

# Comparison of Viral Clearance between Ivermectin with Doxycycline and Hydroxychloroquine with Azithromycin in COVID-19 Patients

MA RAHMAN<sup>a</sup>, SA IQBAL<sup>b</sup>, MA ISLAM<sup>c</sup>, MK NIAZ<sup>d</sup>, T HUSSAIN<sup>e</sup>, TH SIDDIQUEE<sup>f</sup>

### Abstract:

**Introduction:** The whole world is on the brink of collapse due to the outbreak of COVID-19 with no solution to treat these cases with any specific drug. Extensive search for the vaccine or effective treatment is going on while alarming infection and death toll is rising every day.

**Aim:** The study will compare the effect of Ivermectin with Doxycycline and Hydroxychloroquine with Azithromycin on a selective group of COVID-19 positive patients.

**Method:** This is a comparative study that included 400 patients of COVID-19 positive patient who were divided in to two groups. Group-A Received Ivermectin with Doxycycline and the other group-B received hydroxychloroquine (HCQ) with azithromycin.

**Result:** Viral clearance is 132 (66%) on day 5 and 167 (83.5%) on day 6. Among them 33 (16.5%) remain PCR positive after 6th day of Ivermectin ingestion in Group A. Whereas there is 154 (77.0%) viral clearance at 11th day and

163 (81.5%) viral clearance at 12th day of Hydroxychloroquine ingestion in Group B. Among them 37 (18.5%) remain PCR positive after 12 day in group B. The P value is 0.000427 which is significant considering 5th day viral clearance of Ivermectin ingestion and 11th day of Hydroxychloroquine ingestion. But considering 6th day and 12th day the P-value is 0.59 which is not significant.

**Conclusion:** It appears Ivermectin and Doxycycline is safe and effective combination drug therapy in COVID-19 infected patients but need further extensive study to find out the scope of application on other groups of patients.

**Keywords:** COVID-19, Ivermectin, Hydroxychloroquine, Doxycycline, Doxycycline Azithromycin Hydroxychloroquine with Azithromycin

(J Bangladesh Coll Phys Surg 2020; 38: 5-9)

DOI: <https://doi.org/10.3329/jbcps.v38i0.47514>

### Introduction:

While the world is awaiting a vaccine, the death toll is rising day by day. We need to find effective drugs to treat coronavirus disease-19 (COVID-19). Several drugs have been proposed and practiced worldwide but none is confirmed or approved. In this study we are looking for an answer for the large group of population of this poor country.

A novel coronavirus 2019-nCoV was first identified in the state of Wuhan, China, at the end of 2019. Coronaviruses are basically a group of viruses containing nonsegmented, single-stranded RNA. These groups of viruses caused several outbreaks around the world, like 'Severe Acute Respiratory Syndrome (SARS) pandemic' in 2002-2003 and the 'Middle East Respiratory Syndrome (MERS) outbreak' in South Korea in 2015. But most recently, COVID-19 triggered an outbreak in China in December 2019, subsequently become pandemic. Though some of corona patient reached in to devastating epidemics outcome, but others manifested mild to moderate respiratory infections, like the common cold.<sup>1</sup>

Ivermectin is a broad spectrum anti-parasitic agent<sup>2</sup> seems to have some anti-viral activities against a large number of viruses<sup>3,4,5,6</sup> in vitro. Originally identified as an inhibitor of interaction between the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and the importin (IMP) heterodimer responsible for IN nuclear import.<sup>7</sup> Studies on SARS-CoV proteins have

- Md Azizur Rahman, Adv Spl in Medicine & Pulmonology, Brigadier General
- Syed Asif Iqbal, Chief Physician General, Brigadier General
- Md Azizur Islam, Consultant Physician General, Major General
- MD. Kaiser Niaz Classified Specialist Medicine, Major.
- Tahmeed Hussain Classified Specialist Medicine, Major.
- Taufiqul Hasan Siddiquee, Commandant CMH, Brigadier General

