UAMS Journal Club Summary
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In patients with COVID-19, does convalescent plasma compared to standard therapy improved clinical outcomes?

Clinical Bottom Line

We are unable to draw statistical conclusions based on these two meta-analyses due poor-quality data included in the studies. The studies included in both meta-analyses were at high risk of bias because they were mostly retrospective, observational, and case series. Of significant note, they were all uncontrolled studies. However, since the risk of convalescent plasma is low and reliable treatments for COVID-19 are limited, it is reasonable to use convalescent plasma in the critically ill patient infected with COVID-19 until more definitive studies are available.

PICO Question

P- Adult patients with COVID-19
I- Convalescent plasma
C- Standard therapy
O- Clinical improvement

Background

Patients infected with the novel corona virus 2019 have limited treatment options which have proven to be effective. While the majority of patient who become contract COVID-19 improve without treatment, there is a small population who become critically ill and the need for effective therapy has become more evident. Currently these patients receive supportive care, but some patients will not survive with this standard treatment alone. Until a vaccine is created and widely distributed, an effective treatment could save many lives. Convalescent plasma has been used in patients infected with novel respiratory viral infections in the past, however outcomes are unknown for patients who develop COVID-19.

Trial 1

The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-Analysis**.** Mair-Jenkins, et al**.** *Journal of Infectious Diseases.* 2015;211(1):80-90.

Pubmed link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264590/

Validity Rating: Moderate to high risk of bias/poor validity due to the quality of included studies.

The Basics:
This article was a meta-analysis of studies evaluating the use of convalescent plasma in patients who developed a severe acute respiratory infection of a viral etiology. The authors evaluated numerous retrospective studies and 3 meta-analyses covering multiple viral etiologies over the past century including the Spanish influenza, SARS, MERS, avian influenza, and the 2009 H1N1 influenza. The studies were varied but they primary evaluated convalescent plasma and clinical outcome.

Inclusion Criteria:
Inclusion criteria consisted of all retrospective, prospective, or randomized controlled trials using convalescent plasma in patients who developed a severe acute respiratory infection of a viral etiology to include the Spanish flu, SARS, MERS, avian influenza, or the 2009 H1N1 influenza. It included all languages and included the grey literature.

Exclusion Criteria:
Exclusion criteria was only small study sizes (less than 5 patients were excluded).

Primary Outcomes:
Mortality

Secondary Outcomes:
Varied by individual study

Results:
Twenty-seven studies on adults with severe respiratory infections of viral etiology were included into the final meta-analysis. The authors reported their main outcomes as a mortality pooled odds ratio of 0.25 which favored treatment with convalescent plasma, however this only included eight of the original studies. The secondary outcomes were so varied within each single study that the results were unreliable.

Limitations/Bias:
-Mostly retrospective, observational, and case series were included which introduces bias
-Only three meta-analyses were included and only two were deemed low risk by the authors, however we question this evaluation as the primary studies were of poor quality
-Their odds ratio (OR) is statistically significant, however their quality of data analyzed is very poor and therefore the OR is unreliable

Trial 2

Rajendren K, Krishnasamy N, Rangarajan J, et al. *Convalescent plasma transfusion for the treatment of COVID-19: Systematic review.* Journal of Medical Virology, 2020;1-9.

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/32356910/

Validity Rating: High risk of bias/poor validity due to the quality of included studies.

The Basics:

This article was a systematic review of available data for the clinical effectiveness of CPT for the treatment of COVID-19. The authors evaluated 5 articles including a pilot study, a preliminary communication, a novel report, a case report and a descriptive study for a total of 27 patients. They included the dosage of CPT, mortality, length of hospital stay, critical care interventions, clinical outcomes, viral load, and adverse events.

Inclusion Criteria:

Inclusion criteria consisted of all clinical trials including randomized control trials, controlled clinical trials, prospective and retrospective comparative cohort studies, case-control studies; cross-sectional studies, case series and case reports.

Exclusion Criteria:

Exclusion criteria included preclinical trials (in vitro trials and animal models) and in silico drug screens.

Primary Outcomes:

Mortality/survival benefits and clinical effects

Secondary Outcomes:

Viral load & antibody titers, adverse events

Results:

Five studies, consisting of 27 patients, were selected for analysis. All the studies were conducted in China except for 1 in South Korea. The dosages of CPT and time they were administered differed between the studies and all the patients were also receiving one or more antiviral agents at the same time. Each study showed decreased viral load and increased antibody titers over time and almost all the patients had improvement in symptoms. All the studies reported zero mortality and no adverse effects (with the exception of mild facial erythema in one patient), however all the patients were on multiple other antiviral and antibiotic treatments at the same time. Overall, there was not enough data to conduct any statistical analysis and there were way too many confounding variables and lack of standardization.

Limitations/Bias:

-Case series or case reports with no controls for comparison
-There is likely selection bias as zero mortality was reported
-Way too many confounding variables with multiple other therapies involved
-No standardization of timing or dosage of CPT
-Variation in outcome measures between studies
-Small sample size