Potential of Arbidol for Post-exposure Prophylaxis of COVID-19 Transmission

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Abstract

Background: The efficient transmission of Severe Acute Respiratory Syndrome-2 Coronavirus (SARS-CoV-2) from patients to healthcare workers or family members has been a worrisome and prominent feature of the ongoing outbreak. On the basis of clinical practice and in-vitro studies, we postulated that post-exposure prophylaxis (PEP) using Arbidol is associated with decreased infection among individuals exposed to confirmed cases of COVID-19 infection.

Methods: We conducted a retrospective case-control study on family members and health care workers who were exposed to patients confirmed to have SARS-CoV-2 infection by real-time RT-PCR and Chest CT from January 1 to January 16, 2020. We collected demographic information, work location of exposure, post-exposure prophylaxis information, and symptoms, if any, 24 days after exposure. The relation between post-exposure prophylaxis and infection in household contacts and healthcare workers were respectively analyzed.

Results: 27 families and 124 health care workers had evidence of close exposure to patients with confirmed COVID-19. There were no differences in age, profession and sex distribution in the two groups with different post-exposure prophylaxis, table 1. Logistic regression based on the data of the family members and health care workers with Arbidol or Oseltamivir prophylaxis showed that Arbidol PEP was a strong protective factor against the development of COVID-19 (Odds ratio $0 \cdot 011$, 95% CI $0 \cdot 001$-$0 \cdot 125$, P=$0 \cdot 0003$ for family members and Odds ratio $0 \cdot 049$, 95%CI $0 \cdot 003$-$0 \cdot 717$), P= $0 \cdot 0276$ for health care workers). On the contrary, Oseltamivir was associated with an increase in COVID-19 infection (Odds ratio $20 \cdot 446$, 95% CI $1 \cdot 407$-$297 \cdot 143$, P= $0 \cdot 0271$).

Conclusions: Our findings suggest Arbidol could reduce the infection risk of the novel coronavirus in hospital and family settings. This treatment should be promoted for PEP use and should be the subject of further investigation.

Full Text

Potential of Arbidol for Post-Exposure Prophylaxis of COVID-19 Transmission: Preliminary Report of a Retrospective Case-Control Study

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Abstract

Objective: We hypothesized that post-exposure prophylaxis (PEP) using Arbidol is associated with reduced infection risk among individuals exposed to confirmed cases of COVID-19.

Methods: We conducted a retrospective case-control study on family members and healthcare workers exposed to patients with SARS-CoV-2 infection confirmed by real-time RT-PCR and chest CT from January 1 to January 16, 2020. We collected demographic information, exposure location, PEP details, and symptom development up to 24 days post-exposure. The relationship between PEP and infection was analyzed separately for household contacts and healthcare workers.

Results: Twenty-seven families and 124 healthcare workers had evidence of close exposure to confirmed COVID-19 patients. There were no differences in age, profession, or sex distribution between groups receiving different PEP regimens . Logistic regression analysis of family members and healthcare workers receiving Arbidol or Oseltamivir prophylaxis showed that Arbidol PEP was

a strong protective factor against COVID-19 (odds ratio 0.011, 95% CI 0.001-0.125, P = 0.0003 for family members and odds ratio 0.049, 95% CI 0.003-0.717, P = 0.0276 for healthcare workers). Conversely, Oseltamivir was associated with increased infection risk (odds ratio 20.446, 95% CI 1.407-297.143, P = 0.0271).

Limitations: Study limitations include its retrospective case-control design and potential selection bias due to telephone-based data collection.

Conclusions: Our findings suggest that Arbidol may reduce the risk of SARS-CoV-2 infection in both hospital and family settings. This treatment should be promoted for PEP use and warrants further investigation.

Keywords: Arbidol; COVID-19; SARS-CoV-2; Post-exposure prophylaxis

Introduction

Literature and clinical evidence indicate that person-to-person transmission of SARS coronavirus 2 (SARS-CoV-2), the pathogen causing COVID-19, is highly efficient. A study of 1,099 patients with laboratory-confirmed COVID-19 in China found that 31.30% had traveled to Wuhan and 71.80% had contact with people from Wuhan [1], the outbreak's source city. Family transmission of COVID-19 is particularly efficient; in one report of a family of six that traveled to Wuhan, five members were infected [2]. Transmission aboard the Diamond Princess cruise ship may serve as a model for understanding SARS-CoV-2 transmission efficiency in dense hospital environments housing thousands of patients and healthcare workers. More than 3,600 passengers were quarantined on the cruise ship beginning February 4, after the primary case was confirmed on February 1. Following a 14-day quarantine period, 624 people tested positive for SARS-CoV-2 [3].

