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## RESEARCH NOTE

### Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients

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## ABSTRACT

Treatment of severe acute respiratory syndrome (SARS) is experimental, and the effectiveness of ribavirin–steroid therapy is unclear. Forty SARS patients with progressive disease after ribavirin treatment and 1.5 g of pulsed methylprednisolone were given either convalescent plasma ( $n = 19$ ) or further pulsed methylprednisolone ( $n = 21$ ) in a retrospective non-randomised study. Good clinical outcome was defined as discharge by day 22 following the onset of symptoms. Convalescent plasma was obtained from recovered patients after informed consent. Patients in the plasma group had a shorter hospital stay ( $p 0.001$ ) and lower mortality ( $p 0.049$ ) than the comparator group. No immediate adverse effects were observed following plasma infusion.

**Keywords** Convalescent plasma, methylprednisolone, ribavirin, SARS, severe acute respiratory syndrome, treatment

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In Hong Kong, the first major outbreak of severe acute respiratory syndrome (SARS) commenced on 10 March 2003 in the Prince of Wales Hospital, with >130 persons becoming infected [1]. This highly infectious respiratory illness was caused by a novel coronavirus [2,3]. Treatment was mainly empirical and, in the Prince of Wales Hospital, ribavirin and steroids were used as first-line treatment to suppress viral replication and minimise autoimmune pneumonitis. In *c.* 74% of the patients, the ribavirin–steroid combination was associated with recovery [4]. However, there was great debate as to whether ribavirin was effective against coronavirus, as well as concern about the side effects of high-dose steroids. Patients with persistent fever, radiographic progression and hypoxaemia, despite receiving 1.5 g of methylprednisolone, responded poorly to further courses of high-dose steroids, and an alternative therapy was needed. It was postulated that convalescent plasma from recovered SARS patients would carry antibodies against the coronavirus and might suppress viraemia.

A retrospective comparison study was performed on SARS patients admitted between

10 March and 10 April 2003. The patients were treated empirically with ribavirin and methylprednisolone [4]. Inclusion criteria were as follows: SARS diagnosed according to the Centers for Disease Control guidelines [5]; and clinical and radiographic deterioration despite ribavirin and three doses (500 mg each) of pulsed methylprednisolone. Patients who had received intravenous immunoglobulin, pentaglobulin, protease inhibitors or fewer than three doses of methylprednisolone were excluded. The patients studied were given either convalescent plasma (plasma group) or further pulses of methylprednisolone (steroid group) at the discretion of the attending clinicians and according to the availability of convalescent plasma. The potential benefits and side effects of convalescent plasma were explained carefully to the patients and their families. Patients in the plasma group could receive pulsed steroids if their condition worsened after plasma therapy, and were then classed as plasma therapy failures. Similarly, if patients in the steroid arm deteriorated after further pulses of methylprednisolone, they could receive convalescent plasma, but were then classed as steroid therapy failures.

Following informed consent, convalescent plasma was obtained from patients who had recovered from SARS, and who were seronegative for hepatitis B, hepatitis C, HIV and syphilis. All serum donors were seropositive for coronavirus (titre 160–2560). Apheresis was performed with a CS 300 cell separator (Baxter, Deerfield, IL, USA), with 600–900 mL of plasma obtained from each donor. Based on experience with Ebola virus [6], 200–400 mL of convalescent plasma was used to treat each of the recruited patients.

Good response to therapy was defined as discharge by day 22 following the onset of SARS symptoms. Poor response was defined as death or hospitalisation beyond 22 days. Discharge criteria, according to Hospital Authority guidelines, were as follows: afebrile for 4 consecutive days; improvement of previously abnormal laboratory tests (white cell counts, platelet counts, creatinine phosphokinase, lactate dehydrogenase, liver function tests and C reactive protein); radiographic improvement; and a period of at least 21 days following the onset of illness, since there is evidence that coronavirus is still detectable in the stools of some recovered patients for up to 3 weeks [7].

