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Original Article

Maoto, a traditional herbal medicine, for post-exposure prophylaxis for Japanese healthcare workers exposed to COVID-19: A single center study

Atsuko Nabeshima [a], Atsuhiko Sakamoto [b], Kaoru Iwata [a], Yuji Kitamura [a], Shinta Masui [a], Shinjiro Inomata [a], Masahiro Iida [a], Takeshi Iida [a], Shigeki Nabeshima [b,*]

[a] Meotoiwa Hospital, Fukuoka, Japan
[b] General Medicine, Fukuoka University Hospital, Fukuoka, Japan

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ABSTRACT

Background: Little research has been done on post-exposure prophylaxis (PEP) for COVID-19. This study was done to determine if maoto, a traditional herbal medicine commonly used for diseases with symptoms similar to those of COVID-19, can be repurposed for post-exposure prophylaxis to prevent the spread of nosocomial infection with SARS-CoV-2.

Methods: A cohort analysis was done of the data of 55 health care workers (HCWs) whether to get infected with SARS-CoV-2 in a Japanese hospital experiencing a COVID-19 cluster in April of 2021. Of these subjects, maoto granules for medical use were prescribed for PEP to 42 HCWs and taken for three days in mid-April. Controls were 13 HCWs who rejected the use of maoto. Polymerase chain reaction was performed routinely once or twice a week or when a participant presented with symptoms of COVID-19.

Result: There were no background differences between the maoto and control groups by profession, sex, or mean age. No severe adverse reactions were observed. During the observation period of 1 week, significantly fewer subjects were diagnosed with COVID-19 in the maoto group (N = 3, 7.1%) than in the control group (N = 6, 46.2%). The prophylactic effectiveness of maoto was 84.5%.

Conclusion: Oral administration of maoto is suggested to be effective as PEP against nosocomial COVID-19 infection.

1. Introduction

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is having great impact on the worldwide health system. Because healthcare workers (HCWs) in hospitals are at extreme risk of exposure to SARS-CoV-2, the management of exposure events to limit nosocomial infections is of great concern [1–4]. Long term, pre-exposure prophylaxis (PrEP) for COVID-19 through vaccination has been shown to be effective [5], however, it is possible that vaccines for COVID-19 will become less effective against SARS-CoV-2 variants that can escape natural or host immunity provided by these vaccines [6–8]. Various methods of post-exposure prophylaxis (PEP) administered soon after exposure to COVID-19 have been done, with numerous studies reporting PEP or PrEP for COVID-19 [9–12]. However, at present, no chemoprophylaxis regimen for COVID-19 is available. Although some research has reported some effectiveness for hydroxychloroquine [13–15], recent WHO guidelines do not recommend its use as prophylaxis [16]. Ivermectin is widely used for the treatment of COVID-19, especially in India and South America, but there is little evidence of benefit [17–19]. Vitamins C and D, povidone iodine gargle, iota-carrageenan spray, and monoclonal antibodies against SARS-CoV-2 are candidates for the prophylaxis for COVID-19, but there is little evidence so far to support them [20–22].

Traditional herbal medicines have long played important roles in the Far East, especially Japan, China, and Korea. Traditional herbal medicines, called Kampo, are accepted by the national medical insurance system of Japan, and there is widespread use of these medicines by Japanese physicians [23]. We previously reported two clinical trials showing that maoto (ma-huang-tang in Chinese) was effective in treating seasonal influenza in a comparison with neuraminidase inhibitors [24,25]. The mechanism suggested was that influenza virus particles remained in endosomes because of a failure in viral fusion with the endosome membrane through the elevation of the endosomal pH condition [26]. The anti-viral effect of maoto was confirmed in an

* Corresponding author. Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan.
E-mail address: snabeshi@fukuoka-u.ac.jp (S. Nabeshima).

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experimental mouse infection model of influenza [27]. Other than influenza, we recently reported a case of COVID-19 treated with maoto in which high fever and viral load were reduced [28].

Some kampo medicine candidates for COVID-19 have recently been reported, but no large-scale clinical trials have been done [29–31]. We herein report our retrospective investigation of the efficacy of maoto as PEP for HCWs in a hospital that experienced an outbreak of nosocomial infection with SARS-CoV-2.

