Review Articles

Convalescent plasma therapy for Covid-19: A systematic review

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ABSTRACT

Background. Covid-19 has emerged as a pandemic affecting more than 20 million people till date with few, if any, proven therapy. Convalescent plasma (CP) containing antibodies against the virus has been used with some success. We did a systematic review to synthesize the available data on CP therapy for treatment of Covid-19 to study the efficacy and safety outcomes.

Methods. Two reviewers searched the published and pre-published literature between 1 January 2019 and 23 June 2020 for studies comparing the use of CP with standard therapy for Covid-19 patients. Data from the selected studies were abstracted and analysed for efficacy and safety outcomes. Critical appraisal of the evidence was done by using the Joanna Briggs Institute tool and the quality of evidence was graded as per GRADE.

Results. We found 13 case series and 1 randomized trial that fulfilled our search criteria. Of the 12 case series with a total of 264 patients that reported the efficacy outcomes, 11 studies showed favourable results with survival benefit. The only RCT with 103 patients did not show any mortality benefit but was terminated early prior to complete enrolment. A single large study of 5000 patients reported safety outcomes and showed no major adverse events in patient streated with CP.

Conclusion. There is very low-quality evidence to suggest efficacy and safety of CP in patients with Covid-19 infection. Well-designed randomized trials are urgently needed to provide robust data.

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INTRODUCTION

The history of passive immunotherapy using plasma from patients convalescing from an infection started in 1890s when it was used for the treatment of infectious diseases.[1] The biological rationale being that convalescent plasma (CP) contains antibodies against the specific pathogen which may neutralize the pathogenic organism and modify the inflammatory response of the host to the organism.[2,3] The effect of CP varies with the severity of disease, dose of antibodies and usually works better in the initial phases of illness or as prophylaxis.[1,2]

The efficacy of CP was supported by anecdotal evidence from H5NI,[4] H7N9,[5] MERS,[6] and SARS or SARS CoV-1[7] viral infections. The experience from outbreaks of SARS-CoV-1, another corona virus disease, had shown that neutralizing antibodies in CP could reduce viraemia in sick patients.[7–10] Therefore, in the absence of a pharmacological therapy or a vaccine for Covid-19/SARS-CoV-2, passive antibody administration via CP seems a valid method of reducing viraemia and providing immediate enhanced antibody-mediated immunity to infected patients. However, the risks of passive antibody administration via CP are well known. These include the risk of adverse reactions, transfusion-related acute lung injury (TRALI) and transmission of infections. A theoretical risk of antibody-dependent enhancement of infection (ADE) is also a possibility[10] but seems unlikely as plasma containing high titres of neutralizing antibody against the SARS-CoV-2 are being used.[11]

We did a systematic review of the available studies to determine if the use of CP is effective and safe in reducing mortality in patients with Covid-19 compared to those not given CP.

METHODS

Criteria for selecting studies

We sought to identify all clinical studies including randomized controlled trials (RCTs), cohort studies with control groups, observational studies—both prospective and retrospective, and case series for the purpose of this review. We included both published studies as well as pre-print and non-peer reviewed literature as Covid-19 is a new disease and information available on pre-print servers may be valuable in guiding clinical practice given the rapidly increasing number of cases worldwide and a

lack of effective therapy. We included papers available in English only. We excluded single case reports from the review.

Types of participants

We included human studies in which patients with confirmed Covid-19 of all ages, sexes and grades of severity were recruited.

Types of intervention

We included studies in which patients with Covid-19 were administered CP collected from patients who had recovered from the infection.

Outcomes

For each study, we sought the following efficacy and safety outcomes:

- *Clinical outcomes*: Death, improvement in oxygen requirement, and need for mechanical ventilation
- *Radiological outcomes*: Improvement in computed tomography (CT) chest findings
- *Biochemical outcomes*: Reduction in C-reactive protein (CRP) and change in interleukin (IL)-6 levels
- *Safety outcomes*: Adverse effects and complications associated with CP therapy

Search strategy

Two authors (TS and AS) independently searched the PubMed, Embase, Google Scholar and MedRxiv databases using the following search terms: '[(Convalescent plasma OR Plasma OR serum) AND (COVID-19 OR SARS-CoV-2)]' from 1 January 2019 till 23 June 2020. No limits were applied to the search results except studies in humans. Hand searching of cross-references of original articles, reviews and pre-published articles was also done.

