target viral antigens based on geography. There are various approaches that may be considered to obtain CP samples. A cost-effective approach is to enroll patients who have just been discharged from the hospital following recovery from COVID-19. A costly approach is to screen the general public for the presence of antibodies against SARS-CoV-2. An approach that is intermediate is to approach patients who have been diagnosed with COVID-19 and are quarantined at

home. As per recently conducted trials, donors have not been screened for their neutralizing antibodies.[9] Nevertheless, as soon as the urgent requests are satisfied and a buffer stock has been created, repeat donations should preferably focus on donors with high titers.

CONCLUSION

In conclusion, plasma therapy may have some clinical benefits and can lead to a reduction in mortality. However, RCTs must assess the optimal time to administer convalescent plasma and ensure that the antibody titers in donated plasma are at an optimal level for efficacy. Larger placebo controlled trials may further assess survival and clinical benefits in reducing in-hospital adverse events and mortality.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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