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ORIGINAL PAPER

Early experience with convalescent plasma as immunotherapy for COVID-19 in China: Knowns and unknowns

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Vox Sanguinis

Background and objectives In the absence of a vaccine or specific drug treatment options for coronavirus disease (COVID-19), attention has been shifted in China to the possible therapeutic use of convalescent plasma. COVID-19 convalescent plasma (CCP) is currently under investigation. We summarized clinical studies and other research data available as of 5 May 2020 on CCP therapy according to the *Clinical Treatment Guideline of COVID-19 Convalescent Plasma* in China, as well as clinical experience at the First Affiliated Hospital of Zhejiang University, as part of a comprehensive anti-epidemic strategy.

Materials and methods As of 5 May 2020, when the epidemic was well-controlled in China, healthcare databases and sources of English literature relating to convalescent plasma were searched and reviewed. Sources of clinical and methodological heterogeneity were identified.

Results As of 5 May 2020, up to 2000 samples of CCP had been collected across China and administered to 700 COVID-19 patients. From donors, 200–400 ml of plasma was collected at each donation, with antibody titres > 1:160. We identified three clinical studies for COVID-19 in China. Analyses showed a statistically significant improvement in clinical outcomes compared with untreated cases ($P < 0.001$). No adverse effects were reported.

Conclusion From initial studies, convalescent plasma therapy appears effective and safe for COVID-19. However, there is clearly a need for well-designed RCTs (randomized controlled trials) or other formal studies to further evaluate the efficacy and any potential adverse effects of CCP.

Key words: COVID-19 convalescent plasma (CCP), therapy, COVID-19, SARS-CoV-2.

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Introduction

The outbreak of novel coronavirus disease (COVID-19) at the end of 2019 was caused by a novel coronavirus, SARS-CoV-2, that is highly contagious [1] and resulted in a crude mortality rate of about 2.3% for all cases [2] and 25.5% for severe cases [3]. In the absence of a vaccine for SARS-CoV-2, COVID-19 convalescent plasma (CCP) represents a form of passive immunotherapy. Although current clinical experience with CCP is encouraging, well-designed control studies are lacking.

Convalescent plasma has long been used as a therapeutic tool in blood transfusion, and this procedure involves extracting plasma containing anti-viral antibodies from patients who have recovered and then injecting this convalescent plasma into other patients to treat diseases. It has become an emergency or empirical therapy, and has been successfully applied in the field of cell therapy and immunotherapy [4]. The application of convalescent plasma in the treatment of Ebola [5, 6], SARS [7–9], pandemic influenza [10–12] and MERS [13, 14] has suggested that

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CCP may be an effective, timely and widely available treatment option in the case of COVID-19. This article discusses the application of convalescent plasma as an immunotherapy in the treatment of emerging infectious diseases, focusing on the recent COVID-19 outbreak in China.

Methods

Search strategy

The PubMed, Embase and Medline databases were searched from 8 December 2019 (first breakout) to 5 May 2020, for newly published literature using the search term "convalescent plasma AND COVID-19". All search records were imported into EndNote X9 software and screened manually using paper records.

Study selection

Publications were selected that involved the assessment of CCP treatment for COVID-19 patients in China including clinical trials such as randomized controlled trials, controlled clinical trials, case series, case reports, prospective and retrospective comparative cohort studies, and case–control studies.

Clinical information

Clinical information for the 19 patients identified before and after convalescent plasma transfusion was obtained from three clinical trials. These patients included 10 severely ill patients from a pilot study in three participating hospitals in Wuhan (Wuhan Jinyintan Hospital, the Jiangxia District Hospital of Integrative Traditional Chinese and Western Medicine, and the First People's Hospital of Jiangxia District), five critically ill patients from case series from Shenzhen Third People's Hospital and one case report of four critically ill patients from three participating hospitals (Dongguan Ninth People's Hospital, Xiangtan Central Hospital and Xiaolan People's Hospital of Zhongshan). The details regarding patients' inclusion criteria and neutralizing antibody titres have been previously reported [15, 16]. Adverse events and serious adverse events were assessed as part of the CCP safety evaluation. Improvements in clinical outcomes were defined as symptomatic relief, oxygen saturation normalization, a decrease in lymphocytes and C-reactive protein levels, and decreased mortality rates.

Statistical analysis

Continuous variables (i.e. age, laboratory test parameters) were presented as median (IQR) values and were compared using a Mann–Whitney *U* test. Categorical variables were expressed as *n* (%), where n was the total number of patients with available data, and were compared by Fisher's exact test between the convalescent plasma treatment group and the control group. Statistical software used was SPSS 24.0. For all analyses, $P < 0.05$ was considered statistically significant.