**Table 1.** Clinical demographics of patients in the plasma-treated and steroid-treated groups

	Plasma group <sup>a</sup>	Steroid group <sup>b</sup>	p
No. of patients	19	21	
Age (years)	38.7 ± 12.39	47.9 ± 19.60	0.087
Admission LDH (IU/L)	256.1 ± 90.75	247.7 ± 94.58	0.7
Co-morbidities <sup>c</sup>	1 (DM, old TB)	1 SLE, 2 DM with old TB, 4 hypertension, 1 atrial fibrillation	0.05

<sup>a</sup>Three doses of methylprednisolone, followed by convalescent plasma.

<sup>b</sup>Four or more doses of methylprednisolone.

<sup>c</sup>Two patients were hepatitis B carriers (one in each group), but without clinical evidence of cirrhosis; they were not considered as having co-morbidities.

DM, diabetes mellitus; LDH, lactate dehydrogenase; SLE, systemic lupus erythematosus; TB, tuberculosis.

**Table 2.** Comparison of treatment outcome between patients in the plasma-treated and steroid-treated groups

	Plasma group <sup>a</sup>	Steroid group <sup>b</sup>	p
Discharge rate by day 22 following onset of illness	73.4% ( <i>n</i> = 14)	19% ( <i>n</i> = 4)	0.001
Discharge rate by day 22 after adjustment for co-morbidities	77.8% (14/18)	23% (3/13)	0.004
Death rate	0%	23.8% ( <i>n</i> = 5)	0.049

<sup>a</sup>Three doses of methylprednisolone, followed by convalescent plasma.

<sup>b</sup>Four or more doses of methylprednisolone.

The charts were reviewed and data entered independently by the first two authors. Treatment outcome, age and lactate dehydrogenase levels on admission were compared between patients in the plasma group and those in the steroid group. Numerical data were compared by the independent samples Student *t*-test, and categorical data were compared by Fisher's exact test. Differences were considered significant at the level of  $p < 0.05$ .

Nineteen patients received convalescent plasma after three doses of pulsed methylprednisolone (plasma group); two also received additional pulsed steroids. Nine patients in the steroid group ( $n = 21$ ) were given convalescent plasma subsequently after four to eight doses of pulsed methylprednisolone. Age, sex and lactate dehydrogenase levels on admission were comparable between the two groups (Table 1). In the plasma group, 74% of patients were discharged by day 22, compared with 19% in the steroid group ( $p = 0.001$ ; Table 2). Five people died in the steroid group, all of whom were patients who received steroids only, compared with no deaths in the plasma group ( $p = 0.049$ ). Nine patients in the steroid group who received

convalescent plasma were given it in the third week of the disease (mean 15.56 days), while those in the plasma group usually received the sera in the second week (mean 11.42 days;  $p < 0.001$ ). Patients receiving convalescent plasma after day 16 had a poor clinical response. No immediate adverse effects were observed following the infusion of convalescent plasma.

In most viral illnesses, viraemia peaks in the first week of infection. The patient then develops a primary immune response by day 10–14, followed by virus clearance. Therefore, convalescent plasma should be more effective when given early in the course of the disease. In SARS, viral load also peaks in the first week [5], and this might explain the lack of clinical effectiveness of convalescent plasma when given after day 16.

There were several limitations to this study. First, it was not a randomised study and the steroid group had more co-existing morbidities. However, when the analysis was repeated after excluding patients with co-morbid illness in each group, the difference in clinical outcome remained statistically significant ( $p 0.004$ ). Second, the amount of antibodies given to each patient was not standardised, which could contribute to the variable clinical outcome in patients receiving convalescent plasma. Finally, it is arguable whether the ribavirin–steroid combination was effective at all in SARS patients, and the poorer outcome in the continuing high-dose methylprednisolone group might be caused sim-

ply by the deleterious effects of steroids. However, no fungal or opportunistic infections were observed in these patients.

In summary, these preliminary data showed that convalescent plasma therapy was associated with a more favourable outcome in SARS patients who deteriorated despite ribavirin and high-dose steroid therapy than continuing high-dose methylprednisolone. A larger randomised study is required to confirm these preliminary results.

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