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Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review.
Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD013600.
DOI: 10.1002/14651858.CD013600.pub3.

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[Intervention Review]

Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review

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Editorial group: Cochrane Haematology Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 10, 2020.

Citation: Chai KL, Valk SJ, Piechotta V, Kimber C, Monsef I, Doree C, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD013600. DOI: 10.1002/14651858.CD013600.pub3.

ABSTRACT

Background

Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with viral respiratory diseases, and are currently being investigated in trials as potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding the benefits and risks is required.

Objectives

To continually assess, as more evidence becomes available, whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in treatment of people with COVID-19.

Search methods

We searched the World Health Organization (WHO) COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, Centers for Disease Control and Prevention COVID-19 Research Article Database and trial registries to identify completed and ongoing studies on 19 August 2020.

Selection criteria

We followed standard Cochrane methodology.

We included studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of study design, disease severity, age, gender or ethnicity.

We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) and studies evaluating standard immunoglobulin.

Data collection and analysis

We followed standard Cochrane methodology.

To assess bias in included studies, we used the Cochrane 'Risk of bias' 2.0 tool for randomised controlled trials (RCTs), the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool for controlled non-randomised studies of interventions (NRSIs), and the assessment criteria for observational studies, provided by Cochrane Childhood Cancer for non-controlled NRSIs. We rated the certainty of evidence using the GRADE approach for the following outcomes: all-cause mortality at hospital discharge, mortality (time to event), improvement of clinical symptoms (7, 15, and 30 days after transfusion), grade 3 and 4 adverse events (AEs), and serious adverse events (SAEs).

Main results

This is the second living update of our review. We included 19 studies (2 RCTs, 8 controlled NRSIs, 9 non-controlled NRSIs) with 38,160 participants, of whom 36,081 received convalescent plasma. Two completed RCTs are awaiting assessment (published after 19 August 2020). We identified a further 138 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 73 are randomised (3 reported in a study registry as already being completed, but without results). We did not identify any completed studies evaluating hyperimmune immunoglobulin.

We did not include data from controlled NRSIs in data synthesis because of critical risk of bias. The overall certainty of evidence was low to very low, due to study limitations and results including both potential benefits and harms.

Effectiveness of convalescent plasma for people with COVID-19

We included results from two RCTs (both stopped early) with 189 participants, of whom 95 received convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma.

We are uncertain whether convalescent plasma decreases all-cause mortality at hospital discharge (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.22 to 1.34; 1 RCT, 86 participants; low-certainty evidence).

We are uncertain whether convalescent plasma decreases mortality (time to event) (hazard ratio (HR) 0.64, 95% CI 0.33 to 1.25; 2 RCTs, 189 participants; low-certainty evidence).

Convalescent plasma may result in little to no difference in improvement of clinical symptoms (i.e. need for respiratory support) at seven days (RR 0.98, 95% CI 0.30 to 3.19; 1 RCT, 103 participants; low-certainty evidence). Convalescent plasma may increase improvement of clinical symptoms at up to 15 days (RR 1.34, 95% CI 0.85 to 2.11; 2 RCTs, 189 participants; low-certainty evidence), and at up to 30 days (RR 1.13, 95% CI 0.88 to 1.43; 2 studies, 188 participants; low-certainty evidence).

No studies reported on quality of life.

Safety of convalescent plasma for people with COVID-19

We included results from two RCTs, eight controlled NRSIs and nine non-controlled NRSIs assessing safety of convalescent plasma. Reporting of safety data and duration of follow-up was variable. The controlled studies reported on AEs and SAEs only in participants receiving convalescent plasma. Some, but not all, studies included death as a SAE.

The studies did not report the grade of AEs. Fourteen studies (566 participants) reported on AEs of possible grade 3 or 4 severity. The majority of these AEs were allergic or respiratory events. We are very uncertain whether convalescent plasma therapy affects the risk of moderate to severe AEs (very low-certainty evidence).

17 studies (35,944 participants) assessed SAEs for 20,622 of its participants. The majority of participants were from one non-controlled NRSI (20,000 participants), which reported on SAEs within the first four hours and within an additional seven days after transfusion. There were 63 deaths, 12 were possibly and one was probably related to transfusion. There were 146 SAEs within four hours and 1136 SAEs within seven days post-transfusion. These were predominantly allergic or respiratory, thrombotic or thromboembolic and cardiac events. We are uncertain whether convalescent plasma therapy results in a clinically relevant increased risk of SAEs (low-certainty evidence).