Data extraction

The citations were retrieved into a reference management software (Zotero version 5.0.85). Duplicate citations were removed. All the remaining studies were reviewed by going through their title and abstract to select the studies meeting our inclusion criteria mentioned above. Data on outcomes were extracted by one reviewer (TS) and cross-checked by another reviewer (AS). We looked at various aspects of each study such as the type of study, inclusion criteria, dose and timing of CP therapy, additional treatments received, severity and phase of illness, antibody titre and outcomes as mentioned above. The severity of illness was defined as mild, moderate, severe and critical as per the sixth interim edition of diagnosis and treatment protocol of CDC, China.[12]

Assessment of quality of studies

We critically appraised the selected studies with complete information as per the Joanna Briggs Institute (JBI) tool[13] for this systematic review. The evidence was graded using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology.[14]

RESULTS

Description of studies

The search yielded 584 articles on PubMed, 2800 articles on Google scholar, 470 on Embase and 827 on MedRxiv. No additional articles were retrieved on hand searching of references of reviews and original articles. We excluded papers that were commentaries or expert opinions and not clinical studies as they did not fit our inclusion criteria. Single case reports were also excluded. After removal of duplicate citations, we had 14 articles for complete review. We found 13 descriptive studies and only one RCT of CP use for Covid-19 (Table I).[15] The PRISMA flow chart is provided as Figure 1.

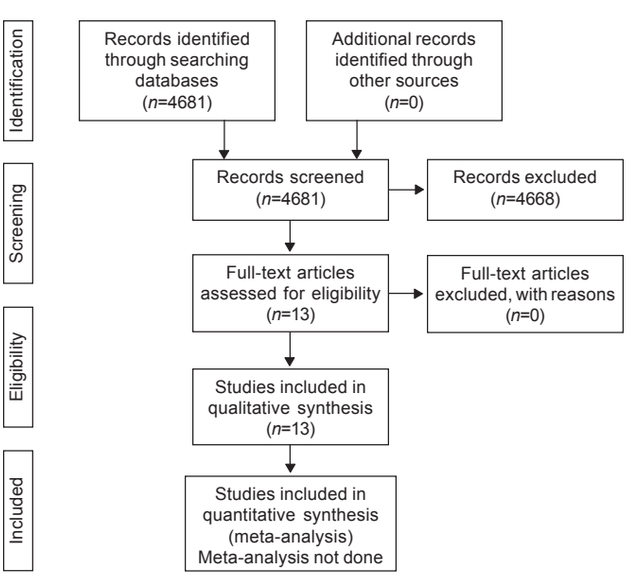
Risk of bias

An appraisal of the included case series using the JBI tool has been summarized in Table II. Since the cohort studies had non-blinded assessment of outcomes, they were subject to multiple sources of bias. The risk of bias was low in the RCT.

Summary results

A total of 5264 patients included in the 13 cohort studies/observational studies[16–29] were treated with CP. Their age range was 18–97 years; the largest study included 5000 patients with severe or life-threatening illness and had 72% patients on mechanical ventilation and 18% in shock. This study reported only safety outcomes. The interval between onset of symptoms and treatment with CP varied from 3 to 38 days; most patients received the therapeutic intervention in the third week of illness (Table I). The dose of CP varied from 200 to 400 ml given 1–3 times over 1–3 days with most patients receiving 2 doses. In one study, the dose was very high, i.e. 2400 ml.[23] The IgG antibody concentration in the CP varied from 1:640 to 1:1000 as reported in two studies.[17,20] Pre-infusion antibody titres in the treated patients were reported in one study and were 72–217 mg/dl for IgG and 16–273 mg/dl for IgM antibodies.[21] Among the co-medications, all patients received various medications including antivirals, methylprednisolone and intravenous immunoglobulin but had not shown any improvement. The outcomes of each of the series are summarized in Table I.