Quarantine and post-exposure prophylaxis (PEP) are options to prevent disease transmission. Oseltamivir is a well-known PEP agent for influenza infections [4]; however, no pharmacologic agent has been demonstrated to prevent COVID-19 transmission after unprotected exposure. Arbidol (Umifenovir) is a broad-spectrum antiviral agent widely used in China for influenza treatment and, more recently, for its potential efficacy against COVID-19. Several in vitro studies indicate that Arbidol possesses inhibitory effects against coronaviruses [5-7], and its derivative, arbidol mesylate, demonstrates even stronger activity against SARS-CoV [7]. One study reported that Arbidol's therapeutic index (or selectivity index) against coronaviridae was 11.8, substantially higher than against orthomyxoviridae (2.4 for influenza A/Aichi/2/68 [H3N2] and 2.5 for B/Beijing/184/93) [4]. Clinical trials on Arbidol's efficacy for COVID-19 treatment are ongoing. Given increasing awareness of Arbidol, healthcare workers and the public have begun using it for both treatment and PEP. We conducted this retrospective case-control study to evaluate the potential efficacy of Arbidol PEP in reducing SARS-CoV-2 transmission.

2.1 Definition and Identification of Cases and Controls

We analyzed two case-control cohorts: family members and healthcare workers. In the first cohort, cases were family members of confirmed COVID-19 patients who became infected after exposure, while controls were exposed family members who did not become infected. Each of the 27 families had one primary confirmed COVID-19 case. The families included in the analysis had consulted our hospital regarding PEP and potential treatment options for COVID-19 .

The second case-control cohort comprised 124 healthcare workers at Wuhan Union Hospital (WHUH) initially exposed to a cluster of COVID-19-infected colleagues without standard respiratory protection. Cases were workers who became infected, and controls were workers who did not. All source patients (primary cases and the healthcare worker cluster) were infected between January 1 and January 16, 2020.

2.2 Data Collection

For all cases and controls, we collected demographic information, details of how and where the primary case was diagnosed, PEP usage among family members or healthcare workers (including specific individuals), medications used, dosages, and treatment duration. We also inquired about the development of fever and/or respiratory symptoms for up to 24 days post-exposure, which represents the longest reported incubation period for COVID-19 [1]. Data collection was conducted via telephone interviews. COVID-19 diagnosis was confirmed by real-time RT-PCR of sputum or throat swab samples [8,9] together with viral pneumonia findings on chest CT.

2.3 Statistical Analysis

We excluded all primary cases from the analysis. Chi-square tests and logistic regression were performed using R 3.3.0, with infection status (COVID-19 infected vs. not infected) as the dependent variable and age stratification, gender, time delay to PEP initiation, adult/child status (for family members), Arbidol PEP, and non-Arbidol PEP as independent variables. $P < 0.05$ was defined as statistically significant. Missing data were coded as "unknown" and subjects were retained in the logistic regression analysis.

3.1 General Characteristics of Cases and Controls

We surveyed 27 families with one primary COVID-19 case and collected data from 66 family members . Thirteen family members were cases and 53 were controls . Overall, 45 family members used Arbidol PEP and one became infected , while 21 family members used Oseltamivir or no PEP and 12 became infected

. Univariate analysis showed no significant differences in gender (P = 0.09), age (P = 0.25), or adult/child distribution between cases and controls (P = 0.22) .

We analyzed data from 124 healthcare workers ; 55 used Arbidol PEP and one became infected, while 68 used Oseltamivir and seven became infected . There was no significant difference in gender (P = 0.15), age (P = 0.60), or professional distribution (doctor vs. nurse) between cases and controls (P = 0.74). All cases worked in the inpatient department (IPD), while controls were distributed across the fever clinic, quarantine ward, and inpatient ward. There was no statistically significant difference in workplace distribution between the two groups (P = 0.07) .

3.2 Logistic Regression

Logistic regression demonstrated that age stratification, gender, PEP dosage, PEP duration, time from COVID-19 case confirmation to PEP initiation, and healthcare worker occupation were not statistically significant predictors of infection outcome . The only significant factor was the medication used for PEP. Arbidol demonstrated a very strong protective effect against COVID-19 infection (odds ratio 0.011, 95% CI 0.001-0.125, P = 0.0003 for family members and odds ratio 0.049, 95% CI 0.003-0.717, P = 0.0276 for healthcare workers) . In the healthcare worker cohort, Oseltamivir prophylaxis was not protective and was associated with increased infection risk (odds ratio 20.446, 95% CI 1.407-297.143, P = 0.0271) .

