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Short report

Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers

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SUMMARY

An effective post-exposure prophylaxis (PEP) strategy may limit the spread of infection. However, there is no consensus regarding PEP for Middle East respiratory syndrome coronavirus (MERS-CoV) infection. This study assessed the efficacy of ribavirin and lopinavir/ritonavir as PEP for healthcare workers (HCWs) exposed to patients with severe MERS-CoV pre-isolation pneumonia. The safety of the PEP regimen was assessed. HCWs with high-risk exposure to MERS-CoV pre-isolation pneumonia were retrospectively enrolled. HCWs who received PEP therapy were classified into the PEP group. PEP therapy was associated with a 40% decrease in the risk of infection. There were no severe adverse events during PEP therapy.

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Introduction

The spread of infection between individuals in healthcare settings principally contributes to infection outbreak [1]. Healthcare workers (HCWs) are at high risk for acquiring emerging infection while caring for patients. Among 186 laboratory-confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) during the 2015 outbreak in South Korea, 39 (21.0%) were HCWs who were exposed to MERS-CoV at 12 healthcare facilities [2]. Thirty (83.3%) HCWs were infected with MERS-CoV during the course of their treatment without knowing whether the patient was infected with MERS-CoV [2]. There is no approved post-exposure prophylaxis (PEP) therapy for the prevention of MERS-CoV infection. The objective of this study was to assess the efficacy of PEP therapy for HCWs exposed to patients with severe MERS-CoV pre-isolation pneumonia. Safety of the PEP regimen was also evaluated.

Methods

Sample MERS-CoV pneumonia case, study setting, and study population

A 70-year-old woman henceforth known as patient A was admitted to hospital A complaining of back pain. At the time of admission, the patient had pneumonia with fever lasting 10 days. Two days later, patient A was transferred to intensive care unit where she received endotracheal intubation. Since a diagnosis of MERS-CoV infection was not suspected during this period, HCWs did not use appropriate personal protective equipment (PPE). As no specific pathogen was identified, testing for MERS-CoV infection was conducted. Real-time reverse transcriptase–polymerase chain reaction (rRT–PCR) was strongly positive for MERS-CoV [3]. Patient A had cycle threshold (C_T) values of 17.9 for envelope protein gene and 18.2 for open reading frame 1a gene. After patient A had been diagnosed with MERS-CoV, rapid contact tracing was performed and possible contact exposures were divided into two groups: high-risk and non-high-risk exposure groups. HCWs with high-risk exposure were isolated and immediately offered oral ribavirin (Viramid capsules; Ilsung Pharmaceuticals, Seoul, South Korea) and lopinavir/ritonavir (Kaletra; Abbvie Inc., North Chicago, IL, USA). The PEP protocol was initiated between days 1 and 3 after the last unprotected exposure to patient A. PEP therapy was administered until day 14 after the last exposure according to the incubation period of the disease [1]. Ribavirin was administered orally at a loading dose of 2000 mg followed by 1200 mg every 8 h for 4 days and then 600 mg every 8 h for 6–8 days. Lopinavir/ritonavir was administered orally at a dose of 400 mg/100 mg every 12 h for 11–13 days. Laboratory testing for HCWs in the PEP group was performed on days 3, 7, and 11 after treatment initiation. HCWs who received PEP therapy also underwent two-point sputum screening with MERS-CoV rRT–PCR. To improve detection of unrecognized MERS-CoV infection in the PEP group, enzyme-linked immunosorbent assay (ELISA; Euroimmun, Lübeck, Germany) was also performed to detect MERS-CoV immunoglobulin G (IgG) after completion of PEP therapy [4].