The RCT included 103 patients (median age 70 years; 60 [58.3%] male) with severe or critical Covid-19. Patients were



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic *R*eviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

FIG 1. PRISMA flow diagram for study selection

TABLE I. Summary of the 12 case series and one randomized trial for convalescent plasma (CP) therapy in Covid-19

Author (Country)	Type of study	Patients (*n*); median age (range in years); comorbid conditions	Controls (*n*)	Severity of illness	Dose and day of CP therapy	Concomitant medicines	Outcome	Overall benefit
Shen *et al.*[20] (China)	Case series	*n*=5; age 60 years (30–70); men 3, women 2; hypertension, mitral insufficiency	Nil	All critical, ARDS present; all received mechanical ventilation; one received ECMO; 2 patients had bacterial/ fungal pneumonia	400 ml infusion during days 10–22 of illness; plasma had a specific IgG antibody titre of 1:1000 and viral neutralization assay was done. CP neutralization titre used in the study was >40	Methylprednisolone and antivirals in all	All 5 patients improved, 3 of them discharged home	Yes
Duan *et al.*[17] (China)	Case series with controls	*n*=10; age 52 years (34–78); men 6, women 4	10	3 critical, 7 severe (3 mechanical ventilation, 5 on high-flow oxygen, 2 low-flow oxygen; none received ECMO)	200 ml single dose with variable neutralizing antibody titres but minimum titre of 1:640 Median time of CP transfusion was 16.5 days (range 10–20) Pathogen inactivation done	5 received methylprednisolone; all were on antivirals	All 10 patients improved; 2 of 3 off ventilation, 3/7 improved and discharged, 7 improved but not discharged at the time of report. Control group: 3 deaths, 6 stable, one improved ($p<0.001$)	Yes
Ahn *et al.*[16] (South Korea)	Case series	*n*=2; age 69 years (67–71); men 1, women 1; hypertension in both	Nil	Critical patients, ARDS; both on mechanical ventilation	500 ml plasma divided in 2 doses and given 12 hours apart; day 22 and day 7 of illness Anti-SARS-CoV-2 IgG (OD) 0.586.	All on methylprednisolone and antivirals, HCQs, empirical antibiotics	Both improved clinically; complete recovery—one patient discharged, one on tracheostomy at the time of publication	Yes
Zhang *et al.*[23] (China)	Retrospective case series	*n*=4; age 62 years (31–73); men 2, women 2; renal failure, COPD, hypertension, pregnancy	Nil	Critically ill with comorbid conditions; 3 invasive ventilation, 1 NIV; 2 received ECMO following mechanical ventilation	200–2400 ml administered as one or 8 doses. Given on days 3–22 of illness	Methylprednisolone in one, all on antivirals	Complete recovery in all, 3/4 discharged	Yes
Ye *et al.*[21] (China)	Case series	*n*=6; age 60 years (28–75); men 3, women 3, Sjogrens syndrome in 1	NA	Critically ill with abnormal CT findings or on oxygen therapy; One patient asymptomatic no radiology findings on day 32 of illness. None needed mechanical ventilation or ICU admission	200 ml infused over 30 minutes. Given 1–3 doses on day 20–38 of illness; antibody titre in treated patients for IgG varied 72–217, IgM 16–273, not reported for 2 patients.	Not clearly defined, patients treated at other hospitals	All recovered, all discharged	Yes

contd.