3.3 Post-Exposure Prophylaxis Dosages

There were no differences in dose, treatment duration, or PEP delay time after diagnosis of the primary case between family and healthcare worker cohorts with or without Arbidol PEP, as shown in Tables 3 and 5. Arbidol PEP dosage among healthcare workers was more consistent: all but one used 200 mg three times daily (Tid) for 5-10 days (one person used 100 mg Tid for 7 days). All individuals who chose Oseltamivir PEP used 75 mg once daily (Qd).

Discussion

Wuhan Union Hospital was among the first in China to recommend compassionate use of Arbidol for patients with confirmed or suspected COVID-19. The early release and subsequent publication of the “Therapeutic and Triage Strategy for 2019 Novel Coronavirus” by WHUH [10] helped healthcare workers identify a potential approach for post-exposure prophylaxis, and this information was disseminated to community families directly or indirectly through hospital staff.

The low odds ratios for both family members and healthcare workers using Arbidol PEP suggest a strong protective effect against COVID-19 transmission. In

contrast, the odds ratio for healthcare workers using Oseltamivir PEP was substantially higher (20.446). However, it is difficult to conclude that Oseltamivir increases susceptibility to COVID-19 infection. Work location may have played a significant role in disease transmission despite lacking statistical significance in our analysis. The neurology department where the healthcare worker infection cluster originated is located in the internal medicine building, which houses 800 beds. All healthcare workers using Arbidol prophylaxis worked in the fever clinic and quarantine ward with proper protection, while those taking Oseltamivir worked in the inpatient building where protection protocols were less stringent than in high-exposure areas. Considering the transmission model observed on the Diamond Princess cruise ship [3], a likely explanation is that infected healthcare workers experienced continuous exposure in a high-risk inpatient environment without adequate protection. Additionally, workers in the fever clinic and quarantine ward may have been more vigilant about PEP adherence than their inpatient ward counterparts.

Study limitations include the retrospective case-control design and potential selection bias due to telephone-based data collection. We did not assess family members' awareness of Arbidol PEP, which may have influenced their decision to choose Oseltamivir instead. The significant association between Arbidol PEP and COVID-19 transmission prevention necessitates a well-designed, large-scale prospective study to further validate Arbidol for post-exposure prophylaxis.

Conclusions

Our findings suggest that Arbidol may reduce the risk of SARS-CoV-2 infection in both hospital and family settings. This treatment should be promoted for PEP use and warrants further investigation.

Author Contribution Statement: Wenjing Wang, Yanan Li, and Yifan Zhou conducted the literature search; Bo Hu and Jinnong Zhang conceived the study; Jinnong Zhang, Bo Hu, and Bo Peng designed the study; Yisheng Zhang, Yanan Li, Yifan Zhou, Wenjing Wang, Yan Wan, Yaling Wang, and Ling Mao collected data; Jiang Chang, Wei Peng, and Xiaoping Miao analyzed data; Bo Hu, Jinnong Zhang, and Bo Peng interpreted data; Jinnong Zhang, Bo Hu, Wei Peng, Bo Peng, Wenjing Wang, Yanan Li, and Yifan Zhou wrote the manuscript.

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Table 1: Evidence of post-exposure prophylaxis potential of Arbidol on COVID-19 transmission in families with household contact

Family ID	Primary Case*	Family Members (gender and age)	Who on Chemo-prophy-laxis	Delay Days of PEP	ABD Chemo-prophylaxis, Dosage, Length	Outcome (24 days post-exposure)
FamilyYCb	Primary case (M, 58)	Wife (F,58)	Wife	1	ABD, 0.2g, Tid, 7 ds	No symptom
FamilyZYc	Primary case (F, 66)	Husband (M,69)	Husband	6	ABD, 0.2g, Tid, 14 ds	No symptom
FamilyCXLe	Primary case (F, 30)	Husband (M,31)	Husband	1	ABD, 0.2g, Tid, 5 ds	No symptom
FamilyHLBg	Primary case (F, 27)	Wife (F,28)	Wife	1	ABD, 0.2g, Tid, 10 ds	No symptom
FamilyZYg	Primary case (M, 44)	Wife (F,39), Mother (F,62), Father (M,62), Daughter (F,8), Brother (M,35), Sister-in-law (F,34), 2 Nieces (F,12 and F,6)	All on PEP	8	ABD, 0.2g, Tid, 8 ds (adults); 0.1g, Tid, 8 ds (children)	No symptom for all
FamilyLQHg	Primary case (F, 54)	Husband (M, unclear), Son (M, unclear)	Husband and son	9	ABD, 0.2g, Tid, 14 ds	No symptom
FamilyWJg	Primary case (M, 40)	Wife (F,38), Father (M,76), Mother (F, unclear), Son (M,18)	Father, mother, wife, son	6	ABD, 0.2g, Tid, 4 ds	No symptom