2. Methods

2.1. Study design

This was a cohort study done in a private Japanese hospital that experienced a nosocomial COVID-19 cluster in 2021. The primary endpoint was to evaluate the efficacy and tolerability of maoto as PEP for at-risk HCWs. The hospital has three wards with 175 beds. Most of the inpatients are elderly and are undergoing long-term care. Standard precautions were taken in this hospital. When febrile inpatients were observed in ward 1 of this hospital in early April, on 11 April all inpatients in this ward were tested for COVID-19 by real-time polymerase chain reaction (PCR), with 18 testing positive. The outbreak then spread to ward 2, which is located next to ward 1 and shares the same dining room. During the outbreak period from 11 to 30 April, 44 inpatients and 26 HCWs were positive by PCR for SARS-CoV-2. Our infection control team (ICT) implemented procedures for strict infection zoning and began requiring personal protective equipment (PPE) for the 55 HCWs in and around wards 1 and 2 on 14 April (Fig. 1).

At the beginning of this study on 17 April, there were 55 HCWs working in the Covid-19 zone in all, and maoto granules for medical use were prescribed to 42 of these 55 HCWs during 17–19 April for three days by the infection control doctor. The HCWs who rejected PEP (N = 13) were assigned to a control group. None of the subjects had been infected with COVID-19 or been vaccinated. None had severe underlining diseases, and none were examined by blood tests or X-rays on the day of prescription. The observation period was from 17 to 24 April, during which all participants received PCR once or twice a week or when presenting the symptoms of COVID-19. The duration of the observation period was determined based on the fact that maoto prescription was for three prescription days. PCR samples were collected from nasopharyngeal swab for examination by the Fukuoka Public Health Center. The day of diagnosis was the day of sampling. The result of PCR was generally reported on the day after sampling.

After the observation period, the authors confirmed whether or not the subjects completed the maoto regimen, presented adverse reactions, or had been infected with COVID-19. If a subject was diagnosed with COVID-19, the authors questioned them about fever and other symptoms and where they recuperated during the acute stage of COVID-19: at home, an assigned hotel, or in a hospital. The study was approved by the Institutional Review Board of Meotoiwa Hospital (#2021–001).

2.2. PEP

Maoto was selected for PEP because 1) it is a clinically proven drug for common cold and influenza, which have many common symptoms with COVID-19, 2) its cost effectiveness, and 3) a case report describing the efficacy of maoto for COVID-19 [28]. Maoto is a multicomponent formulation extracted from four plants: Ephedrae Herba, Cinnamomi Cortex, Armeniacae Semen, and Glycyrrhize Radix [32]. Maoto granules in commercial medical dosage form (TJ-27) were purchased from Tsumura, Tokyo. It was prescribed without insurance, and administered orally at 2.5 g, three times a day, for three days, total 22.5 g. No other PEP was administered.

2.3. Statistical analysis

Statistical analysis of PEP efficacy and background factors of the participants was by Fisher's exact test, except for the mean age between the groups, which was done by student's t-test. *P* values less than 0.05 were considered significant. Data were analyzed with GraphPad Prism software (San Diego, California, US). The efficacy of prophylaxis was calculated as follows.

$$\text{Prophylactic effectiveness } \% = (\text{ARU} - \text{ARP}) / \text{ARU} \times 100$$

ARU: Attack rate without prophylaxis, ARP: Attack rate with prophylaxis.

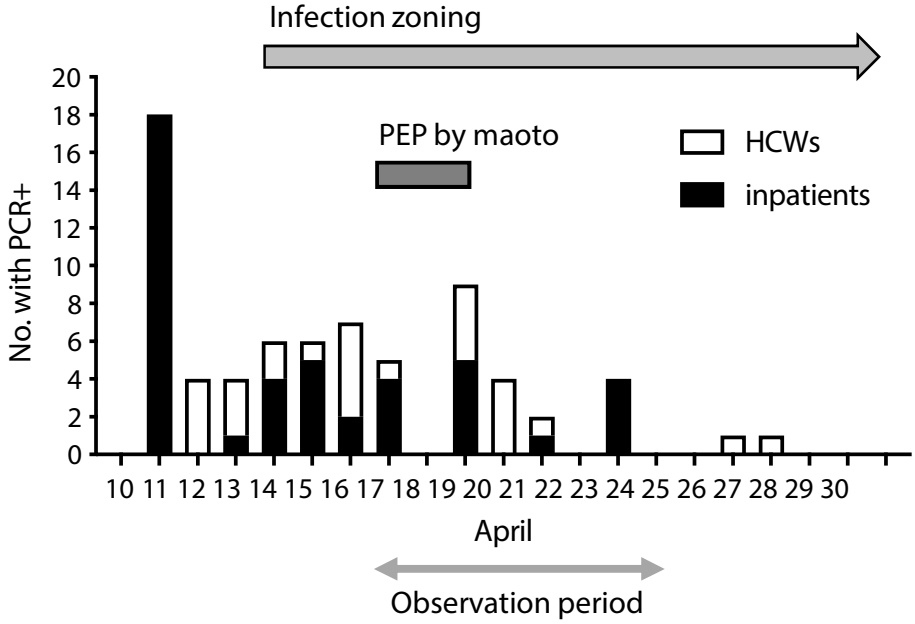

Fig. 1. Hospital outbreak of COVID-19 and the administration of maoto for post-exposure prophylaxis. On 11 April, 18 inpatients were positive for COVID-19, followed by 53 inpatients and HCWs over the next few weeks. Maoto 2.5 g, three times a day for 3 days, was given as PEP to 42 HCWs from 17 to 19 April.

