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Relationship between COVID-19 and use of Chlorine Dioxide Gas-Releasing Agents in Elementary Schools

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Abstract- **Chlorine dioxide has an inactivating effect on various types of viruses in vitro, including severe acute respiratory syndrome coronavirus 2. Therefore, chlorine dioxide gas can be used as a new preventive measure against coronavirus disease 19 (COVID-19). However, no studies have been conducted to investigate the relationship between the incidence of COVID-19 and chlorine dioxide. We retrospectively studied the occurrence of COVID-19 in 164 public elementary schools under the jurisdiction of boards of education located in urban areas in Japan, provided with chlorine dioxide gas-releasing agents or not, from January to March 2022. The odds of developing COVID-19 were lower (odds ratio: 0.934, 95% confidence interval: 0.895–0.975) in schools provided with chlorine dioxide gas-releasing agents than in schools without them. This suggested a relationship between the use of chlorine dioxide-releasing agents and the incidence of COVID-19. Further studies are needed to prove a causal relationship between them.**

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I. Introduction

Since December 2019, coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Shang et al., 2020; Zhou et al., 2020) has been a global public health problem (Chen et al., 2020; Xu et al., 2020). Although pediatric patients with COVID-19 often have a milder course than adults, the COVID-19 infection has had a negative impact on children in terms of lost learning opportunities, malnutrition, poverty, and disruption of health services such as routine childhood immunizations (UNICEF, 2022). In the first and second waves of COVID-19 in Japan, the proportion of cases under 20 years of age was less than 15% (Imamura et al., 2021), and children did not suffer from secondary infections (Ko et al., 2022). However, in the sixth wave of the omicron variant, the proportion of cases under 20 years of age rose to 35% (Aizawa et al., 2022). Standard infection control measures include routine precautions such as hand washing, wearing masks, and environmental cleaning. Thorough implementation of these measures is important for the prevention of infection. However, it has been reported that young children often not wash properly their hands and hand washing is less effective. (Harada, 2004)

In addition, in terms of environmental cleaning, it is practically impossible to clean areas where hand contact occurs with high frequency, and standard precautions alone are not sufficient to prevent infection. Despite the prevalence of highly infectious variants in all age groups, parents are hesitant to vaccinate their children (Horiuchi et al., 2021; Yoda & Katsuyama, 2021). Therefore, to reduce the adverse effects of COVID-19 on children and prevent the spread of infection, it is desirable to reduce the incidence of COVID-19 through new preventive measures.

SARS-CoV-2 is transmitted among human beings primarily through close contact in confined spaces, droplets of respiratory origin, and contaminated surfaces (Cheng et al., 2020; Lai et al., 2020; Sungnak et al., 2020). SARS-CoV-2 can remain on the surface of the vector for several days (Chin et al., 2020; van Doremalen et al., 2020) and is stable for several hours if aerosolized (van Doremalen et al., 2020). Therefore, environmental factors can have a significant impact on transmission in buildings where people are in close proximity, such as schools (Azuma, Kagi, et al., 2020; Azuma, Yanagi, et al., 2020). Especially in Japan, during the sixth wave of SARS-CoV-2 infection, the proportion of infections in children in schools, nursery schools, and kindergartens increased, while the proportion of infection in the family, the main source of infection, decreased (Aizawa et al., 2022). Therefore, schools are considered an important place for the prevention of COVID-19 in children.

Chlorine dioxide (CD) exists as a diffusible gas at room temperature that can be distributed over a wide area (Gates, 1998). The effectiveness of low-concentration CD gas, which poses almost no risk to the human body, was demonstrated in an in vitro

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experiment in a closed space in which 0.01 ppmv CD gas inactivated more than 99% of all floating viruses (Ogata et al., 2016). More than 99% of the viruses adhering to the surface of objects were also inactivated by 0.007 ppmv CD gas (Morino et al., 2013).In vivo experiments suggested that 0.03 ppmv CD gas prevented influenza infection in mice (Ogata & Shibata, 2008). In vitro experiments using a CD gas-releasing agent have also shown inactivation of the avian influenza virus A (H7N9) (Sun et al., 2022). Further, studies in humans have suggested that the use of CD gas-releasing agents is effective against viral infections (Mimura et al., 2010; Ogata & Shibata, 2009).

Although CD gas-releasing agents can be expected to be useful for COVID-19 prophylaxis, no studies have been conducted to investigate the relationship between COVID-19 infection and CD gas-releasing agents. Therefore, the purpose of this study was to conduct a retrospective study of the relationship between the use of CD gas-releasing agents and the incidence of COVID-19 in elementary schools.

