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The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study

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Abstract *Objective*: To study the effect of corticosteroids in the treatment of severe acute respiratory syndrome (SARS).

Methods: A retrospective cohort of 78 consecutive adult SARS patients admitted to a regional hospital in Hong Kong between March and May 2003 was analysed to study the effectiveness of corticosteroid. They were categorized according to whether or not corticosteroid therapy was given, and compared in terms of demographic characteristics, comorbidities, peak lactate dehydrogenase (LDH) levels and clinical outcomes. Established adverse prognostic factors including old age, comorbidities and high LDH levels were used as covariates in multiple logistic regressions to adjust for their confounding effect on adverse outcomes.

Results: Among 78 patients, 66 patients (84.6%) received corticosteroid. The LDH level was similar in both groups. The corticosteroid group had more adverse outcomes (37.9% vs. 16.7%) despite younger age and less comorbidity. In multivariate analysis, corticosteroid treatment was associated with a 20.7-fold increase in risk of either ICU admission or mortality, independent of age and disease severity.

Conclusion: Despite more favourable baseline characteristics and similar peak LDH levels, SARS patients given corticosteroid had more adverse outcomes.

Introduction

Hong Kong was hampered by the severe acute respiratory syndrome (SARS) epidemic from early March to June 2003. In total there were 1775 SARS cases and 299 deaths. Our hospital is a regional

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hospital serving a population of 1 million in the northwestern part of Hong Kong.

Treatment during the epidemic had been empirical. While corticosteroid had been the mainstay of treatment of SARS in Hong Kong,[1-5] it was not a routine treatment elsewhere.[6-8] The use of corticosteroid in the treatment of SARS has since become controversial. Some had been sceptical about its therapeutic value, especially in higher dosages, which carry immediate and long-term side effects. We performed a retrospective cohort study on the effect of corticosteroid in a group of SARS patients admitted between March and May 2003.

Patients

Eighty consecutive adult patients fulfilling the WHO criteria of SARS admitted between March and May 2003 were studied. Demographic characteristics, modes of exposure, clinical features, chest imaging results, biochemical, haematological and serology test results, corticosteroid treatment options, and their clinical outcomes were recorded.

Methods

Upper respiratory tract secretions including nasopharyngeal aspirate, sputum, and endotracheal aspirate, as well as urine, saliva and stool specimens were tested for the presence of SARS-CoV (SARS-Coronavirus) by reverse-transcriptase polymerase chain reaction (RT-PCR). Paired acute and convalescent sera were collected.

Laboratory confirmed SARS was defined as either a positive test in RT-PCR or an antibody titre rise of fourfold or above in convalescence. Adverse outcome was defined as either mortality or intensive care unit (ICU) admission.

All patients were treated in the SARS infection isolation wards. Their vital signs and oxygen saturation were closely monitored. Serial biochemical, haematological tests, chest imaging including radiography and high resolution computerized tomography (HRCT) were performed.

All patients were empirically treated with beta-lactam and macrolide for atypical and typical pneumonia, together with intravenous ribavirin at 24 mg/kg per day as antiviral therapy. Corticosteroid therapy was commenced at the discretion of the attending clinicians. The corticosteroid regimen options were: intravenous hydrocortisone at 10 mg/kg per day; intravenous methylprednisolone at 1–3 mg/kg per day; or pulse intravenous methylprednisolone 500–1000 mg per day for 2–3 days. Other treatment options included lopinavir/ ritonavir, immunoglobulin, pentaglobulin, convalescence serum or any combination of the above.

Statistical method

The adverse outcome group and the uncomplicated group were compared in terms of age, sex, laboratory results, and clinical outcomes by univariate analysis. The corticosteroid therapy group was compared with the non-corticosteroid therapy group in terms of their demographic characteristics, presence of comorbidities, peak LDH (lactate dehydrogenase) levels and adverse clinical outcomes by univariate analysis. Mann–Whitney *U* test, Chi-Square test and Fisher-Exact test were used as appropriate.

The established adverse prognostic factors for SARS mortality including old age, presence of comorbidities and high LDH levels[1,3,6,8,9] were used as covariates in multiple logistic regressions to adjust for their confounding effect on adverse outcomes. All tests were two-tailed. p values less than 0.05 were taken as significant.

Results

A total of 80 patients older than 18 years old fulfilling the WHO criteria of probable SARS were admitted during that period. Two patients transferred to other hospitals were excluded. Seventy-eight patients, of which 61 were laboratory confirmed SARS, were analysed.