Family ID	Primary Case*	Family Members (gender and age)	Who on Chemo-prophy-laxis	Delay Days of PEP	ABD Chemo-prophylaxis, Dosage, Length	Outcome (24 days post-exposure)
FamilyFJg	Primary case (M, 44)	Mother (F,69), Uncle (M,52)	Mother and uncle	3	ABD, 0.2g, Tid, 5 ds	All no symptom
FamilyCJPg	Primary case (F, 40)	Mother (F,69), Husband (M,40), 2 Kids (unclear)	Mother and husband	1	ABD, 0.2g, Tid, 14 ds	Husband confirmed COVID-19, kids showed no symptom
FamilyJXe	Primary case (F, un-clear)	Husband (M,31)	Husband	10	ABD, 0.2g, Tid, 4 ds	No symptom
FamilyFQCg	Primary case (F, 37)	Mother (F,60), Father (M,63)	Mother	13	ABD, 0.2g, Tid, 5 ds	Father confirmed COVID-19
FamilyWML	Primary case (M, 62)	Wife (F,45), 2 Kids (unclear, 12 and 14)	Wife	2	ABD, 0.2g, Tid, 6 ds	All no symptom
FamilyHZYg	Primary case (F, 68)	Daughter (F,40), Son (M,38)	Daughter	3	ABD, 0.2g, Tid, 4 ds	Son confirmed COVID-19
FamilyWCYg	Primary case (F, 81)	Husband (M,69)	Husband	1	ABD, 0.2g, Tid, 7 ds	No symptom
FamilyYMg	Primary case (F, 67)	Son (M,41), Daughter-in-law (F,42), 2 Grandchil-dren (unclear, 12 and 16)	Son, daughter-in-law, 2 grand-children	9	ABD, 0.2g, Tid (adults); child aged 12: 0.1g, Tid, 5 ds	All no symptom

Family ID	Primary Case*	Family Members (gender and age)	Who on Chemo-prophy-laxis	Delay Days of PEP	ABD Chemo-prophylaxis, Dosage, Length	Outcome (24 days post-exposure)
FamilyLZHe	Primary case (M, 48)	Wife (F,45)	Husband (M,69), Son (M,41), Daughter-in-law (F,39), Grand-son (M,6)	6	ABD, 0.2g, Tid, 6 ds	All no symptom
FamilyLMf	Primary case (F, 63)	Husband (M,65), Daughter (F,36), Son-in-law (M,37)	Husband, daugh-ter, son-in-law	1	ABD, 0.2g, Tid, 9 ds	All no symptom
FamilyLMg	Primary case (F, 42)	Husband (M,41), Daughter (F,12)	Husband and daugh-ter	9	ABD, 0.2g, Tid, 5 ds	No symptom
FamilyFXLg	Primary case (F, 31)	Mother (F,68), Husband (M,32)	Mother and husband	6	ABD, 0.2g, Tid, 6 ds	No symptom
FamilyCXLg	Primary case (F, 36)	Husband (M,38)	Husband	5	ABD, 0.2g, Tid, 6 ds	No symptom
FamilyZDHg	Primary case (M, 34)	Wife (F,33)	Wife	11	ABD, 0.2g, Tid, 5 ds	No symptom

The primary cases of COVID-19 were confirmed by SARS-CoV-2 RT-PCR positive in throat swab and viral-like pneumonia in chest CT.

Footnotes: a Both are clinical doctors; wife took Arbidol for prophylaxis on husband's advice; the husband is an expert in respiratory and emergency medicine.
b A family with no medical knowledge; daughter inquired about COVID-19 treatment strategy from an expert in respiratory and emergency medicine and

took Arbidol 0.4 g Qd for prophylaxis without physician advice.
c A family with no medical knowledge; husband inquired about COVID-19 treatment strategy from an expert in respiratory and emergency medicine.
d A family with no medical knowledge; wife was exposed to the same index patient as the wife in Family ZY.
e Patient is a clinical doctor or nurse who inquired about treatment strategy from a reference source.
f Wife is a clinical doctor; grandmother took Arbidol on her advice.
g A family with no medical knowledge; family members inquired about treatment strategy through online consultation and advice from physician friends.