Authors' conclusions

We are uncertain whether convalescent plasma is beneficial for people admitted to hospital with COVID-19. There was limited information regarding grade 3 and 4 AEs to determine the effect of convalescent plasma therapy on clinically relevant SAEs. In the absence of a control group, we are unable to assess the relative safety of convalescent plasma therapy.

While major efforts to conduct research on COVID-19 are being made, recruiting the anticipated number of participants into these studies is problematic. The early termination of the first two RCTs investigating convalescent plasma, and the lack of data from 20 studies that

have completed or were due to complete at the time of this update illustrate these challenges. Well-designed studies should be prioritised. Moreover, studies should report outcomes in the same way, and should consider the importance of maintaining comparability in terms of co-interventions administered in all study arms.

There are 138 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 73 are RCTs (three already completed). This is the second living update of the review, and we will continue to update this review periodically. Future updates may show different results to those reported here.

PLAIN LANGUAGE SUMMARY

Is plasma from people who have recovered from COVID-19 an effective treatment for people with COVID-19?

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory illness caused by a newly recognised type of coronavirus. Some people have severe infection, leading to hospitalisation, admission to intensive care or death. Currently, no vaccine or specific treatment is available.

People who have recovered from COVID-19 develop natural defences in their blood (antibodies). Antibodies are found in part of the blood called plasma. Plasma from blood donated from recovered patients, which contains COVID-19 antibodies, can be used to make two preparations. Firstly, convalescent plasma, which is plasma that contains these antibodies. Secondly, hyperimmune immunoglobulin, which is more concentrated, and therefore contains more antibodies.

Convalescent plasma and hyperimmune immunoglobulin have been used successfully to treat other respiratory viruses. These treatments (given by a drip or injection) are generally well-tolerated, but unwanted effects similar to those from standard plasma transfusion can occur.

What did we want to find?

We wanted to know whether plasma from people who have recovered from COVID-19 is an effective treatment for people with COVID-19, and whether this causes any unwanted effects.

Our methods

We searched major medical databases for clinical studies on treatment with convalescent plasma or hyperimmune immunoglobulin for people with COVID-19. Studies could be conducted anywhere in the world and include participants of any age, gender, ethnicity or disease severity.

The evidence is up to date to 19 August 2020.

Key results

We included 19 completed studies with 38,160 participants; 36,081 participants received convalescent plasma.

We found two randomised controlled trials (RCTs), with 189 participants; 95 participants received convalescent plasma. RCTs are clinical studies where people are randomly allocated to receive the treatment (intervention group) or to receive different or no treatment (control group). Methods used in RCTs are designed to produce the most reliable evidence.

We found eight studies that were not randomised but included a control group of participants who did not receive convalescent plasma (controlled NRSIs), with 2471 participants; 485 participants received convalescent plasma. Because of critical study limitations or missing data, we did not include these studies to evaluate the benefit of convalescent plasma.

The remaining nine studies were not randomised and did not include a control group (non-controlled NRSIs) but provided information about unwanted effects of convalescent plasma for 20,622 of the included participants.

To assess whether convalescent plasma is effective for COVID-19, we evaluated results from the RCTs. The control groups received standard care at the time of treatment without convalescent plasma. There was not enough evidence to determine whether convalescent plasma affected the risk of death at hospital discharge and our confidence in the evidence is low. Convalescent plasma may decrease the need for breathing support, but our confidence in the evidence is low.

To assess whether convalescent plasma causes unwanted effects, we also evaluated nine non-controlled NRSIs. We identified some serious unwanted effects, which could be related to convalescent plasma, including death, allergic reactions or respiratory complications. There was not enough evidence to determine whether convalescent plasma therapy causes serious unwanted events and our confidence in the evidence is low.

None of the included studies reported effects on quality of life.

Certainty of the evidence

Our certainty (confidence) in the evidence was low or very low because there were only two RCTs and most studies did not use reliable methods to measure their results. Furthermore, participants received various treatments alongside convalescent plasma, and some had underlying health problems.

Conclusion

We are uncertain whether plasma from people who have recovered from COVID-19 is an effective treatment for people hospitalised with COVID-19 and whether convalescent plasma affects the number of serious unwanted effects. These findings could be related to the natural progression of disease, other treatments or to convalescent plasma. Our searches found 138 ongoing studies, of which 73 are randomised. This is the second update of our review, and we will continue to update this review.