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CONCISE ARTICLE

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Use of convalescent plasma therapy in SARS patients in Hong Kong

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Abstract In order to evaluate the efficacy of convalescent plasma therapy in the treatment of patients with severe acute respiratory syndrome (SARS), 80 SARS patients were given convalescent plasma at Prince of Wales Hospital, Hong Kong, between 20 March and 26 May 2003. Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death or hospitalization beyond 22 days. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; $P<0.001$) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; $P=0.001$).

Introduction

Severe acute respiratory syndrome (SARS) is a highly infectious respiratory illness caused by a novel coronavirus, which has affected more than 8,000 patients worldwide and caused more than 700 deaths [1–3]. In the absence of effective established therapy, treatment of SARS to date has mainly been empirical and experimental. In Hong Kong, ribavirin and steroids have been used, and 74% of patients have recovered without requiring admission to the intensive care unit [4]. However, no control study has yet been conducted comparing ribavirin/steroid treatment with a placebo, and the potential efficacy of ribavirin against the SARS-coronavirus has been controversial. Many experts are also concerned about the side-effects of high-dose steroids.

Convalescent plasma therapy has been used to treat patients with Machupo virus (Bolivian hemorrhagic fever) [5], Junin virus (Argentinian hemorrhagic fever) [6], Lassa fever [7] and Ebola virus [8]. The use of pooled plasma or immunoglobulin from patients who recovered from West Nile encephalitis has demonstrated protective effects in infected mice and clinical benefits in patients [9, 10]. Despite some limitations in the methodologies described in these previous reports, the data has suggested there is a clinical benefit to convalescent plasma therapy. Postulating that convalescent plasma of SARS patients carries antibodies against coronavirus and may suppress viremia, we administered convalescent plasma to 80 SARS patients who had progressive disease after initial treatment with ribavirin and steroids. The results of this experience are presented here.

Patients and methods

The records of 80 patients with SARS who had received convalescent plasma between 20 March and 26 May 2003 at the Prince of Wales Hospital in Hong Kong were analyzed. In each case SARS was diagnosed according to CDC criteria [11]. Starting in mid-March 2003, patients admitted with suspected SARS were given cefotaxime and levofloxacin (or clarithromycin) on the day of admission to cover community-acquired pneumonia. If fever persisted, ribavirin (administered as 1200 mg p.o. t.i.d. or i.v. 400 mg q8h) and prednisolone (0.5–1 mg/kg) were started on day 3. Patients with radiographic progression and

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Table 1 Comparison of clinical characteristics of patients with SARS according to outcome

[a]Discharged by day 22 from symptom onset

[b]Death before day 22 or late discharge

[c]Calculated from day of symptom onset

[d]Status at time plasma was given

Characteristic	Good outcome[a]	Poor outcome[b]	*P* value	Logistic regression *P* value
No. of patients	33	47		
Age	37.9±12.5	50.2±15.1	<0.001	0.009
Admission LDH (IU/l)	268.6±117.6	334±183.7	0.08	0.014
Mean day of plasma infusion[c]	11.7±2.3	16.0±6.0	<0.001	0.012
Mean plasma volume	253.6±99.9	297.23±141.4	0.11	0.174
PCR positive and seronegative for SARS[d]	20	10	<0.001	0.006

hypoxemia were given pulsed methylprednisolone (500 mg i.v. daily for 2–3 doses). Patients whose condition continued to deteriorate, as defined by SaO_2<90% on 0.5 FiO_2, were then given 200–400 ml (4–5 ml/kg) of ABO-compatible convalescent plasma at the discretion of the attending clinicians and according to convalescent plasma availability. The potential benefits and risks of convalescent plasma were carefully explained to the patients and their families.

Convalescent plasma was obtained from patients who had recovered from SARS patients. Recovery was defined as an afebrile status for at least 7 days, radiographic improvement of 25%, no further need of an oxygen supplement, and at least 14 days following symptom onset. Informed consent was obtained from the donors who needed to be seronegative for hepatitis B and C, HIV and syphilis and seropositive for coronavirus (titer range, 160–2,560).

Apheresis was performed using a Baxter CS 300 cell separator (Baxter, Deerfield, IL, USA). A 600–900 ml plasma sample was harvested from each donor, and each sample was divided and stored as 200–225 ml aliquots at −70°C without any detergent or heat treatment.

Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death before day 22 or hospitalization beyond 22 days. The discharge criteria of the Hospital Authority were as follows: (i) afebrile status for 4 consecutive days; (ii) improvement in previously abnormal leukocyte counts, platelet counts, creatinine phosphatase kinase, lactate dehydrogenase, liver function tests and C-reactive protein; (iii) radiographic improvement; and (iv) at least 21 days following the onset of illness. This last factor led us to define good outcome as discharge by day 22. Using this definition, we were able to divide the patients into two distinct non-overlapping outcome groups.

Age, sex, lactate dehydrogenase level at admission, time of convalescent plasma administration and co-morbidities were analyzed to determine whether or not they were predictive of clinical outcome. Numerical data were compared using independent samples and Student's *t*-test, and categorical data by Fisher's exact test. Differences were considered significant at the level of $P<0.05$. All values were expressed as mean ± standard deviation unless stated otherwise. Logistic regression analysis was performed for age, lactate dehydrogenase level, time of convalescent therapy and viral status.

Results and discussion

Among the 339 patients with suspected SARS admitted to the Prince of Wales Hospital between10 March and 20 May 2003, 92 demonstrated clinical deterioration despite treatment with methylprednisolone. Eighty of these patients (43 females and 37 males) were given convalescent plasma around day 14 (range, 7–30 days) following the onset of symptoms. The median age of the patients receiving convalescent plasma was 45 years (range, 21–82 years). The mean volume of plasma infused was 279.3±127.1 ml (range, 160–640 ml). Thirty-three patients had a good clinical outcome; they were given convalescent plasma earlier than the patients with a poor outcome (11.67±2.3 vs 16.04±6.0 days; $P<0.001$; Table 1). Patients ($n=48$) given convalescent plasma before day 14 had a better outcome than those given plasma after day 14 (58.3% vs 15.6%; $P<0.001$). The mortality rates in the two groups were 6.3% and 21.9%, respectively ($P=0.08$). One major factor affecting the timing of convalescent plasma administration was plasma availability. Overall, the mortality rate was 12.5% among the 80 patients given convalescent plasma. The overall SARS-related mortality rate in Hong Kong was 17% (299/1755) during the SARS epidemic from 6 March to 24 May.

Sixty-one percent of the patients with a good outcome were PCR positive and seronegative for coronavirus at the time of plasma infusion as compared with 21% in the group with a poor outcome ($P<0.001$). The 30 patients who were PCR positive and seronegative for coronavirus at the time of convalescent plasma therapy had a better outcome than those who were already seropositive (66.7% vs 20%; $P=0.001$). Age was a poor prognostic factor (Table 1). In the multivariate analysis, only the time of convalescent plasma therapy and coronavirus PCR positivity were significant factors.

No immediate adverse effects were observed with convalescent plasma infusion. There was no correlation between clinical outcome and either the volume of plasma infused or the coronavirus antibody titers of the donors.

In our experience, patients whose clinical condition deteriorated after receiving ribavirin and methylprednisolone had a higher discharge rate by day 22 when convalescent plasma was administered before day14 of illness onset. Patients receiving convalescent plasma after day 14 had a longer hospital stay and a higher mortality rate.

For most viral illnesses, viremia peaks in the first week of infection. The patient usually develops a primary immune response by day 10–14, which is followed by clearance of the virus. Therefore, convalescent plasma should, theoretically, be more effective when given early in the course of disease. In a study of patients with Lassa fever in Nigeria, all eight patients who received convalescent plasma on or before day 10 of illness recovered and survived, while only three of eight patients who received plasma after day 10 survived [7]. In SARS, the viral load also peaks in the first week of infection [12], and clinical deterioration in the third week is thought to be the result of inflammatory or hyperimmune attacks on lung tissue rather than direct viral-induced tissue damage. This was consistent with our finding of better clinical outcome in patients given convalescent plasma early in the course of the disease (i.e., before day 14, or during the viremic and seronegative stage).

The volumes of convalescent plasma we administered were similar to those given to patients with Ebola hemorrhagic fever [8]. Although we did not observe any correlation between clinical outcome and either the volume of convalescent plasma given or the antibody titers of the donors, this observation could be misleading; since the attending physicians tend to give repeated infusions from multiple donors to patients responding poorly in a desperate attempt to reverse the course.