II. Material and Methods

a) Design

This multicenter, retrospective study investigated the relationship between the incidence of COVID-19 and the use of CD gas-releasing, from January to March 2022, using a database created by the City Board of Education. This study was approved by the Juntendo University School of Medicine Medical Research Ethics Committee (Research Project No. E22-0382).

b) Subjects

The subjects of this study were first- to sixth-grade (approximately 6 to 12 years old) male and female students in public elementary schools under the jurisdiction of a municipal board of education in an urban area in Japan. Since there was no precedent for this study, the sample size could not be calculated. No exclusion criteria were established as this was an exploratory study.

c) CD gas-releasing agent

CD gas-releasing agents (Cleverin® pro Gel Large type for 50m2(Taiko Pharmaceutical Co.) and Cleverin Pro Pouch type for 30 m2, Taiko Pharmaceutical Co., Ltd., Japan) are made by adding sodium dihydrogen phosphate to sodium chlorite and solidifying the mixture by adding superabsorbent polymers, which then generate and release CD gas continuously for several months. Those agents, which can be safely used in an inhabited environment, were provided free of charge by Taiko Pharmaceutical Co., Ltd. to city school boards for marketing purposes. They were further distributed by city school boards to elementary schools that requested them from January 2022 through March 2022. It was recommended that those agents be provided in classrooms at a rate of one unit per 30 m2 or 50 m2 in the case of Cleverin Pro Pouch type or Placeable type, respectively.

d) Incidence of COVID-19

The number of infections of COVID-19 was investigated in all elementary schools from January to March 2022. The parents of the children were requested to notify the schools when the PCR test for COVID-19 was positive, when the antigen test was positive, or when a physician determined that COVID-19 was strongly suspected. These reports were compiled by the elementary schools and reported to the city's board of education. The city school board created a database of the CD gas-releasing agents provided and the number of COVID-19 infections.

e) Statistical analysis

The distribution by a number of elementary school students was shown as the median (25th–75th percentile values), since the Kolmogorov-Smirnov normality test did not allow for a normal distribution. The association between the use of CD gas-releasing agents and the incidence of COVID-19 was analyzed using crude odds ratios of the subjects who suffered from COVID-19. Incidence as cases were defined as the number of reported COVID-19 incidences, and controls (non-incidence) were defined as the number of children minus the number of reported COVID-19 infections. The significance level was $p<0.05$, and IBM SPSS Statistics® ver. 28 was used for statistical analysis.

III. Results

A summary of the elementary schools analyzed in this study is shown in Table 1. Sixty-eight elementary schools (n = 34,810) did not use any CD gas-releasing agent, whereas 96 (n = 38,714) used those agents.

Table 2 shows the odds ratio for incident COVID-19. Elementary schools that did not use chlorine dioxide-releasing agents had higher odds (odds ratio: 0.934, 95% confidence interval: 0.895–0.975) of COVID-19 incidence than those that did.

IV. Discussion

This exploratory study investigated the relationship between the use of CD gas-releasing agents in classrooms and COVID-19 infections in elementary schools and showed that elementary schools that used those agents had significantly lower odds ratios for COVID-19 incidence than those that did not.

A previous study showed that in an intervention study of Ground Self-Defense Forces personnel, a group that used those CD gas-releasing agents in a room had significantly lower numbers of cases of influenza-like illnesses than the non-intervention group

(Mimura et al., 2010). In addition, a retrospective observational study of elementary school students reported significantly lower cumulative absenteeism rates in classes where those CD gas-releasing agents were used than in classes where they were not used (Ogata & Shibata, 2009). The results of this study support the findings of these previous studies. A potential mechanism by which the CD gas-releasing agent suppressed COVID-19 infections is that CD gas, once dissolved in water, reduces the binding activity of the SARS-CoV-2 spike protein as demonstrated in in vivo experiments (Ogata & Miura, 2020, 2021). It has been suggested that this mechanism can reduce the viral infectivity of SARS-CoV-2 (Hatanaka et al., 2021). In summary, these findings suggest that the use of CD gas-releasing agents in elementary school classrooms could be linked to lower COVID-19 infections in students.

The strength of this study is that it was a relatively large survey of many public elementary schools in the city. However, this study has several limitations. First, chlorine dioxide-releasing agents were distributed only to elementary schools that requested them, which may have biased the characteristics of the target population. Second, we did not have access to information from elementary schools located outside urban areas. Therefore, caution should be exercised when generalizing the results of this study. Moreover, the odds ratio could not be adjusted for confounding factors. Third, the route of infection was not considered. Hence, future randomized controlled trials should be conducted to evaluate the efficacy of CD gas-releasing agents against COVID-19.

V. Conclusion

A retrospective study in an urban elementary schools in Japan suggested that the use of chlorine dioxide gas-releasing agents may be linked to the reduced development of COVID-19 infections. Further studies are needed to prove a causal relationship.

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Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 19; CD, chlorine dioxide.

Conflict of Interest

Yoshinori Kubo, Takanori Miura, Norio Ogata, Jo Shibata, and Takashi Shibata received a salary from Taiko Pharmaceutical Co., Ltd., which manufactures the chlorine dioxide gas-releasing agents (Cleverin®) used in this study. Yoshinori Kubo, Takanori Miura, Kaoru Obinata, Ken Hisata, Mitsuyoshi Suzuki, Eisuke Inage, Naotake Yanagisawa, Jo Shibata, Takashi Shibata, Toshiaki Shimizu belong to the Department of Mass Infection Prevention, which is funded by Taiko Pharmaceutical Co., Ltd.

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Table 1: Characteristics

Chlorine dioxide releasing agent	Number of Elementary Schools	Number of students per elementary school			
		Total	Median	25th	75th
Not used	68	34,810	466	279	668
Used	96	38,714	332	236	526

Table 2: Odds ratio for incident COVID-19

CD gas-releasing agent	COVID-19		Odds ratio	95%CI	*p*-value
	Number of Incidences	Number of Controls			
Not used	4,787	30,023	Reference	-	
Used	5,019	33,695	0.934	0.895-0.975	0.0017