TABLE I. Summary of the 12 case series and one randomized trial for convalescent plasma (CP) therapy in Covid-19 (*contd.*)

Author (Country)	Type of study	Patients (*n*); median age (range in years); comorbid conditions	Controls (*n*)	Severity of illness	Dose and day of CP therapy	Concomitant medicines	Outcome	Overall benefit
Zeng *et al.*[22] (China)	Case series	*n*=6; age 61.6 years (31–77); CLD, CKD, DM, hypertension	*n*=15; age 73 years (60–79); CLD, CKD, DM, hyper-tension	Critically ill; 5/6 in CP arm and 13/15 in control arm were on mechanical ventilation; 4/6 in CP arm and 12/15 in control arm received ECMO	6 received median of 300 ml (range 200–600 ml) at 1–3 time points, no anti-body titres done; infusion in one patient on day 25 and 27 of illness; details not provided for other 5 cases	All patients on multiple antivirals, antibiotics, Chinese traditional medicine, IVIG, and steroid pulse	5/6 died in the intervention group while 14/15 died in the control group (p=0.184); all intervention patients had viral clearance	No
Salazar *et al.*[19] (USA)	Case series	*n*=25; age (19–77); 64% had comorbid conditions DM/ hypertension/ hyperlipidaemia	Nil	Severe/life-threatening illness; 12 on mechanical ventilation; 10 on low-flow oxygen; 3 on high-flow oxygen and one on ECMO	300 ml infused, one patient received twice; ABO matched; IgG titres 0–1350; neutrali-zation assays done; on days 3–10 of illness	Tocilizumab, steroids, antivirals including ribavirin/lopinavir–ritonavir/remdesivir, HCQ, azithromycin	On day 14, 11/25 discharged; 8/25 improved 3/25 unchanged 3/25 deteriorated 1/25 died	Yes
Joyner *et al.*[18] (USA)	Case series	*n*=5000 conse-cutive patients; age 62 years (18–97)	Nil	Severe/life-threatening illness or at high risk of progression to severe/life-threatening illness; 72% respiratory failure; 18% multi-organ dysfunction; 15% shock	200–500 ml of ABO-compatible plasma from donors; titres not mentioned	Supportive care; medications not explicitly mentioned	602/5000 patients died; serious adverse events leading to death 15/5000 (0.3%); serious adverse effects not leading to death 21/5000; transfusion-associated circulatory overload 7/5000; transfusion-associated lung injury 11/5000; severe allergic reaction 3/5000	Not appli-cable
Pei *et al.*[24] (China)	Case series	*n*=3; age 18–55 years (sex not specified)	Nil	Moderately ill and critical, duration of disease <3 weeks	200–500 ml; antibody titre >1:160; exclusion criteria IgA deficiency or allergy to plasma	Not reported	Serious allergic reaction in one patient after 30 ml of infusion, therapy aborted; one moderately ill and one critically ill patient had clinical response; 2/3 patients improved; follow-up 36 days	Yes

contd.

TABLE I. Summary of the 12 case series and one randomized trial for convalescent plasma (CP) therapy in Covid-19 (*contd.*)