Our study has several limitations. (i) It was not randomized: whether or not patients received convalescent plasma was at the discretion of the attending physicians and according to plasma availability. Fluctuations in plasma availability also resulted in some patients receiving plasma earlier in the course of illness than others, but this allowed us to make an interesting comparison of the effects of early versus late plasma therapy. (ii) The amount of antibodies given to each patient was not standardized. This might have contributed to the variations in clinical outcome. (iii) Even though we did not observe any immediate adverse reactions, the potential risk of transfusion-transmitted infection was present. Ideally, convalescent plasma should go through a viral inactivation procedure before being infused into recipients. (iv) We did not have a placebo group for comparison. Although there were 12 patients whose condition deteriorated after methylprednisolone treatment and never received plasma therapy, these patients were given further doses of methylprednisolone, penta-globulin or other antiviral drug-like protease inhibitors. Using them for comparison, one may argue that methylprednisolone or another therapy may have a deleterious effect and convalescent plasma had minimal benefits or vice versa.

Despite the many limitations, our data suggest it may be worthwhile to test the effectiveness of therapy with convalescent plasma or SARS-specific hyperimmune globulin in patients in the early phase of SARS during the next outbreak.

References

1. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, Tong S, Urbani C, Comer JA, Lim W, Rollin PE, Dowell SF, Ling AE, Humphrey CD, Shieh WJ, Guarner J, Paddock CD, Rota P, Fields B, DeRisi J, Yang JY, Cox N, Hughes JM, LeDuc JW, Bellini WJ, Anderson LJ, SARS Working Group (2003) A novel coronavirus-associated severe acute respiratory syndrome. N Engl J Med 348:1953–1966
2. Drosten C, Gunther S, Preiser W, van der Werf S, Brodt HR, Becker S, Rabenau H, Panning M, Kolesnikova L, Fouchier RA, Berger A, Burguiere AM, Cinatl J, Eickmann M, Escriou N, Grywna K, Kramme S, Manuguerra JC, Muller S, Rickerts V, Sturmer M, Vieth S, Klenk HD, Osterhaus AD, Schmitz H, Doerr HW (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 348:1967–1976
3. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, Nicholls J, Yee WK, Yan WW, Cheung MT, Cheng VC, Chan KH, Tsang DN, Yung RW, Ng TK, Yuen KY, SARS Study Group (2003) Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361:1319–1325
4. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, Ahuja A, Yung MY, Leung CB, To KF, Lui SF, Szeto CC, Chung S, Sung JJ (2003) A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 348:1986–1994
5. Stinebaugh BJ, Schloeder FX, Johnson KM, Mackenzie RB, Entwisle G, De Alba E (1966) Bolivian hemorrhagic fever. A report of four cases. Am J Med 40:217–230
6. Ruggiero HA, Perez Isquierdo F, Milani HA, Barri A, Val A, Maglio F, Astarloa L, Gonzalez Cambaceres C, Milani HL, Tallone JC (1986) Treatment of Argentine hemorrhagic fever with convalescent's plasma 4433 cases [in French]. Presse Med 15:2239–2242
7. Frame JD, Verbrugge GP, Gill RG, Pinneo L (1984) The use of Lassa fever convalescent plasma in Nigeria. Trans R Soc Trop Med Hyg 78:319–324
8. Mupapa K, Massamba M, Kibadi K, Kuvula K, Bwaka A, Kipasa M, Colebunders R, Muyembe-Tamfum JJ (1999) Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. J Infect Dis 179(suppl 1):18–23
9. Ben-Nathan D, Lustig S, Tam G, Robinzon S, Segal S, Rager-Zisman B (2003) Prophylactic and therapeutic efficacy of human intravenous immunoglobulin in treatment of West Nile virus infection in mice. J Infect Dis 188:1–4
10. Solomon T, Ooi MH, Beasley DW, Mallewa M (2003) West Nile encephalitis. Br Med J 326:865–869
11. Centers for Disease Control and Prevention (2003). Update: severe acute respiratory syndrome. Morb Mortal Wkly Rep 52:388–390
12. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y, Yuen KY, HKU/UCH SARS Study Group (2003) Prospective study of the clinical progression and viral load of SARS-associated coronavirus pneumonia in a community outbreak. Lancet 361:1767–1772