No statistical differences were detected between the laboratory confirmed and the laboratory test negative groups in terms of demographic characteristics, clinical features, biochemical and haematological tests, and clinical outcomes. No patient in the laboratory test negative group had diarrhoea, as compared to 11 (18%) patients in the laboratory confirmed group, but the difference did not reach statistical significance ($p=0.053$). As both groups were similar in clinical features, laboratory features and outcomes, they were combined for all subsequent analysis.

Demographic characteristics

There were 33 males (42.3%) and 45 females (57.7%). The mean age was 47.7 ± 19.9 years (range 18–95) (Table 1). Nineteen patients (24.4%) were healthcare workers. Thirty-seven patients

Table 1 Characteristics of all, probable SARS and laboratory confirmed SARS patients

	All patients ($n=78$)	Laboratory confirmed SARS ($n=61$)	Probable SARS ($n=17$)	p value
Age (median [range], years)[a]	44 (18-95)	43 (18-95)	46 (26-88)	0.45
Male[b]	33 (42.3%)	25 (41.0%)	8 (47.1%)	0.65
Chills or rigor[b]	33 (42.3%)	26 (42.6%)	7 (41.2%)	0.92
Myalgia[b]	20 (25.6%)	18 (29.5%)	2 (11.8%)	0.14
Cough[b]	42 (53.8%)	32 (52.5%)	10 (58.8%)	0.64
Headache[b]	9 (11.5%)	7 (11.5%)	2 (11.8%)	0.97
Diarrhoea[c]	11 (14.1%)	11 (18.0%)	0 (0%)	0.054
Ground glass HRCT[b]	57 (72.9%)	44 (72.3%)	12.75 (75.0%)	0.85
Lymphocyte count on admission (median [range], $\times 10^9$ cells/l)[a]	0.8 (0.1-3.1)	0.85 (0.1-3.1)	0.70 (0.4-1.7)	0.16
Peak LDH (median [range], U/l)[a]	558 (257-5470)	558 (257-4120)	487 (289-5470)	0.74
Corticosteroid use[b]	66 (84.6%)	53 (86.9%)	13 (76.5%)	0.29
ICU or mortality[b]	27 (34.6%)	21 (34.4%)	6 (35.3%)	0.95

All comparisons were done between the probable SARS and laboratory confirmed SARS group.
[a] Mann-Whitney *U* test.
[b] Chi-Square test.
[c] Fisher-Exact test.

(47.4%) contracted the disease in the hospital, 30 (38.5%) in the community and 11 (14.1%) through household contact.

Clinical features

Fever was the commonest presenting symptom (98.7%), followed by cough (53.8%), chills or rigor (42.3%), myalgia (25.6%), diarrhoea (14.1%) and headache (11.5%). On presentation, 61 patients (78.2%) were lymphopenic (lymphocyte count $<1.2\times10^9$ cells/l) and 22 (28.2%) thrombocytopenic (platelets count $<153\times10^9$cells/l). Thirty-four patients (43.6%) were hyponatraemic (Na$<$ 140 mmol/l) and 22 (28.2%) were hypokalaemic ($<$3.0 mmol/l) (Table 1).

Laboratory confirmation

Thirty-one patients (39.7%) were saliva RT-PCR positive, 24 (30.8%) stool RT-PCR positive, 14 (17.9%) upper respiratory tract secretion RT-PCR positive and 3 (3.8%) urine RT-PCR positive. In total, 55 patients (70.5%) were positive for one or more RT-PCR tests. Forty patients (51.3%) had more than fourfold rise of SARS-CoV antibody titre in the convalescence phase.

Corticosteroid treatment

Sixty-six patients (84.6%) received corticosteroid of various dosages. Twelve patients (15.4%) were not given any corticosteroid. Seventy-four patients (94.9%) were treated with ribavarin and 22 patients (28.2%) received lopinavir/ritonavir as antiviral therapy.

Outcomes

Twenty-one (26.9%) of our patients died and 16 (20.5%) were admitted to the ICU. Patients with adverse outcomes were older, had more comorbidities, and were more likely to be hypokalaemic on presentation. Their trough lymphocyte count was lower, their peak neutrophil count and LDH level were higher (Table 2).

Comparison of patients with and without corticosteroid treatment

When patients were categorized according to whether corticosteroid treatment was given, and compared in terms of age, presence of comorbidities, peak LDH level and outcomes, the corticosteroid group was found to be younger and had less comorbidity. The peak LDH level, reflecting disease severity, was similar in both groups. The corticosteroid group however had more adverse outcomes (37.9 vs. 16.7%), although it did not reach statistical significance (Table 3).

Multivariate analysis was performed to adjust for the confounding effect of age and disease severity. Patients who were treated with corticosteroid were found to have a 20.7-fold increased risk of either ICU admission or mortality, independent of their age and disease severity as represented by peak LDH level (Table 4).