For control group selection, four hospitals with super-spread events were retrospectively selected. A retrospective comparative study was conducted for five hospitals of South Korea. Hospitals A–D are secondary referral hospitals whereas hospital E is a tertiary referral hospital. Each hospital had a corresponding MERS-CoV pre-isolation pneumonia patient (patients A–E). Pre-isolation pneumonia patients visited participating hospitals without knowing that they were infected with MERS-CoV. C_T data were available for all five MERS-CoV pre-isolation pneumonia patients. C_T values of the five patients were similar. HCWs with unprotected exposure to patients with MERS-CoV pre-isolation pneumonia were enrolled from the above five hospitals between May and July 2015. We only included HCWs with high-risk exposure. HCWs from hospital A treated with PEP represented the PEP group. HCWs from other hospitals who did not receive PEP were classified as the non-PEP group. HCWs in the non-PEP group were isolated and monitored for the development of MERS-like symptoms for 14 days from the date of exposure to a patient with MERS. The incidence of MERS-CoV infection was compared between these groups.

Data collection and exposure assessment

During the MERS outbreak in South Korea, each hospital had conducted a contact survey to evaluate exposure levels. Five investigators at each hospital individually collected data and reviewed potential exposures. Epidemiological data were obtained by medical record review and personal interview between May and July of 2015.

Definitions

MERS-CoV infection was confirmed using rRT–PCR. Pre-isolation pneumonia was defined when a patient was diagnosed with pneumonia prior to quarantine without knowledge of their MERS-CoV infection. High-risk exposure was arbitrarily defined as any of the following: direct care without aerosol-generating procedures with inappropriate PPE, or unprotected exposure to patients with MERS-CoV pre-isolation pneumonia during aerosol-generating procedures. The definition of appropriate PPE was based on previous recommendations [5]. The absence of any part of the PPE constituted an unprotected exposure. We defined the following as aerosol-generating procedures: airway suction, application of a high-flow O_2 instrument, bronchoscopy, endotracheal intubation, tracheostomy, nebulizer treatment, sputum induction, positive pressure ventilation, manual ventilation and cardiopulmonary resuscitation. Several HCWs had more than one type of exposure. Duplicate exposures were recorded.

Statistical analyses

Baseline characteristics of PEP and non-PEP groups were compared using χ^2-tests or Fisher's exact tests for categorical variables and Student's *t*-tests or Mann–Whitney *U*-tests for continuous variables. MERS-CoV attack rate was compared between groups using Fisher's exact test. Categorical variables are presented as frequencies and proportions where continuous variables are presented as mean and standard deviation or median and interquartile ranges (IQR). No multivariate analysis was conducted due to small sample size. Odds ratio (OR) and 95% confidential interval (CI) were also calculated for each variable. All *P*-values were two-tailed. $P < 0.05$ was considered

statistically significant. PASW version 18.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Study approval

The PEP group in this study was informed that the efficacy of PEP for MERS-CoV infection was unknown and that adverse effects were possible. Individual participation was voluntary. All participants provided written informed consent prior to initiating PEP therapy. This study was approved by the institutional review board of each respective hospital.

Results

Demographic characteristics and MERS-CoV exposure

In all, 123 HCWs with unprotected exposure to MERS-CoV pre-isolation pneumonia patients were identified at five participating hospitals. Of these, 43 HCWs met the definition of high-risk exposure (Figure 1). Twenty-two HCWs were classified into the PEP group; the remaining 21 HCWs were classified into the non-PEP group. Baseline characteristics were generally similar between the two groups (Table I) except that the median age of the PEP group was significantly lower than that of the non-PEP group. None of these HCWs with high-risk exposure had worn an N95 respirator, isolation gown, goggles, or facial shield. The most common type of exposure to MERS-CoV was via direct care without aerosol-generating procedure for MERS-CoV patient (39.5%), followed by airway suction (39.5%) and nebulizer treatment (34.9%). Eighteen (41.9%) HCWs were only exposed to MERS-CoV via direct care without aerosol-generating procedure. Of these, 17 were in the non-PEP group and one was in the PEP group ($P < 0.001$).