Results

CCP and COVID-19: recent experience with CCP in China

The treatment of COVID-19 in China has focused on preventing patients with mild disease from progressing to severe or critical illness. Therapeutic agents including steroids, antivirals and traditional Chinese medicines that have been considered are summarized in Table 1 [17–23]. Indications, directions and clinical trials located in China up until 5 May 2020 are listed for each agent, respectively. For severely and critically ill individuals, besides the agents above, patients have been treated with CCP, tocilizumab, stem cells and artificial liver therapy. A recent publication reporting a trial of lopinavir–ritonavir showed no clinical benefits beyond standard care in adults hospitalized with severe COVID-19 [24]. While most of the agents listed above remain under investigation (status: recruiting, suspended, terminated or not yet recruiting), none have been proven to be specific for COVID-19. Thus, CCP may be a promising immunotherapy for COVID-19, especially among severely and critically ill patients.

The first dose of convalescent plasma from a COVID-19 patient was collected on 1 February 2020, and the first severely ill patient received CCP treatment at a hospital in Wuhan, the capital of Hubei Province that was first to be hit by the virus, on 9 February 2020. China has established expert task forces at the provincial and national levels to analyse and improve the use of plasma therapy, and the National Health Commission (NHC) has worked with other authorities to motivate more recovered patients to donate plasma. According to a press conference by the Joint Prevention and Control Mechanism of the State Council on 5 May 2020, as many as 2000 doses of CCP had been collected across China and 700 COVID-19 patients had received this therapy. Patients had shown improvements in clinical indicators and symptoms, and the median length of hospital stays in ICU for patients receiving CCP was also significantly shorter than for those in the control group.

Effectiveness and safety of CCP in early clinical trials

Recent studies have reported that plasma therapy is safe and effective [15, 16, 25] and the details from these three

Table 1 Overview of the 'Chinese-Way' Therapeutic Agents for COVID-19 (Modified from [17-23]).

Agent	Indication	Direction	ClinicalTrials.gov Identifier Number* (Current Recruitment Status)
IFN-alpha	Broad-spectrum antivirus	5 million U bid inh	ClinicalTrials.gov identifier number not available
Lopinavir/ritonavir	Anticoronavirus	400 mg/100 mg bid po	NCT04255017 (R)
Ribavirin	Nucleoside analogs	500 mg bid/tid iv	ClinicalTrials.gov identifier number not available
Chloroquine phosphate	Antimalaria; $18 \leq$ age ≤ 65	W $\geq$ 50 kg: d1-d7 500 mg bid; W < 50 kg: d1-d2: 500 mg bid, d3-d7: 500 mg qd. time $\leq$ 7d	ClinicalTrials.gov identifier number not available
Arbidol	Anticoronavirus	200 mg tid po	ClinicalTrials.gov identifier number not available
Tocilizumab	Antagonist of IL-6R	4–8 mg/kg	NCT04306705 (R), NCT04310228 (R)
Remdesivir	Anticoronavirus	—	NCT04252664 (S), NCT04257656 (T), NCT04292899 (R)
TCM	—	syndrome differentiation	NCT04306497 (R), NCT04251871 (R), NCT04323332 (NR)

NR, not yet recruiting; bid, bis in die; inh, inhalation; iv, intravenous; po, per os; qd, quaque die; R, recruiting; S, suspended; T, terminated; TCM, traditional Chinese medicine; tid, ter in die; W, weight.

*Only numbers from clinical trials which conducted in China till 5 May 2020. URL: https://clinicaltrials.gov/ct2/results?cond=COVID-19.

studies (one pilot study, one case series and one case report) are presented in Table 2 (including patient demographics (age and sex), clinical classification (severe or critical), days from symptom onset to admission and CCP transfusion, comorbidities, adverse events, other treatments besides CCP and clinical outcomes). Across the three studies, the age of patients varied from 30 to 78 years. The median time from onset of symptoms to admission and CCP transfusion was 4 days (IQR, 2–8 d) and 19 days (IQR, 14–20 d), respectively. Seven patients had underlying chronic diseases, including cardiovascular and/or cerebrovascular diseases, chronic renal failure, COPD and hypertension. The most common comorbidity in critically ill patients was ARDS/MODS (5 of 9 patients). Prior to CCP therapy, 12 patients received steroids (methylprednisolone) and all patients received antivirals (such as arbidol, ribavirin, remdesivir, oseltamivir, favipiravir and lopinavir/ritonavir). Furthermore, 12 patients received mechanical ventilation, six received high-flow nasal cannula oxygenation and two received conventional low-flow nasal cannula oxygenation. Patient 2 showed an evanescent facial red spot but no other adverse effects. No serious adverse reactions were recorded after CCP therapy in any of the 19 patients. Most patients were discharged (9 of 19 patients) or showed clinical improvements (8 of 19 patients) following CCP therapy.