**Address of the Correspondence:** Brigadier General Md Azizur Rahman, Adviser Specialist in Medicine & Pulmonology, CMH, Dhaka. E-mail: [majazizur765@yahoo.com](mailto:majazizur765@yahoo.com)

revealed a potential role for IMPá/â1 during infection in signal dependent nucleocytoplasmic shuttling of the SARS-CoV nucleocapsid protein,<sup>8,9,10</sup> that may impact host cell division,<sup>11,12</sup> addition of the SARS-CoV accessory protein ORF6 has been shown to antagonize the antiviral activity of the STAT1 transcription factor by sequestering IMPá/â1 on thorough ER/ Golgi membrane.<sup>13</sup> Taken together, these reports suggested that Ivermectin's nuclear transport inhibitory activity may be effective against SARS-CoV-2. When doxycycline was combined with macrocyclic lactones in adult worms, ivermectin efficacy was 80% compared with 9% when treatment was performed with doxycycline alone.<sup>14</sup> The largest dose intensity with registered pharmacokinetic parameters in healthy subjects is 120 mg, corresponding to up to 2000 µg/kg.<sup>15</sup>

HCQ has shown antiviral effects at both preinfection and postinfection stages. HCQ could interfere with the glycosylation of angiotensin-converting enzyme 2, thereby reducing the binding efficiency between angiotensin-converting enzyme 2 on host cells and the SARS-CoV-2 spike protein. Moreover, HCQ could be able to block virus fusion with the host cell through the inhibition of protease activity in cleaving corona virus surface spike proteins.<sup>16</sup>

Far less is known about the antiviral effects of azithromycin, which has been suggested to interfere with influenza virus internalization.<sup>17</sup> Interestingly, CLQ is also considered as an inhibitor of endocytic pathways through an elevation of endosomal pH.<sup>18</sup> azithromycin was added to hydroxychloroquine, the efficiency of SARS CoV-2 elimination was significantly improved.<sup>19</sup>

Regarding diagnosis till now no test is gold standard making it more challenging in diagnosing the disease. Specificity of RT-PCR is dependent on site, like 63% for nasal swabs, and only 32% for throat/ pharyngeal swabs.<sup>20</sup>

#### Method:

It's a **prospective comparative** study conducted at Combined Military Hospital Dhaka. Total 400 Covid-19 PCR positive patients were included in this study. Among them 200 cases received **ivermectin 18 mg** on first day and Doxycycline 100 mg twice daily for 05 days comprising Group A and the rest 200 patients were given hydroxychloroquine 800 mg on first day then 400mg daily

for 10 days and azithromycin 500 mg one day then 250 g daily for 4 days comprised Group B. Diagnosis of Covid-19 was done by RT-PCR from nasal and pharyngeal swab. The patients who had mild to moderate disease according to 'National Guideline on clinical management of coronavirus disease 2019 (COVID-19) version 7.0' were included in this study. Severe and critical patients were excluded from the study. Patients were admitted in corona ward in April 2020 were given RT-PCR on 11th day and 12th day in Group B after completion of the recommended dose. Whereas the PCR test were done on 5th and 6th day after ingestion of Ivermectin in corona ward during May 2020 in Group A. The date of check Rt-PCR was determined by the recommended dose of different drugs used in this study.

#### Result:

Total 400 patients were included in this study. None developed severe or critical disease during study.

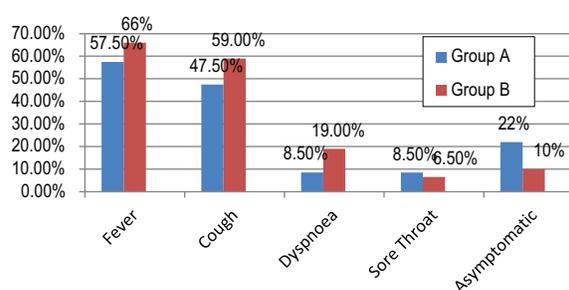
**Table-I**

*Demographic profile (n=400)*

Demographic profile	Group A	Group B
Mean age in years	36.4	39.42
Age range in years	17-74	20-79
Male	78.5%(157)	188(94%)
Female	21.5%(43)	12(6%)

Above table shows demographic profile in which 78.5% (157) were male; 21.5% (43) were Female in Group A and 188 (94%) male and 12 (6%) female in group B. Their age range was 17-74 with mean 36.46 years in group A and in group B age range 20-79 with mean 39.42 years.