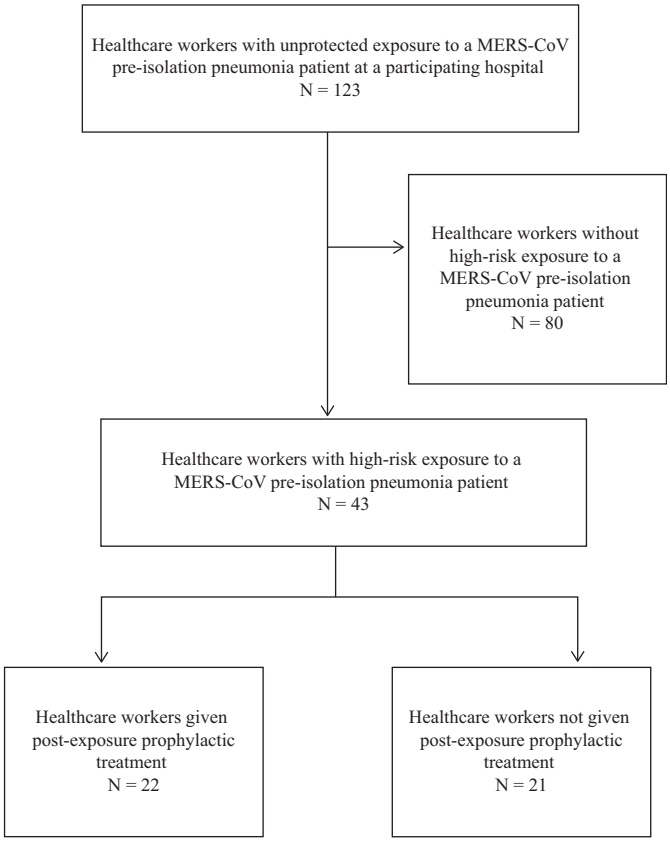

Figure 1. Study profile. MERS-CoV, Middle East respiratory syndrome coronavirus.

MERS-CoV infection

Six (14.0%) out of 43 HCWs developed MERS-CoV infection. The attack rate was lower in the PEP group compared to that in the non-PEP group (0% vs 28.6%; OR: 0.405; 95% CI: 0.274–0.599; $P = 0.009$). There was no instance of MERS-CoV infection in the PEP group. Of the six HCWs infected with MERS-CoV, one was exposed to two events (cardiopulmonary resuscitation and airway suction). Only PEP therapy was a significant factor (OR: 0.714; 95% CI: 0.545–0.936; $P = 0.009$) that reduced the risk of MERS-CoV infection.

Safety of PEP with ribavirin and lopinavir/ritonavir

In the PEP group, PEP therapy was initiated within a median of 36 h (range: 16–80 h) after unprotected exposure to a MERS-CoV pre-isolation pneumonia patient. HCWs received PEP therapy for a median duration of 12 days (IQR: 11–12 days). PEP therapy was generally well tolerated, although some minor adverse effects were reported. Overall, 21 (95.5%) out of 22 HCWs in the PEP group reported one or more symptoms during the course of therapy. The most common symptoms were diarrhoea (40.9%), nausea (40.9%), stomatitis (18.2%), and fever (13.6%). Twenty out of 22 HCWs in the PEP group underwent laboratory testing. Anaemia and leucopenia were observed in nine (45.0%) and eight (40.0%) HCWs, respectively, during PEP therapy. Hyperbilirubinaemia was observed in all 20 HCWs. However, other liver function tests were within normal ranges. Elevated total bilirubin and decreased values of haemoglobin and leucocyte were normalized after completion of PEP therapy.

MERS-CoV rRT–PCR and ELISA

MERS-CoV rRT–PCR was performed on samples obtained from HCWs in the PEP group immediately after and seven days after completion of the PEP protocol. All test results were negative. Serum samples collected at six and 12 weeks after unprotected high-risk exposure were negative for MERS-CoV antibody.

Discussion

In this preliminary study, we assessed the efficacy and safety of PEP in HCWs after unprotected high-risk exposure to patients diagnosed with severe MERS-CoV pre-isolation pneumonia. Despite more severe exposure, no MERS CoV infection occurred in the PEP group. PEP therapy appeared to reduce the risk of MERS-CoV in HCWs with unprotected high-risk exposure to MERS patients by 40% in this study.