A historic control group was formed by the random selection of 10 patients from the cohort that were matched by age, sex and severity of disease to the 10 cases in the same hospital in Duan's trial. Then, we compared the clinical features and outcomes between the treatment (CCP) group and the historic control (non-CCP) group, as shown in Table 3. In total, 19 patients (11 males and eight females; 10 severely ill and nine critically ill) received CCP therapy. The median age was 55 years (IQR, 46–67 years). The baseline characteristics of the patients between the CCP treatment group and the control group showed no significant differences ($P > 0.05$), whereas the clinical outcomes for these two groups were different. For the CCP group, nine cases were discharged with eight of these showing a much-improved status, two cases were considered stable and the mortality rate was zero. By comparison, in the control group, there were three deaths, six cases were considered stable and one case showed clinical improvement ($P < 0.001$; Supplementary File S1). Lymphocytopenia, an important index in the prognosis in COVID-19, tended to be improved after CCP transfusion (median: 0.65×10^9 per L vs. 0.76×10^9 per L). Regarding the data from other laboratory tests, increased levels of C-reactive protein (CRP) were detected (median: 65.02 mg/L vs. 96.70 mg/L), indicating inflammation following CCP therapy. The increase detected in SaO_2 levels following CCP therapy (median: 93.00% vs. 96.00%) may be indicative of recovering lung function.

Recommendations for the use of CCP

According to the *Clinical Treatment Guideline of COVID-19 Convalescent Plasma* updated by the National Health Commission of the People's Republic of China [26], as well as clinical experience from the First Affiliated Hospital of Zhejiang University [27], the following recommendations for the use of CCP are provided.

Plasma collection and testing

CCP donors

Donors are eligible for CCP donation at least 2 weeks after recovery and discharge from hospital. Donors should be between 18 and 55 years of age, with a body weight

Table 2 Clinical characteristics of COVID-19-infected patients who received CCP transfusion (modified from [15, 16, 25])

Patient NO.	Age, year	Sex	Clinical classification	T (a), day	T (c), day	Comorbidity	Adverse effects of CCP	Other treatments			Clinical outcomes
								Steroids	Antivirals	Oxygen supports	
1	46	Male	Severe	8	11	Hypertension	None	None	Arbidol;ribavirin	High-flow nasal cannula, mechanical ventilation	Improved
2	34	Female	Severe	0	11	None	Evanescent facial red spot	None	Arbidol	None	Discharged
3	42	Male	Severe	8	19	Hypertension	None	Methylprednisolone	Arbidol	High-flow nasal cannula, mechanical ventilation	Improved
4	55	Female	Severe	10	19	None	None	Methylprednisolone	Ribavirin	Mechanical ventilation	Improved
5	57	Male	Severe	4	14	None	None	Methylprednisolone	Arbidol; redesivir; IFNα	Low-flow nasal cannula	Improved
6	78	Female	Severe	8	17	None	None	Methylprednisolone	Arbidol	High-flow nasal cannula	Improved
7	56	Male	Severe	4	16	None	None	Methylprednisolone	Arbidol	High-flow nasal cannula	Discharged
8	67	Male	Severe	10	20	Cardiovascular and cerebrovascular diseases	None	None	Arbidol;ribavirin	None	Improved
9	49	Female	Severe	1	10	None	None	None	Arbidol;oseltamivir; peramivir	Low-flow nasal cannula	Discharged
10	50	Male	Severe	3	20	Hypertension	None	Methylprednisolone	Arbidol;IFNα	High-flow nasal cannula	Improved
11	70	Male	Critical	2	22	Severe ARDS; MODS	None	Methylprednisolone	Lopinavir/ritonavir;IFNα-1b; favipiravir	Mechanical ventilation	Stable
12	60	Male	Critical	4	10	Hypertension; severe ARDS; cardiovascular and cerebrovascular diseases;	None	Methylprednisolone	Lopinavir/ ritonavir; arbidol; darunavir	Mechanical ventilation, ECMO	Stable
13	50	Female	Critical	2	20	Severe ARDS	None	Methylprednisolone	Lopinavir/ritonavir;IFNα-1b	Mechanical ventilation	Discharged
14	30	Female	Critical	2	19	Severe ARDS	None	Methylprednisolone	IFNα-1b;favipiravir	Mechanical ventilation	Discharged
15	60	Male	Critical	3	20	Severe ARDS	None	Methylprednisolone	Lopinavir/ritonavir; IFNα-1b	Mechanical ventilation	Discharged
16	69	Female	Critical	5	23	Hypertension	None	None	Lopinavir/ritonavir;IFNα, oseltamivir	Mechanical ventilation	Discharged
17	55	Male	Critical	4	15	COPD	None	Methylprednisolone	Lopinavir/ritonavir;IFNα-2b, arbidol	High-flow nasal cannula, mechanical ventilation	Discharged
18	73	Male	Critical	4	18	Hypertension; chronic renal failure	None	None	Lopinavir/ritonavir;IFNα-2b, arbidol; oseltamivir; ribavirin	Mechanical ventilation, ECMO	Improved
19	31	Female	Critical	4	23	Severe ARDS; MODS; septic shock	None	None	Lopinavir/ritonavir; ribavirin	Mechanical ventilation, ECMO	Discharged