Author (Country)	Type of study	Patients (*n*); median age (range in years); comorbid conditions	Controls (*n*)	Severity of illness	Dose and day of CP therapy	Concomitant medicines	Outcome	Overall benefit
Hegerova *et al.*[26] (USA)	Case series with controls	*n*=20; age 60 years (29–95) with 20% of patients >80 years	20, age and comorbid conditions matched	All patients had severe/ critical illness; most common comorbid conditions were hypertension (60%), DM (45%) and obesity (20%); one-third of patients required mechanical ventilation	Dose and antibody titre not specified	Azithromycin (60%), HCQ (55%) or multiple combinations	Intervention 4 deaths; controls 11 deaths; no patients died if they received intervention prior to 7 days of hospitalization	Yes
Xia *et al.*[28] (China)	Case series with controls	*n*=138; age 65 years (57–73); men 77, women 61	*n*=1430; age 63 years (53–71); men 720, women 710	All patients had severe/ critical disease; comorbid conditions: hypertension, DM, cardiovascular disease commonest	Median time from first symptom to CP was 45 days; 200–1200 ml (based on body weight and clinical status)	Not specified	2.2% and 4.1% of cases died in the CP and in the standard treatment group, respectively; 2.4% and 5.1% of patients in the CP and the standard treatment group were admitted to ICU eventually; 70% of patients who had severe respiratory symptoms improved and were removed from oxygen support within 7 days after CP; 76.8% of cases had radiological improvement within 14 days after CP	Yes
Liu *et al.*[25] (USA)	Case series with controls	*n*=39; age 55 years (+13); men 25, women 14	156 (propensity matched)	All patients had severe/ life-threatening disease; 54% were obese (body mass index ≥30) and 18% had a current or previous history of tobacco use; one patient had end-stage renal disease	High-flow oxygen, high-flow nasal cannula or BiPAP 27; mechanical ventilation 4; median time between admission and transfusion was 4 (1–7)	Azithromycin, broad-spectrum antibiotics, HCQ, therapeutic anticoagulants, corticosteroids, antivirals, stem cells, and interleukin-1 and interleukin-6 inhibitors	Day 14 CP; 12.8% worsened or died *v.* 24.4% worsened or died in controls (p=0.039). In a covariates-adjusted Cox model, CP-treated patients had improved survival for non-intubated patients (hazard ratio [HR] 0.19 (95% CI 0.05–0.72; p=0.015) but not for intubated patients (HR 1.24; 95% CI 0.33–4.67; p=0.752)	Yes

contd.

TABLE I. Summary of the 12 case series and one randomized trial for convalescent plasma (CP) therapy in Covid-19 (*contd.*)

Author (Country)	Type of study	Patients (*n*); median age (range in years); comorbid conditions	Controls (*n*)	Severity of illness	Dose and day of CP therapy	Concomitant medicines	Outcome	Overall benefit
Jin *et al.*[29] (China)	Case series	*n*=6; men 4, women 2	Nil	5 critically ill patients with Covid-19 and ARDS; 3 patients upfront, 3 patients used for recurrent Covid-19; comorbid conditions of hypertension, heart disease and DM	SARS-CoV-2-specific ELISA antibody titre >1:1000 and a neutralizing antibody titre >40	Antivirals and steroids	All improved within 12 days	Yes
Li *et al.*[15] (China)	RCT	*n*=52; mean age 70 years	*n*=51	Life-threatening disease (48) Severe disease (55)	4–13 ml/kg once, median dose 200 ml; S-RBD-specific IgG titre of at least 1:640	Multiple medications in both groups	Clinical improvement (51.9% with the CP *v.* 43.1% with standard care (difference, 8.8%; 95% CI –10.4% to 28.0%; HR 1.40 [95% CI 0.79–2.49; p=0.26); subgroup analysis of patients with severe disease, clinical improvement in 91.3% (21/23) in the CP group *v.* 68.2% (15/22) in controls (HR 2.15 [95% CI 1.07–4.32]; p=0.03)	No

ARDS acute respiratory distress syndrome ECMO extracorporeal membrane oxygenation HCQ hydroxychloroquine COPD chronic obstructive pulmonary disease NIV non-invasive ventilation ICU intensive care unit CLD chronic liver disease CKD chronic kidney disease DM diabetes mellitus IVIG intravenous immunoglobulin RCT randomized controlled trial S-RBD S protein-receptor binding domain

randomized to CP or standard treatment stratified by disease severity. The recipient patients with high titre of S protein–RBD (receptor binding domain)-specific IgG antibody (≥1:640) were excluded. The donor plasma units with an S-RBD-specific IgG titre of at least 1:640 were used for therapy. The median dose received was 200 ml (IQR 200–300 ml), and 96% of patients received a single dose of plasma infusion. The median interval between the onset of symptoms and randomization was 30 days. Primary outcome was time to clinical improvement within 28 days defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale. The trial was terminated early after 103 of a planned 200 patients were enrolled because the number of cases fell sharply midway through the trial in China.