Symptoms of the patients during admission (n=400)



**Fig-1:** Showing Symptoms of Patient during admission

It shows that maximum patient had fever 57.5% and 66% in group A and B. Then next common symptom was Cough 47.5% and 59%. There were 22% patient who had no Covid symptoms in group A and only 10% in group B

Co-Morbidities of the patients (n=400)

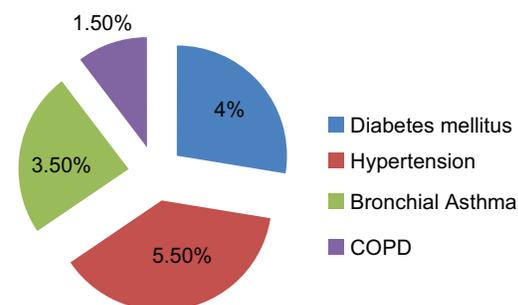


Fig.-2: Pie chart Showing Co-morbidities of Group A

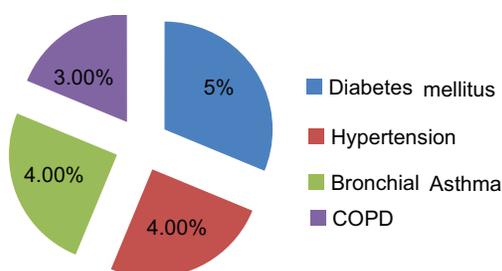


Fig.-3. Pie chart showing Co- morbidities of Group B

Among the patients 11 (5.5%) had hypertension in group A and 8 (4%) in Group B, 8 (4%) and 10 (5%) had diabetes mellitus respectively, 7 (3.5%) and 8 (4%) had Bronchial Asthma and 3 (1.50%) and 6 (3%) had COPD.

Viral Clearance of Group A and B (n=400)

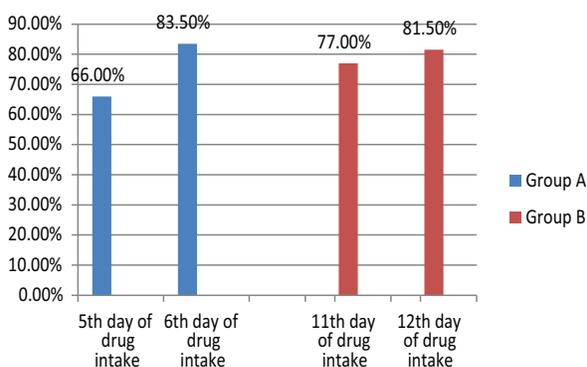


Fig.-4: showing Viral Clearance

Diagram showing viral clearance is 132 (66%) on day 5 and 167 (83.5%) on day 6. Among them 33 (16.5%) remain PCR positive after 6th day of ivermectin ingestion in Group A. Whereas there is 154 (77.0%) viral clearance at 11th day and 163 (81.5%) viral clearance at 12th day of hydroxychloroquine ingestion in Group B. Among them 37 (18.5%) remain PCR positive after 12 day in group B. The P value is 0.000427 which is significant considering 5th day viral clearance of ivermectin ingestion and 11th day of hydroxychloroquine ingestion. But considering 6th day and 12th day the P-value is 0.59 which is not significant.

Table-II

Uncommon Symptoms in Group A and B			
Group A (n=200)		Group B (n=200)	
Symptoms	n (%)	Symptoms	n (%)
Anorexia	47 (23.5)	Anorexia	62 (31)
Vomiting	7 (3.5)	Vomiting	4 (2)
Diarrhoea	24 (12)	Diarrhoea	14 (7)
Skin Rash	20 (10)	Skin Rash	2 (01)

Above table shows some uncommon symptoms of the disease which can also be considered as drug effect due to sharing of the nature of presentation where anorexia (23.5% and 31%) is the predominant feature is also a documented symptoms of Covid. Next effect was diarrhea (12%) in group A. Others were skin rash (10% and 1%) and vomiting (3.5% and 2%).