The 2015 MERS-CoV outbreak in South Korea is an important example of healthcare-associated MERS-CoV transmission. During the 2015 MERS-CoV outbreak, HCWs were infected with MERS-CoV after caring for patients with undiagnosed MERS-CoV infection. The use of PPE was inconsistent among these HCWs

Table I
Clinical and demographic characteristics of healthcare workers in the prophylaxis and non-prophylaxis groups

Characteristics	Total ($N = 43$)	PEP group ($N = 22$)	Non-PEP group ($N = 21$)	*P*-value
Age (years), median (IQR)	29.0 (24–33)	27.5 (24–33)	31 (28–43)	0.031
Female	28 (65.1)	15 (62.2)	13 (61.9)	0.666
Occupation				0.658
Doctor	19 (44.2)	9 (40.9)	10 (47.6)	
Nurse	24 (55.8)	13 (59.1)	11 (52.4)	
Protective equipment use				
Surgical mask	2 (4.7)	0	2 (9.5)	0.233
Gloves	3 (7.0)	0	3 (14.3)	0.108
Types of exposure situation[a]				
Direct care without aerosol-generating procedure	39 (90.7)	22 (100.0)	17 (81.0)	0.048
Airway suction	17 (39.5)	16 (72.7)	1 (4.8)	<0.001
Nebulizer treatment	15 (34.9)	15 (68.2)	0	<0.001
Intubation	6 (14.0)	5 (22.7)	1 (4.8)	0.185
Manual ventilation	3 (7.0)	2 (9.1)	1 (4.8)	>0.999
Cardiopulmonary resuscitation	2 (4.7)	0	2 (9.5)	0.233
Bronchoscopy	2 (4.7)	0	2 (9.5)	0.233
MERS-CoV infection	6 (14.0)	0	6 (28.6)	0.009

PEP, post-exposure prophylaxis; IQR, interquartile range; MERS-CoV, Middle East respiratory syndrome coronavirus.
Values are no. (%) unless otherwise indicated.
[a] Several healthcare workers had more than one type of exposure, and duplicated exposures were recorded.

[2]. The infection rate of MERS-CoV was estimated to be 16% among HCWs, which was more than four-fold the average estimated household transmission rate [6]. The main mode of MERS-CoV transmission is via respiratory droplets, indicating that HCWs are at particularly high risk for MERS-CoV infection [1]. Therefore, high-risk exposure during aerosol-generating procedures including tracheal intubation without appropriate PPE may increase the risk of MERS-CoV contamination.

It was decided to administer prophylactic antiviral agents to HCWs with high-risk exposure to MERS patients, taking these various factors into consideration, although currently there is no recommendation for MERS-CoV PEP. Our PEP regimen was based on available literature and evidence obtained from animal and patient studies [7–10]. In the absence of current guidelines for PEP therapy, PEP agents were administered until the 14th day after the last exposure based on incubation period of the disease.

PEP therapy was associated with several adverse effects, although most of them were mild. All adverse events were reversed following completion of therapy. No HCWs discontinued treatment due to adverse effects. The frequency, severity, duration and reversibility of adverse effects are important considerations when formulating a prophylactic regimen. In this regard, PEP regimen appears to be a reasonably safe choice for prophylaxis after MERS-CoV exposure.

Our study has several limitations. This was a retrospective study with a small number of participants. Inevitable selection and unmeasured confounding bias could not be completely excluded. During a large outbreak of MERS-CoV in South Korea, only hospital A administered PEP to HCWs with high-risk exposure to MERS patients. To minimize selection bias, five MERS-CoV pre-isolation pneumonia patients who had severe pneumonia and similar C_T values as source of exposure were selected. In addition, our comparator group was carefully selected with a focus on degree of exposure.

Self-report was used to determine MERS-CoV exposure experience of HCWs. This might have a recall bias. The best method to evaluate novel therapies is via a randomized controlled clinical trial setting. However, such a method is neither feasible nor ethical in the context of an emerging and relatively uncommon infectious disease under unexpected outbreak. Despite a small number of participants, this is a study with the largest sample size to date to assess the effectiveness of a PEP therapy for the prevention of MERS-CoV infection.

We believe that our PEP guidelines for MERS-CoV infection can be useful for the management of outbreaks. Nonetheless, prospective analyses and randomized clinical studies are needed in the future.

Conflict of interest statement
None declared.

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