Safety outcomes

The largest study of 5000 patients by Joyner *et al*.[18] focused only on safety profile and adverse events of CP and did not report on efficacy outcomes. Serious adverse events occurred in 36 of 5000 patients in this series. Of these, 15 patients (0.3%) died in less than 4 hours after receiving plasma therapy. Serious adverse events not leading to death included TRALI in 11/5000 patients, transfusion-associated circulatory overload (TACO) in 7/5000 patients and allergic reactions in 3/5000 patients. No significant adverse events were reported in the other studies. One patient in Pei *et al.*[24] had a severe allergic reaction to CP and could not continue therapy.

Efficacy outcomes

We found 12 case series and 1 RCT that reported efficacy outcomes. Included amongst these 12 studies were a total of 367 patients. All patients except one had severe or critical illness (Table I). Most series (11/12) showed significant benefit with the use of CP.

In the small case series by Zeng *et al*.,[22] 5 of 6 patients who received CP died. In this study, all 6 treated patients had bilateral pneumonia and respiratory failure and 5 of them had acute respiratory distress syndrome (ARDS). All these patients were placed on mechanical ventilation and 3 required extracorporeal membrane oxygenation (ECMO). In addition, 3 of 6 patients had

septic shock and 3 required dialysis. Five patients were given IVIG, 4 antivirals and 4 steroids without any improvement. The median dose of CP was 300 ml and the antibody titre in donor plasma was not mentioned. The mean duration of illness was 45.5 (37.8–59) days before CP was administered. Despite negative results, all 6 patients cleared the virus after therapy with CP. In this study, 14 of 15 control patients died.

In a large observational study of 138 patients with 1430 controls, the authors reported a 50% reduction in mortality with CP. However, the overall mortality was low in both the treated and control groups (2.2% and 4.1%, respectively) despite all the patients having severe or critical illness.[28]

The results of the RCT by Li *et al.*[15] showed no difference between the treated and control groups with regard to the primary outcome, i.e. clinical improvement (51.9% with the CP *v.* 43.1% with standard care (mean difference 8.8% [95% CI –10.4% to 28.0%]; hazard ratio [HR] 1.40 [95% CI 0.79–2.49]; p=0.26) among all patients. However, in a subgroup analysis of patients with severe disease, clinical improvement occurred in 91.3% (21/23) in the CP group *v.* 68.2% (15/22) in the control group (HR 2.15 [95% CI 1.07–4.32]; p=0.03). Treatment with CP led to a higher rate of viral reverse transcriptase-polymerase chain reaction (RT-PCR) becoming negative (suggestive of viral clearance) at 72 hours in 87.2% in the CP group *v.* 37.5% in the control group (OR 11.39 [95% CI 3.91–33.18]; p<0.001). There was no difference in secondary outcomes. Only 2/103 patients in the CP group experienced adverse events within hours after transfusion, which improved with supportive care.

Critical appraisal

There was heterogeneity among various studies on multiple factors. First, there was some variability in the inclusion criteria; second, presence of comorbid conditions such as renal failure, chronic obstructive pulmonary disease (COPD) and pregnancy among treated patients; third, variability in dose of CP from 200 to 2400 ml; and finally, the timing of intervention, which was given at different time points of illness. Not all studies reported antibody titres or neutralization assays. The outcome assessments were non-blinded in all studies. The majority of patients were on multiple concomitant therapies including steroids, antiviral agents, Chinese herbal medicines and IVIG.

Table II gives a summary of the JBI critical appraisal. Only five case series had controls and of those only two were explicitly matched controls. Despite these limitations, the effect size was high since majority of patients improved in 11 of the 12 case series. There were many possible reasons for the negative outcome in the only trial that did not show benefit. These include enrolment of extremely sick patients with multi-organ failure, late administration and probably suboptimal dosing of CP. Being an RCT, the study by Li *et al.*[15] provides credible evidence. The limitations of this RCT include premature termination, relatively small sample size for subgroup analysis of patients with severe disease, non-use of normal plasma as placebo, and considerable delay from onset to randomization (median 30 days). Thus, the study showed that CP was unlikely to benefit patients with life-threatening disease late in the clinical course.