Table-III

Group A	Group B	
	Mean	Mean
Serum Bilirubin	0.55±0.19 mg/dl	0.58±0.07 mg/dl
ALT	34.16±21.7 IU/l	29.16±18.8 IU/l
ALP	79.95±28.56 IU/l	88.6±23.77 IU/l
GGT	51.23±56.18 IU/l	49.23±66.18 IU/l
INR	1.142±0.084	1.1±0.062
Serum Creatinine	0.87±0.33 mg/dl	0.91±0.44 mg/dl

Above table showing the distribution of the liver and renal biochemical parameters in Group A and B. It shows that Bilirubine level is 0.55 mg/dl and 0.58 mg/dl respectively. ALT level is 34.16 IU/L and 29.16 IU/L. ALP is 79.95 and 88.6 IU/L in group A and B. GGT is 51.23 IU/L and 49.23 IU/L. INR is 1.14 and 1.1 respectively.

Creatinine is 0.87 mg/dl and 0.91 mg/dl in Group A and group B.

### Discussion:

The search of effective anti-viral treatment against COVID-19 has led us to look into the existing drugs with anti-viral properties which may be effective against this novel CORONA virus. Ivermectin is a well-established anti-parasite drug used in both human and livestock animals. In-vitro studies have found profound anti-viral effect of this drug against several RNA viruses including SARS-CoV-2. Doxycycline has been claimed to have antiviral properties by several mechanisms. It may also have a role of the anti-inflammatory effect of doxycycline in COVID-19 infection. In this study, 200 patients received the combination of ivermectin (18 mg single dose) and Doxycycline (100 mg twice daily for 5 days). Majority (78.5%) were male, mean age was 36 years (range 17 to 74 years). Fever (57.5%) was the commonest symptom followed by cough (47.5%), sore throat (8.5%), dyspnoea (8.5%). A significant number of patients (22%) were asymptomatic (Non-specific symptoms) in Group-A. On 5th and 6th day viral clearance were achieved by 66% and 83.5% respectively. Ivermectin and doxycycline combination were well tolerated by the patients though some unusual symptoms were seen might have been attributed to the effect of drugs or to rare Covid related symptoms which were anorexia (23.5%), diarrhoea (12%), skin rash (10%) and vomiting (3.5%). No significant renal or hepatic impairment was found. Ivermectin was found to be safe at current dose. In Group-B Fever (66%) was also the commonest symptom followed by cough (59%), sore throat (6.5%), dyspnoea (19%). Asymptomatic (Non-specific symptoms) patients were only 10%. The effect of hydroxychloroquine (HCQ) with or without azithromycin, on COVID-19 was promising in several studies where HCQ and azithromycin showed earlier viral clearance than placebo. In this study, 200 patients received HCQ & azithromycin combination. Mean age was 39.4 years (range 20-79 years) and 94% were male. All had mild to moderate disease. Viral clearance by RT-PCR of nasal and pharyngeal swab were 77% at day 11 and 81.5% at day 12. No major adverse effect were observed other than minor overlapping symptoms (anorexia 31%, diarrhoea 7%, vomiting 2%, skin rash 1%). In this study only mild to moderate COVID-19 cases were included. Ivermectin and doxycycline

combination was associated with earlier viral clearance than HCQ & azithromycin combination. No severe adverse effect was observed in either group. This is a new study; So far no definite study was found on human being affecting viral clearance of covid-19. This is an observational study and we have chosen very low dose of ivermectin keeping consideration of individual safety. The exact dose which will be absolutely beneficial for viral clearance of covid-19 on human being needs to be determined in future by further control study.

### Limitations

There are few limitations of the study like a) no severe cases were included in this study, b) effect of drug combination on clinical follow up outcome were not assessed and compared, c) false negative result could not be excluded and d) cardiac effect due to drugs could not be monitored. e) Effective dose of Ivermectin to clear virus not measured.

### Conclusion:

Ivermectin and Doxycycline is a safe combination and found effective in early viral clearance in mild to moderate COVID-19 patients. On the other hand Hydroxychloroquine (HCQ) and Azithromycin was also found safe but took more time in viral clearance and it itself might put extra adverse effect on already compromised heart from viral effect. Nevertheless further control study is required to know more about the effects of ivermectin and doxycycline on covid-19 patient.