3. Results

3.1. Study subjects

Of the 55 HCWs in wards 1 and 2 (zoning area), 42 were administered maoto as PEP for three days (total 22.5 g), and 13 rejected it (Table 1). Adherence to the maoto regimen (22.5 g) was complete for 39, 2 took 15 g, and one took 7.5 g. The mean and median total dosages of maoto were 21.2 g and 22.5 g, respectively. Epigastralgia is a known adverse reaction to maoto, but no adverse reactions were reported for the participants in the present study. No significant differences were found between the test and control groups in terms of profession, sex, or mean age. All of the subjects wore PPE in the isolation wards.

3.2. Prophylactic effect of maoto

During the observation period, laboratory-diagnosed COVID-19 in the maoto group (N = 3, 7.1%) was significantly less than in the control group (N = 6, 46.2%) (Table 2). Fig. 2 shows the subjects who contracted COVID-19. All the HCWs with COVID-19 became positive from 19 to 21 April, within a few days after the prescription of maoto. Fever was seen in one person in the maoto group and in two in the control group. No symptoms were seen in one person in the control group. Other symptoms included rhinorrhea in the maoto group and rhinorrhea, sore throat, and impaired smell in the control group. No hospitalization or death was found in either group. The effectiveness of maoto for prophylaxis in the present study was 84.5%.

4. Discussion

The present study shows that maoto would be useful in outbreak situations for preventing the spread of COVID-19 among HCWs. Significantly fewer subjects were infected with SARS-CoV-2 in the maoto group than in the control group. Although the study was observational and of small size, it has some unique characteristics. The most unique point is that it was done over the course of a COVID-19 cluster in a single hospital, in which 71 HCWs and inpatients were infected with COVID-19 within 4 weeks. Next, all of the subjects were working in a designated COVID zone, where they had high risk of exposure to the virus. This unusual situation provided a good opportunity to evaluate PEP. Because this hospital takes care of many frail elderly needing long-term care, nursing staffs had more risk to catch COVID-19 than physicians and rehabilitation therapists. All subjects were previously unvaccinated and not infected with COVID-19, which avoided the bias of immunity. Last, unlike subjects exposed through household infection, medical follow-up of HCWs in a single hospital is relatively easier, and it is easier to confirm adherence to the maoto regimen. A randomized controlled trial (RCT) would have provided the strongest evidence, but much time is needed to prepare and implement an RCT protocol, thus doing an RCT was not practical in this critical, time-sensitive situation. Although the results of the present study may not be conclusive, they are valuable given the circumstances.

Because COVID-19 has become pandemic, many drugs have been tried for its prevention, however, no effective prophylaxis, except for the vaccine, is available [9–11]. Vaccines have a neutralizing effect against virus epitopes, but take a few weeks to generate the neutralizing antibodies in vaccinated people and thus are not suitable for post-exposure use. The ideal PEP needs both a therapeutic effect and a prophylactic effect because the virus may already have infected the host when they take PEP. Adverse effects are also important, and maoto has been shown to have few. Many prophylactic and therapeutic drugs have been proposed for use against COVID-19 [12], such as hydroxychloroquine, ivermectin, and monoclonal antibodies (casirivimab and imdevimab) [33]. Other traditional herbal medicines became candidates for the treatment of COVID-19 [29]. In Japan, clinical trials of traditional herbal medicines, managed by the Japan Society for Oriental Medicine, are in progress [34,35]. We recently reported a COVID-19 case treated with maoto in which we showed that it relieved fever and reduced viral load [28]. This case led us to the idea of using maoto as prophylaxis against COVID-19. Kampo has many drugs other than maoto for the treatment of acute febrile diseases, such as COVID-19. We think that clinically proven Kampo medicines can be repurposed for PEP, with clinical advantages such as low cost, tolerability, and already widespread use in Japan.