TABLE II. Combined table of assessment of the 13 case series as per the Joanna Briggs Institute tool

Assessment criterion	Shen *et al.*[20]	Duan *et al.*[17]	Ahn *et al.*[16]	Zhang *et al.*[23]	Ye *et al.*[21]	Zeng *et al.*[22]	Salazar *et al.*[19]	Joyner *et al.*[18]	Pei *et al.*[24]	Hegerova *et al.*[26]	Xia *et al.*[28]	Liu *et al.*[25]	Jin *et al.*[29]
Were there clear criteria for inclusion in the case series?	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have consecutive inclusion of participants?	Unclear	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Unclear
Did the case series have complete inclusion of participants?	No	Unclear	No	No	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Unclear	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	No	Yes	Yes	Yes	Yes
Were the outcomes or follow-up results of cases clearly reported?													
Outcomes	Yes	Yes	Clear	Clear	Yes	Yes	Yes	Safety data	Yes	Yes	Yes	Yes	Yes
Follow-up	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete	Not applicable as only safety outcomes mentioned	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Was statistical analysis appropriate?	NA	Yes	NA	NA	NA	Yes	NA	NA	NA	Yes	Yes	Yes	NA

NA not applicable

Quality of evidence

As most were observational studies, the initial assignment of level of quality for the body of evidence was 'low' according to GRADE. It was downgraded to 'very low' as there was substantial heterogeneity and the sample size of the studies individually as well as collectively was small, and hence associated with very serious imprecision of point estimates. Although 11 of 12 case series suggested benefit, the only RCT available did not show benefit. There was no demonstration of a dose–response gradient in any study.

DISCUSSION

The Covid-19 pandemic and lack of therapeutic options have made us revisit an age-old option of CP therapy. This systematic review shows that good quality evidence from multiple RCTs supporting the intervention with CP is lacking. The reported cohort studies with all their limitations suggest that use of CP in Covid-19 patients is feasible and probably safe. The large study on 5000 patients has so far published only safety data[18] and it showed that transfusion-related complications are very rare—transfusion-associated circulatory overload (0.14%, 0.07%–0.29%), TRALI (0.22%, 0.12%–0.39%) and severe allergic transfusion reaction in only 0.06% (0.02%–0.18%) patients. This is less than results reported following transfusion of fresh frozen plasma and other blood component use in critically ill ICU patients.[30,31]

Severe allergic reactions can occur as CP is a biological product, though increased chances of serious reactions are more likely in patients with IgA deficiency or prior allergy to plasma products. Strict monitoring during infusion is mandatory and haemovigliance reporting should be done for all patients to better underst and why some patients develop complications.

With regard to efficacy, the effect size was large in 11 of 12 non-randomized studies, which reported efficacy. This may be questionable as discussed in the critical appraisal and subject to high-risk of bias including publication bias of only positive case series. The RCT by Li *et al.*[15] failed to show overall reduction in mortality but showed that there was a possibility that CP therapy might be effective in severe cases. The authors discussed that because the test for interaction by disease severity was not statistically significant, the findings for the severe and life-threatening subgroups should not be interpreted as different. However, as acknowledged by the authors it was possible that the study was underpowered due to early termination to detect a statistically significant difference. It is now becoming clearer that those with life-threatening illness are less likely to benefit from CP.[15,25] One of the reasons for less than expected benefit could be late administration with the median time to randomization being 30 days. Even a small benefit in elderly patients (median age 70 years) is important in the absence of any other effective therapy. The accompanying editorial for the RCT provides historical and biological justification and shows optimism about possibilities with CP therapy for patients with severe Covid-19.[32]

Conclusion

This systematic review uncovered several important gaps which need to be addressed regarding the efficacy of CP for Covid-19. Well-designed RCTs with blinded assessment and longer follow-up are required to test the hypothesis that CP can help patients with Covid-19. US FDA,[33] and European agency,[34] DCGI, India have approved clinical trials for CP therapy and many trials are ongoing to fill the present gaps in our knowledge.

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