Table 2 Adverse prognostic factors associated with either ICU admission or mortality

	ICU admission or mortality ($n=27$)	Uncomplicated ($n=51$)	p value
Age (median [range], years)[a]	61 (25–89)	40 (18–95)	0.000
Male[b]	10 (37.0%)	23 (45.1%)	0.49
Comorbidities[b]	13 (48.1%)	9 (17.6%)	0.004
Hyponatraemia (<135 mmol/l) on admission[b]	12 (44.4%)	22 (43.1%)	0.91
Hypokalaemia (<3.5 mmol/l) on admission[b]	12 (44.4%)	10 (19.6%)	0.02
Lymphocyte count on admission (median [range], $\times 10^9$ cells/l)[a]	0.8 (0.1–3.1)	0.8 (0.4–1.6)	0.92
Lowest lymphocyte count (median [range], $\times 10^9$ cells/l)[a]	0.2 (0.0–1.4)	0.5 (0.1–1.1)	0.004
Neutrophil count on admission (median [range], $\times 10^9$ cells/l)[a]	4.8 (1.4–12.7)	4.5 (1.6–18.1)	0.22
Peak neutrophil count (median [range], $\times 10^9$ cells/l)[a]	15.2 (1.9–32.8)	11.8 (2.4–28.7)	0.01
Peak LDH (median [range], U/l)[a]	944.5 (328–4120)	479.0 (257–5470)	0.00

[a] Mann–Whitney U test.
[b] Chi-Square test.

Discussion

Corticosteroid has been used extensively in the treatment of SARS in Hong Kong. The theoretical rational is the similarity of the radiological and histological features between bronchiolitis obliterans organising pneumonia (BOOP) and SARS pneumonia. Since corticosteroid has been shown to be effective against BOOP, it was postulated that it could be useful in reducing the complication of adult respiratory distress syndrome (ARDS) in SARS.

Our series had a high mortality rate (26.9%). The adverse prognostic factors were similar to those in other reports, namely advanced age, presence of comorbidities and high peak LDH level.[1,3,6,8,9] Despite more favourable baseline characteristics (younger with less comorbidities) and similar peak LDH levels, the corticosteroid group had more adverse outcomes (37.9% vs. 16.7%), though it did not reach statistical significance. The adverse effect of corticosteroid therapy might have been masked by the younger age and better pre-morbid condition of the corticosteroid therapy group. We have therefore tried to eliminate this confounding effect by multivariate adjustment. Corticosteroid usage had then turned out to be a statistically significant independent adverse factor and was associated with more than 20-fold risk of unfavourable outcomes.

Our series is relatively small. The results could have been biased by many unknown confounding factors. Only advanced age and high peak LDH level were chosen as the two important prognostic factors to make adjustment for.

Due to the limited number of cases, we did not stratify the outcomes according to different corticosteroid regimen and the timing of corticosteroid commencement. However, we recognize that therapeutic effects may vary with different dosages and may be affected by the timing of treatment.[10] Some clinicians believe that the first phase of the illness is viral replication and antiviral therapy should be the mainstay of treatment, while immunemodulation therapy such as corticosteroid should be withheld until the second week to counteract the BOOP-like phase.

Table 3 Comparison of characteristics, adverse prognostic factors and outcome between corticosteroid therapy group and non-corticosteroid therapy group

	Corticosteroid therapy ($n=66$)	Non-corticosteroid therapy ($n=12$)	p value
Age (median [range], years)[a]	41 (18–89)	53.5 (43–95)	0.005
Male[b]	27 (40.9%)	6 (50.0%)	0.56
Comorbidities[b]	15 (22.7%)	7 (58.3%)	0.012
Peak LDH (median [range], U/l)[a]	564 (257–4120)	479 (315–5470)	0.28
Either ICU admission or mortality[b]	25 (37.9%)	2 (16.7%)	0.16

[a] Mann–Whitney U test.
[b] Chi-Square test.

Table 4 Adverse prognostic factors associated with either ICU admission or mortality by multivariate analysis

	Adjusted odds ratio	95% CI	*p* value
Age			
≤70 years	1.0	-	-
>70 years	26.6	2.6–270.6	0.006
High peak lactate dehydrogenase			
≤395 U/l	1.0	-	-
>395 U/l	7.3	1.4–37.1	0.016
Corticosteroid therapy			
No	1.0	-	-
Yes	20.7	1.3–338.0	0.03

Conclusion

Corticosteroid therapy was associated with a 20-fold increase in adverse outcomes in our series. Large-scale randomized controlled trials are needed to look at the effectiveness, as well as the appropriate dosages and timing of corticosteroid treatment in SARS. Until then, clinicians should remain cautious in the use of corticosteroid in this novel disease.

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