ABD = Arbidol, **OSTV** = Oseltamivir, **F** = Female, **M** = Male

Table 2: Demographic data and characteristics of the subjects

Characteristic	Healthcare Workers (n=124)	Family Members (n=66)
	Case (n=8)	Control (n=116)
Age (years), mean ± SD	35.1 ± 4.2	34.3 ± 7.7
Age stratification		
Unknown	0 (0.0)	0 (0.0)
Adulthood	8 (100.0)	116 (100.0)
Gender, n (%)		
Female	3 (37.5)	20 (17.2)
Unknown	0 (0.0)	0 (0.0)
Occupation		
Doctor	3 (37.5)	37 (31.9)
Nurse	5 (62.5)	79 (68.1)
Others	0 (0.0)	0 (0.0)
Working place		
Fever clinic	0 (0.0)	22 (19.0)
Quarantine ward	0 (0.0)	26 (22.4)
Inpatient department (IPD)	8 (100.0)	68 (58.6)

Chi-square test; IPD = Inpatient department; NA = not applicable

Table 3: Arbidol chemoprophylaxis in the members of community family

Variable	Arbidol (n=45)	Case (n=1)	Controls (n=44)
Dose (mg), mean ± SD	560.0 ± 0.1	600.0 ± 0.0	560.0 ± 0.1
Days with Arbidol, mean ± SD	6.9 ± 2.8	14.0 ± 0.0	6.8 ± 2.8

Variable	Arbidol (n=45)	Case (n=1)	Controls (n=44)
Time with Arbidol			
< 7 days	26 (59.1)	0 (0.0)	26 (59.1)
≥ 7 days	18 (40.9)	1 (100.0)	17 (38.6)
Days to prophylaxis, mean ± SD	6.0 ± 3.2	1.0 ± 0.0	6.1 ± 3.2
Time of delay			
< 5 days	14 (31.8)	1 (100.0)	13 (29.5)
≥ 5 days	30 (68.2)	0 (0.0)	30 (68.2)

Chi-square test; digits in parentheses are percentages if not defined; NA = not applicable

Table 4: Relation between Arbidol prophylaxis and infection in community family

Treatment	COVID-19 Infected No. (%)	Control No. (%)	OR (95% CI)*	P-value
No Arbidol	12 (92.3)	9 (17.0)	1.00 (Reference)	
Arbidol	1 (7.7)	44 (83.0)	0.011 (0.001-0.125)	0.0003

Logistic regression calculations, gender, age and occupation adjusted; No. = Number

Table 5: Arbidol or Oseltamivir chemoprophylaxis in health care workers

Variable	Oseltamivir (n=68)	Arbidol (n=55)
	Case (n=7)	Control (n=61)
Dose (mg), mean ± SD	75.00 ± 0.00	75.00 ± 0.00
Days with Arbidol/Oseltamivir, mean ± SD	9.67 ± 4.22	10.57 ± 2.28
Time with Arbidol/Oseltamivir		
< 10 days	1 (14.3)	4 (6.6)
= 10 days	4 (57.1)	46 (75.4)
>10 days	1 (14.3)	11 (18.0)
unknown	1 (14.3)	0 (0.0)
Days to prophylaxis, mean ± SD	2.60 ± 2.88	3.75 ± 5.39
Time of delay (days)		
= 0 day	1 (14.3)	34 (55.7)
1-5 days	2 (28.6)	6 (9.8)
> 5 days	1 (14.3)	21 (34.4)
unknown	2 (28.6)	0 (0.0)

Chi-square test; digits in parentheses are percentages if not defined; NA = not applicable

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Table 6: Relation between Arbidol and Oseltamivir for prevention of COVID-19 infection in health care workers

Treatment	COVID-19 Infection No. (%)	Control No. (%)	OR (95% CI)*	P-value
Oseltamivir	7 (87.5)	61 (53.0)	1.00 (Reference)	
Arbidol	1 (12.5)	54 (47.0)	0.049 (0.003-0.717)	0.0276

Logistic regression calculations, gender, age, occupation and working place adjusted; No. = Number

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Table 7: Relation between two forms of preventive treatment (Oseltamivir or Arbidol) and COVID-19 infection in health care workers

Treatment	COVID-19 Diagnosed No. (%)	Normal No. (%)	OR (95% CI)*	P-value
Oseltamivir	1 (12.5)	55 (47.4)	1.00 (Reference)	
Arbidol	7 (87.5)	61 (52.6)	20.446 (1.407-297.143)	0.0271

Logistic regression calculations, gender, age, occupation and working place adjusted; No. = Number

Note: Figure translations are in progress. See original paper for figures.