We previously reported that maoto inhibited endosomal acidification, showing that influenza viruses could not enter the cytosol [26]. Recently, chloroquine was also reported to inhibit endosomal acidification and to block SARS-CoV-2 infection to the cytosol [36]. Although the anti-SARS-CoV-2 mechanism of maoto is not clear, it has the above-mentioned mechanisms in common with chloroquine. We recently showed in yet to be published data that maoto components

Table 1
Characteristics of the study subjects.

	maoto (N = 42)	control (N = 13)	*P* value
Mean total dose of maoto (g±SD)	21.2 ± 4.8		
Profession			0.5216
Doctor (%)	3 (7.1)	0 (0.0)	
Nursing staff (%)	30 (71.4)	9 (69.2)	
Rehabilitation therapist (%)	9 (21.4)	4 (30.8)	
Female (%)	30 (71.4)	9 (69.2)	1
Mean age±SD	45.7 ± 10.4	39.5 ± 12.3	0.0805
PPE worn (%)	42 (100)	13 (100)	1

PPE: personal protective equipment.

Table 2
The prophylactic effect of maoto for nosocomial COVID-19 infection.

	maoto (N = 42)	control (N = 13)	*P* value
COVID-19 (%)	3 (7.1)	6 (46.2)	0.0033
No symptoms	0	1	
Fever	1	2	
Other symptoms	2	5	
Hospitalization	0	0	1
Death	0	0	1

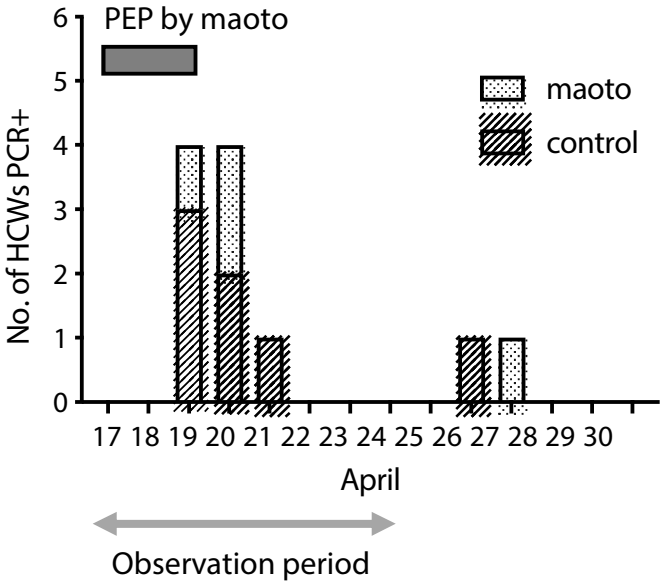

Fig. 2. COVID-19 infection during the observation period. PCR-positive-participants after post-exposure prophylaxis by maoto are shown. Observation period from 17 to 24 April. The numbers of Maoto group 42, control group 13.

specifically interact with G glycoprotein of respiratory syncytial virus (RSV), which blocks the attachment of RSV to the host receptor. It is possible that maoto components may also interact with SARS-CoV-2 surface proteins and block the infectivity. Future, basic research and larger clinical trials of maoto for the treatment and prevention of COVID-19 will be important.

This study has some limitations. First, we could not prepare in advance a protocol for the use of maoto for COVID-19 prophylaxis because the cluster in this hospital happened suddenly. As we left the decision to use maoto up to the subjects, the number of control subjects was much smaller than that of the maoto group, and the subjects taking maoto may have a stronger awareness of infection control against COVID-19 than the control subjects. The day of starting maoto was delayed to mid-April, although it would have been better to start when the cluster was first identified. Clinical studies of chemical prophylaxis for COVID-19 have a major problem because it is not possible to know where or when a cluster will happen, and thus a protocol cannot be prepared in advance. Second, the infection zoning started three days before the start of PEP. It is possible that there was some effect on the reduction of COVID-19 due to the zoning and use of PPE [3,4]. We think the zoning would have taken time to become effective, probably in late April, because patients may be in the early incubation period when zoning is enforced, thus we think the intervention with maoto was the reason for the low number of infections seen. Chemical prophylaxis has the advantage of inhibiting COVID-19 in the incubation period.

5. Conclusion

This is a cohort study of maoto for three days as PEP for HCWs exposed to COVID-19 in the isolation wards of a hospital with a COVID-19 cluster. HCWs who became COVID-19-positive were significantly fewer in the maoto group than in the control group. This suggests that the short-term administration of maoto is effective as PEP for health care professionals working with patients suffering from COVID-19. Although some vaccines have proven highly effective, PEP will continue to be important for protecting HCWs at high risk of infection and for non-immunized populations.

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Authorship statement

All authors meet the ICMJE authorship criteria. Study concept and design: AN, AS, SN. Acquisition of data: AN, KI, YK, SM, SI, MI, TI. Statistical analysis: AN, AS, SN. Drafting and finalization of manuscript: AN, SN. Critical revision of the manuscript: all authors. Study supervision: SN. All authors have read and approved the final manuscript.

Declaration of competing interest

None.

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