### References:

1. Shrikrushna et al. 2020. A review on corona virus (covid-19). *wjpls*, 2020, Vol. 6, Issue 4, 109-115
2. Gonzalez Canga, A., et al., 2008. The pharmacokinetics and interactions of ivermectin in humans—mini review. *AAPS J.* 10(1),42–46
3. Gotz, V., et al., 2016. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Sci. Rep.* 6, 23138.
4. Lundberg, L., et al., 2013. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. *Antivir. Res.* 100(3),662–672.
5. Tay, M. Y., et al., 2013. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antivir. Res.* 99(3),301–306.
6. Wagsta, K. M., et al., 2012. Ivermectin is a specific inhibitor of importin alpha/beta-mediated nuclear import to

- inhibit replication of HIV-1 and dengue virus. *Biochem. J.* 443(3),851–856.
7. Wagstaû ,K. M.,et al., 2011. An Alpha Screen (R)-based assay for high-through put screening for speciûc inhibitors of nuclear import. *J. Biomol. Screen* 16(2),192–200.
  8. Rowland, R .R.,et al., 2005. Intra cellular localization of the severe acute respiratory syndrome corona virus nucleocapsidprotein : absence of nucleolar accumulation during infection and after expression as a recombinant protein in verocells *J. Virol.* 79(17),11507–11512.
  9. Timani, K.A. ,et al., 2005. Nuclear / nucleolar localization properties of C-terminal nucleocapsid protein of SARS corona virus. *Virus Res.* 114(1–2),23–34.
  10. Wulan, W. N.,et al., 2015. Nucleocytoplasmic transport of nucleocapsid proteins of enveloped RNA viruses. *Front. Microbiol.* 6,553.
  11. Hiscox, J. A., et al., 2001. The corona virus infectious bronchitis virus nucleoprotein localizes to the nucleolus. *J. Virol.*75(1),506–512.
  12. Wurm,T.,et al., 2001. Localization to the nucleolus is a common feature of corona virus nucleoproteins, and the protein may disrupt host cell division. *J. Virol.*75(19), 9345–9356.
  13. Frieman, M., et al., 2007. Severe acute respiratory syndrome corona virus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum / Golgi membrane. *J. Virol.* 81(18),9812–9824.
  14. Menozzi A, Bertini S, Turin L, Serventi P, Kramer L, Bazzocchi C. Doxycy-cline levels and anti Wolbachia antibodies in sera from dogs experimentallyinfected with *Diroûlaria immitis* and treated with a combination of ivermectin/doxycycline. *Vet Parasitol* 2015;209: 281–4.
  15. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol* 2002;42: 1122-33.
  16. Zhou D, Dai SM,Tong Q. COVID-19:a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrobechemother* .2020: dkaa 114.
  17. DH Tran, R Sugamata, T Hirose, S Suzuki, Y Noguchi, A Sugawara, et al.Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process *J Antibiot (Tokyo)*, 72 (2019), pp. 759-768,
  18. M Mauthe, I Orhon, C Rocchi, X Zhou, M Luhr, KJ Hijlkema, et al.Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion*Autophagy*, 14 (2018), pp. 1435-1455
  19. P.Gautret, J.C.Lagier, P.Parola, etal., Hydroxychloroquine and azithromycinasa treatment of COVID-19: results of an open-labelnon-randomized clinical trial, *Int. J. Antimicrob. Agents*(2020)105949, <https://doi.org/10.1016/j.ijantimicag.2020.105949> [published Online First:2020/03/25].
  20. Wang W, Xu Y, Gao R, etal . Detection of SARS-CoV-2 in different types of clinical specimens[JAMA.]. *JAMA* 2020. 10.1001/jama.2020.3786. 32159775
  21. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM (2020 Apr) The FDA-approved Drug Ivermectin inhibits the replication of SARSCoV-2 in vitro. *Antiviral Res.* 3:104787
  22. Zakeri B, Wright GD. Chemical biology of tetracycline antibiotics. *Biochem Cell Biol* 2008;86(2):124–36.
  23. Henehan M, Montuno M, De Benedetto A. Doxycycline as an anti-inflammatory agent: updates in dermatology. *J EurAcadDermatolVenereol* 2017;31(11):1800–8.
  24. Parsippany, NJ: Ivermectin tablets [prescribing information].Edenbridge Pharmaceuticals, LLC; January 2014.
  25. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial *International Journal of Antimicrobial Agents* (2020) (prepublication).