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IFNα-1b/2b, interferon-alpha-1b/2b; MODS, multiple organ dysfunction syndrome; T(a), Time from symptom onset to admission; T(c), Time from symptom onset to CCP therapy.

Table 3 Comparison of clinical features and outcomes between the treatment (Convalescent Plasma) group and the control (non-convalescent plasma) group (modified from [15,16,25]).

	CCP treatment group (n = 19)	Control (Non-CCP) group (n = 10)	P value
Demographics			
Age, years	55.00 (46.00–67.00)	53.00 (46.50–60.50)	0.743
Gender			
Male	11 (58)	6 (60)	1.000
Female	8 (42)	4 (40)	
Comorbidity			
Yes	13 (68)	6 (60)	0.698
No	6 (32)	4 (40)	
Laboratory test parameters			
C-reactive protein	65.02 (29.50–157.85)	96.70 (33.92–173.39)	0.7088
Lymphocyte [a]	0.65 (0.53–0.90)	0.76 (0.54–1.32)	0.469
SaO_2[a]	93.00 (89.00–96.50)	93.00 (87.50–97.50)	0.923
Clinical outcome			
Death	0 (0)	3(30)	<0.001*
Stable	2 (10)	6(60)	
Improved	8 (42)	1(10)	
Discharged	9 (48)	0(0)	

Continuous variable (age) is expressed as median (IQR) and compared with Mann–Whitney U test. Categorical data are n (%) of patients, where n is the total number of patients with available data, and compared with Fisher's exact test between convalescent plasma treatment group and control group. SaO_2, oxyhaemoglobin saturation. Reference ranges are as follows: C-reactive protein, normal range $<$ 8 mg/l; lymphocyte count, 1.2–3.4 $\times$ 10^9/l; SaO_2 %, normal range $\geq$ 95%.

[a]Among the 19 patients in CP treatment group, nine patients did not have their blood lymphocyte and SaO_2 data available.

*$P < 0.001$, Fisher's exact test.

of ≥50 kg (male) or ≥45 kg (female). Donors should present at least 14 days after their last blood donation and must qualify as donors after a comprehensive clinical assessment.

Collection method

Plasma is collected by plasmapheresis (200–400 mL) at each donation (based on medical consultation).

Plasma laboratory testing

In addition to routine tests for transfusion-transmitted diseases, CCP samples are subjected to: (1) nucleic acid testing for COVID-19; (2) a qualitative test of COVID-19-specific IgG and IgM detection (involving a 160-fold dilution) or a qualitative test for whole antibody detection (involving a 320-fold dilution). If possible, a test for viral neutralizing antibodies is also performed.

Clinical use

COVID-19 convalescent plasma is being used for severe or critically ill COVID-19 patients or those with rapidly progressive disease who test positive in a virus nucleic acid test. As a general rule, CCP is not used on COVID-19 patients whose disease course exceeds 3 weeks.

Specific contraindications include the following: (1) a history of allergy to plasma or methylene blue; and (2) a history of autoimmune system disease or selective IgA deficiency, in which case, the application of CCP should be evaluated cautiously by clinicians. The dose of CCP is based on a patient's weight and clinical condition. In general, 200–500 ml (4–5 ml/kg) is recommended. It is recommended to transfuse recipients with plasma obtained from donors on the day of collection (fresh collection) to maximize plasma activity [15].

Discussion

In the absence of specific drugs and vaccines, convalescent plasma therapy is an alternative treatment option. However, there are a number of issues to be considered when determining the suitability of a large-scale convalescent plasma infusion strategy.

