CLINICAL RESEARCH STUDY

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Effectiveness of Ribavirin and Corticosteroids for Severe Acute Respiratory Syndrome

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ABSTRACT

OBJECTIVE: Ribavirin and corticosteroids were used widely as front-line treatments for severe acute respiratory syndrome; however, previous evaluations were inconclusive. We assessed the effectiveness of ribavirin and corticosteroids as the initial treatment for severe acute respiratory syndrome using propensity score analysis.

METHODS: We analyzed data on 1755 patients in Hong Kong and 191 patients in Toronto with severe acute respiratory syndrome using a generalized propensity score approach.

RESULTS: The adjusted excess case fatality ratios of patients with severe acute respiratory syndrome receiving the combined therapy of ribavirin and corticosteroids within 2 days of admission, compared with those receiving neither treatment within 2 days of admission, were 3.8% (95% confidence interval, −1.5 to 9.2) in Hong Kong and 2.1% (95% confidence interval, −44.3 to 48.5) in Toronto.

CONCLUSIONS: Our results add strength to the hypothesis that the combination of ribavirin and corticosteroids has no therapeutic benefit when given early during severe acute respiratory syndrome infection. Further studies may investigate the effects of these treatments later in disease course.

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KEYWORDS: Corticosteroids; Effectiveness; Propensity score; Ribavirin; Severe acute respiratory syndrome

The severe acute respiratory syndrome outbreak in 2002 and 2003 infected more than 8000 people in 29 territories with an overall worldwide case fatality ratio of 9.6%.[1] Hong Kong and Toronto bore a significant proportion of the global case burden, together accounting for 25% of all "probable cases."[1] Although there have been only sporadic human infections with the severe acute respiratory syndrome coronavirus since the first global outbreak,[2] the possibility of widespread reemergence cannot be ruled out given the continued trading and consumption of palm civets, a likely animal reservoir.[3,4] Meanwhile, severe acute respiratory syndrome-like coronaviruses are endemic in bats in Hong Kong and southern China.[5,6]

Ribavirin has broad activity against many DNA and RNA viruses.[7] Corticosteroids can be protective against extensive inflammatory lung damage.[8,9] Therefore, these 2 drugs were recommended for use as front-line treatments during the outbreak, although not without controversy.[10] Evaluation of the effectiveness of these 2 drugs in the treatment of severe acute respiratory syndrome has consisted largely of uncontrolled studies and small hospital cohorts. A recent meta-analysis confirmed that there are few reliable data on which to base future treatment decisions in severe acute respiratory syndrome, largely because of the lack of adjustment for important confounding variables in evaluative studies published to date.[11] Although randomized controlled trials would provide more conclusive evidence, they cannot be conducted unless large future out-

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breaks occur,[12] and in the meantime it is critical that current recommendations, both for the treatment of patients and for the identification of those agents that should be prioritized for testing in future trials, are based on the best available data.

We analyzed data on patients with severe acute respiratory syndrome from Hong Kong and Toronto to assess and compare the treatment efficacies, as measured by mortality reduction, of early administration of ribavirin alone, corticosteroids alone, or both in combination. We used propensity score analysis to adjust for potential confounding effects, an approach that has been proposed as the most valid analytic strategy for observational data in the absence of a randomized design[13] and has been used to evaluate drug effectiveness in many observational studies.[14-18] In addition to providing important evidence-based guidance for future human cases of severe acute respiratory syndrome, our work may serve as a template for the evaluation of treatment efficacies for other emerging infectious diseases.

CLINICAL SIGNIFICANCE

- Previous evaluations on the effectiveness of ribavirin and corticosteroids in treating severe acute respiratory syndrome were inconclusive.
- On the basis of a large dataset with 25% of global severe acute respiratory syndrome cases and properly adjusted for treatment selection bias, the combination of ribavirin and corticosteroids was found to have no significant beneficial effect in the initial treatment of patients with severe acute respiratory syndrome.

MATERIALS AND METHODS

Data Sources

We analyzed an integrated database containing clinical and epidemiologic details on all 1755 patients in Hong Kong reported to have "probable severe acute respiratory syndrome" according to the World Health Organization definition,[19] derived from the Hong Kong Hospital Authority Electronic Severe Acute Respiratory Syndrome system and the Hong Kong Department of Health's Master list.[19,20] For the Toronto data, the Canadian Severe Acute Respiratory Syndrome Research Network conducted a retrospective cohort study of all probable severe acute respiratory syndrome cases among adults (age $\geq$ 16 years) admitted to a hospital during the outbreak.[20,21] Medical charts were reviewed by trained research staff, and clinical, radiographic, and laboratory data were double entered into a database.

Key patient characteristics at hospital admission that were extracted from these 2 sources included gender, age, occupation, preexisting comorbid conditions, calendar date of symptom onset, delay between symptom onset and admission, lactate dehydrogenase level, chest radiograph findings, neutrophil count, platelet count, lymphocyte count, and oxygen saturation. We classified patients into 4 treatment groups based on whether they had started a course of ribavirin, corticosteroids, both ribavirin and corticosteroids, or neither drug within 2 days of admission to hospital.

We included all patients in Hong Kong. In Toronto the outbreak occurred in 2 waves (first wave: March 2 to April 21; second wave: April 22 to June 10),[22] and ribavirin was not used at all during the second wave because of clinical experience in the first wave.[12] In this analysis we require that each patient had the opportunity to be treated with ribavirin or corticosteroids, and therefore we excluded the 94 patients in Toronto who were admitted to hospital during the second wave. We excluded the 12 patients (0.6%) in Hong Kong and 2 patients (1%) in Toronto who died within 2 days of admission.

Statistical Analysis

In randomized controlled trials, the randomization process should on average balance patient characteristics across treatment groups, and comparison of crude event rates across treatment groups should be unconfounded,[23] although adjustment for potential confounders may improve precision.[24] However, in situations in which treatment assignment is not random, but may depend on patients' presenting characteristics and clinical course, failure to appropriately adjust for such factors may lead to misleading findings. Standardization or stratification can be carried out for each characteristic but is typically not feasible when there are a large number of potential confounders. Regression adjustment is often used provided there are sufficient events; a simple rule of thumb is 20 events (eg, deaths) per potential confounder.[25]

An alternative approach is the use of propensity score analysis.[13] Under this approach, a model is specified to explain the assignment of treatments in terms of patient characteristics. The predicted probabilities, or "propensity scores" from this model are in turn incorporated in a successive model to assess the association between the treatment and the outcome of interest. In the latter model, the estimate of the treatment effect should reflect adjustment for differences in the observed patient characteristics between treatment groups.

To study the relative effects on mortality of the 4 treatment groups, namely, neither drug, ribavirin alone, corticosteroids alone, or both drugs, we used a generalized propensity score approach that can allow for more than 2 treatment choices.[26] We estimated the propensity scores using a multinomial regression model adjusting for the key patient characteristics at admission as described above and 3 other factors, including calendar date of onset, onset-to-admission delay, and admitting hospital. Because some prognostic factors were only available for a subset of approximately 30% of the patients in Hong Kong and 60% of