Effectiveness of Convalescent Plasma Therapy on Severely ill COVID-19 Patients

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Research Question

Is the use of convalescent plasma therapy (CPT) in combination with Standard of Care (SOC) more effective than SOC alone at decreasing the hospital length of stay for severely ill COVID-19 patients?

Background

Severe COVID-19 infections present as mild to moderate pneumonia evolving into shortness of breath and hypoxia[1]. The current SOC is to provide respiratory support measures to counter COVID-related complications.

Since the start of the pandemic, a total of 31,360 patients have been hospitalized in Ontario with a confirmed diagnosis of COVID-19[2]. It was necessary to investigate novel treatment options, such as CPT, to reduce hospital length of stay and maintain capacity in the healthcare system.

CPT is a form of passive immunotherapy[3]. Pre-formed antibodies present in the plasma of recovered patients are transfused into patients currently suffering from the disease, theoretically helping to fight off infection and reduce symptom burden.

Methods

Between October 10-22, 2021, a literature search was conducted via PubMed and Cochrane Library databases. Initial PubMed searches yielded 1,078 results; MeSH and Boolean logic reduced the number of articles to <100. Search terms used included “COVID-19 convalescent plasma,” “COVID-19 serotherapy,” “Randomized Controlled Trial,” and “Standard of Care.” Initial Cochrane searches yielded 23 results using the search terms “Interventional,” “Convalescent Plasma,” and “Length of ICU Stay.” Of these studies, 11 articles were chosen, excluding studies that enrolled <50 participants and preliminary reports prior to June 2020.

Literature Summary

The 11 articles obtained include: 6 randomized control trials[4–6,8,10,11] (RCT), propensity score-matched analysis[7], systematic review[13], network meta-analysis[9], retrospective cohort study[12], and adaptive clinical trial[14].

Most studies concluded that convalescent plasma with SOC did not have a significant effect in reducing length of hospital stay compared to SOC alone[4–6,8,10–14]. Two articles suggested CPT may provide a clinically significant benefit if administered early[7,8]. Others found CPT effective in improving outcomes in non-ICU settings[9]. Some articles suggest CPT groups experienced more adverse effects[6]. About half of the articles reviewed had a relatively small sample size[7,8,10–12] (n=100-200). The conclusions drawn from these studies could be unreliable due to them being underpowered.

Critical Appraisal

All results were determined to be valid and statistically high-powered due to their large sample sizes. Limitations of each study were evaluated and are listed (Table 1). The two RCTs also found results remained consistent across sub-groups of age, sex, ethnicity, symptom duration, and level of respiratory support.

Local relevance: The results can be generalized to the population of SARS-CoV-2 infected patients in Ontario, Canada and help inform potential treatment options for hospitalized patients (Table 1). As there appears to be no clinical benefit, clinicians and health partners can prioritize alternative treatments, especially in consideration of the potential risks associated with CPT transfusion.

Discussion

Summary: The overall consensus suggests that CPT does not provide any clinical benefit to hospitalized COVID-19 patients in reducing the hospital length of stay or reducing mortality[4–6,8,10–14]. Some studies also demonstrated that patients receiving convalescent plasma experienced more adverse effects than patients receiving standard of care alone[6].

Table 1.

	Abani et al., 2021 (RCT)	Bégin et al., 2021 (RCT)	Wang et al., 2021 (Meta-analysis)
Question	**P:** Hospitalized patients with clinically suspected or confirmed SARS-CoV-2 infection. **I:** Convalescent plasma. **C:** Standard of Care (SOC). **O:** 28-day mortality.	**P:** Hospitalized adults (≥16 years old) with confirmed SARS-CoV-2 infection. **I:** Convalescent plasma. **C:** Standard of Care (SOC). **O:** Intubation or death at 30 days.	**P:** 44068 patients across 45 studies. **I:** Convalescent plasma. **C:** Placebo or no intervention. **O:** Reduced mortality and improved clinical symptoms.
Study Design	Investigator-initiated, individually randomized, controlled, open-label, adaptive platform trial conducted across 177 NHS hospitals in the UK. From May 28, 2020, to Jan 15, 2021, patients were randomly assigned to either the SOC alone (n=5763) or CPT (n=5795) groups.	International, multi-centre, open-label, randomized, controlled trial conducted across 72 hospitals in Canada, the US, and Brazil. Patients (n=923) were randomly assigned to either receive SOC alone (n=303) or 500mL CPT (n=548).	Systematic study evaluating the results of 45 articles (4RCTs, 11 controlled NRSIs, 7 non-controlled NRSIs and 23 case reports). Databases searched: Pubmed, Cochrane Library, Clinical Key, Wanfang Database; China National Knowledge Infrastructure(CNKI) were used to search keywords such as “SARS-CoV-2”, “COVID-19”, “plasma”, “serum”, “immunoglobulins”, “blood transfusion”, “convalescent” and the related words for publications published until Oct 15, 2020.
Results	High-titer convalescent plasma did not significantly improve 28-day mortality rates (rate ratio=1.00, 95% CI 0.93-1.07, p=0.95). The proportion of patients discharged (rate ratio=0.99, 95% CI 0.94-1.03, p=0.57) and the proportion of patients who progressed to mechanical ventilation (rate ratio=0.99, 95% CI 0.93-1.05, p=0.79) were also not significantly affected by convalescent plasma use.	The study was terminated after meeting stopping criteria for futility. Patients in the CCP arm did not see a reduction in risk of intubation or death at 30 days (relative risk, RR=1.16, 95% confidence interval, CI 0.94-1.43, p=0.18) but did see an increase in adverse transfusion-related events (RR=1.27, 95% CI 1.02-1.57, p=0.034).	For RCTs, when time from symptom onset to transfusion was less than 10 days the use of CP transfusion may reduce the mortality of patients, however it was not statistically significant. Similar results were found in controlled NRSI's, but they were statistically significant. The clinical improvement outcome was evaluated from 2RCTs. Compared to the control group, the results of RCTs showed that the use of CP transfusion may be beneficial to the improvement of patients' clinical. But there was no significant difference between the two groups.
Validity	VALID Limitations: open-label design, lack of placebo controls.	VALID Limitations: open-label design, lack of placebo controls, lack of clinician blinding.	VALID Limitations: lack of RCTs and use of non-randomized studies for analysis. Accounted for by bias evaluator.
Local Relevance	YES • Largest RCT study of CPT in UK	YES • Largest North American RCT study of CPT	YES • High powered; large patient population across 45 studies employing CPT • Consistent finding

Future Research: There may be a benefit associated with administering CCP early in the onset of the disease. Further research needs to be conducted to elucidate this relationship.

References

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