Ineffective regulation of cytokine storm syndrome

The neutralizing antibodies present in CCP do not appear to influence the cytokine storm that can result from COVID-19 infection. A cytokine storm is an important pathophysiological event in the transformation of COVID-

19 from a mild to severe disease and from single-organ damage to multiple organ dysfunction syndrome (MODS) [28]. It has been reported that SARS-CoV-2 can induce the excessive release of inflammatory cytokines, causing diffuse alveolar injury, hyaline membrane formation and the exudation of proteins into the lungs. In severe cases, shock, disseminated intravascular coagulation and MODS may occur [29]. The levels of IL-6 in patients with severe COVID-19 were found to have increased significantly [30], which may be related to the poor prognosis of patients and suggests the need for alternative treatments [31]. From this perspective, it is not expected that neutralizing antibodies in the CCP will be able to inhibit an inflammatory storm.

Lack of a gold standard for evidence-based medicine

In China, as of 5 May 2020, at least 95 clinical trials were registered at www.clinicaltrials.gov [32] to investigate potential treatments for the novel coronavirus, and the number of registered trials is increasing every day. Studies are testing both new and traditional medicines. However, at present, the trials lack a unified framework of standards are disordered and have weaknesses in terms of the levels of evidence, ethical standards, and the efficient use of research resources.

Similarly, studies on CCP in China have lacked appropriate control groups and display a moderate to high risk of bias, making it difficult to provide evidence that any clinical improvement in patients is due to CCP, to other therapies, or to the natural process of recovery. A large randomized, double-blind, controlled study is therefore needed for CCP therapy before it can be approved as a routine clinical treatment.

A sufficient titre of neutralizing antibody cannot be guaranteed

The rationale for CCP as a therapeutic tool is to provide higher levels of neutralizing antibodies against the virus [33]. It is anticipated that the higher the titre of neutralizing antibody, the better the therapeutic effect [34]. In China, the difficulty in obtaining high-titre CCP has limited its clinical application. Immune dysfunction may also hinder the efficacy of CCP therapy [33]. In addition, there is a great disparity between plasma demand and supply, as well as the limitations imposed by the need to obtain plasma during the eligible recovery period. Regional imbalances in plasma resources also exist in developed and developing countries. Alternative strategies should be explored to identify CCP with sufficient antibody titres, including serum collection from patients with more severe disease and collection at earlier time-points during disease. Regarding the antibodies present in CCP, antibody-dependent enhancement is another potential limitation [35].

Transfusion-related adverse events

One previous study in China by Duan and colleagues [16] reported a minor side effect of an evanescent, red facial spot in one patient administered convalescent plasma. This minor side effect was not linked to any adverse events, and two other trials showed no side effects. No complications such as TRALI or TACO, or any other adverse events, were reported. However, appropriate risk assessment is still required for high-risk donors before considering relaxing the inclusion criteria.

Conclusions

The effective treatment of disease following infection with SARS-CoV-2 presents an unprecedented challenge in China and worldwide. Studies to date suggested that CCP therapy, performed according to Chinese recommendations, was a promising and safe treatment option with no adverse events. However, there are several points to consider to aid the future success of CCP therapy.

- Attention should be paid to the evaluation of both RDB (reverse dot blot) antibody and neutralization antibody levels in plasma. Convalescent plasma must be collected at the optimum time to ensure a high titre of neutralizing antibodies.
- Large-scale screening is needed for the inclusion of a large number of COVID-19 patients.
- Pathogen reduction and frozen stockpile technology should be applied to ensure safe infusion and to avoid transfusion-related adverse events.
- Further evaluation of the efficacy and safety of convalescent plasma in patients should be carried out in carefully designed RCTs.
- Another new methodology is to select B cells that can produce specific antibodies in convalescent blood, obtain the gene sequence of the antibody at the single-cell level, reconstruct and express it using specialized technology, and finally obtain a large number of B cells that can produce virus neutralizing antibodies. These antibodies can then be injected into patients [36].
- Recently, Zhang and colleagues isolated high-efficiency anti-coronavirus antibodies from COVID-19 patients, which laid the foundation for the further development of antibodies [37]. In the long run, the immunotherapy of COVID-19 still depends on protective virus-specific monoclonal antibodies.

- Blood centres and healthcare agencies should cooperate in calling upon the public to donate.

Along with its research efforts into CCP therapy, China is strengthening communication with the World Health Organization and cooperating with other countries, especially high-risk countries, to promote scientific research, drug and vaccine development, and the sharing of scientific information to address the global epidemic.

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Conflict of interests

The authors report no conflict of interest.

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Data availability statement

All data relevant to this manuscript and available to the authors at the time of publication are included in the main text or Supplementary File S1.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Supplementary File S1