Original Article

A Preventive Study on Hydroxychloroquine Prophylaxis against COVID-19 in Health Care Workers at a Tertiary Care Center in North India

Sudhir Bhandari[1], Govind Rankawat[2], Shivam Priydarshi[3], Nachiketa Vyas[4], Ajeet Singh[5]

[1]Senior Professor, [2]Resident, [3]Professor, [4]Associate Professor, [5]Senior Specialist, [1,2,5]Department of General Medicine, [3,4]Department of Urology, SMS Medical College and Associated Group of Hospitals, Jaipur, Rajasthan, India

DOI:10.37821/ruhsjhs.5.4.2020.331

ABSTRACT

Introduction: The menace of COVID-19 has put a huge burden on health care system, predisposing health care workers engaged in management of COVID-19 infections. Hydroxychloroquine (HCQ) for prophylaxis of COVID-19 had been advocated by some researchers. Hence, this study aimed to describe HCQ as a preventive strategy for healthcare workers against COVID-19 infection.

Methodology: HCQ was prescribed as a prophylactic therapy as per the advisory of National Task Force of Indian Council of Medical Research, India. The data regarding consumption profile, COVID-19 infection, and adverse drug reaction profile of HCQ in healthcare workers was collected.

Results: A record of 4,239 healthcare workers with Hydroxychloroquine consumed was available till date. 93 heathcare workers (2.19%) were infected with COVID-19 infection but in early weeks of prophylactic therapy and were asymptomatic. A few of them (08 participants) had mild symptomatic manifestation with RT- PCR report positive for SARS-CoV-2. No mortality was reported among healthcare workers engaged in management of COVID-19 patients at the tertiary care institute in Jaipur, India. HCQ pre exposure prophylaxis in standard doses produced predominantly gastrointestinal side effects in 20 participants and headache in 10 health care workers.

Conclusion: The present study showed that HCQ pre exposure prophylaxis is safe and effective in standard doses against COVID-19 infection. The front line workers engaged in management of COVID-19 may be given HCQ pre exposure prophylaxis as an extra cover. However, it's broadening usage as preventive strategy in general for people especially in cardiovascular incidences require enhanced research and further validation.

Keywords: Adverse drug reaction, COVID-19, Health workers, Hydroxychloroquine, Pre exposure prophylaxis.

INTRODUCTION

The year 2020 has witnessed one of the worst pandemics in the history of mankind caused by a novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The infection caused is known as Coronavirus disease 2019 (COVID-19).[1] The clinical presentation of COVID-19 is varied, ranging from mild to moderate symptoms like high body temperature, headache, cough and sore throat, difficulty in breathing, body/muscle ache, rhinorrhoea, vomiting, diarrhea, and complex manifestations like pneumonia, acute respiratory distress syndrome, septic shock and/or multiple organ failure.[2] SARS-CoV-2 emerged from Wuhan, a city of Hubei province of China, has swept across 216 countries infecting 7,941,791 people with 4,34,796 deaths globally while in India 343,091 people had been infected with 9,900 deaths as of 16 June 2020.[3] Until the present scenario there are no treatments for COVID-19 but the scientific fraternities around the world are working round the clock in order to develop vaccine against the Coronavirus. But the situation at present is very disheartening as despite using personal protective equipment, health care workers have contracted COVID-19.[4]

Hydroxychloroquine (HCQ), an analog of Chloroquine, has been widely used as an anti- malarial drug as it modifies the immune system by increasing the pH levels in the lysosomes, inhibiting the normal functioning of the

organelle.[5] The repurposed drug Hydroxychloroquine was already being prescribed for treatment of autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis.[6,7]

Since HCQ possess antiviral properties and has shown immune-modulatory action, it has intrigued researchers and clinicians to use this drug in COVID-19 patients. It has been effective against COVID-19 as it suppressed the replication of SARS-CoV-2 and its associated inflammatory process.[8-11] This drug has been the primary choice against COVID-19 than chloroquine due to a milder adverse reaction profile and lesser drug to drug interactions.[12] Moreover, HCQ has shown effectiveness against SARS-COV-2 within safe therapeutic range and still achieving 200-700 times higher concentration in the liver, spleen, kidney, and lung as compared to the plasma.[13,14] A recent study published in a reputed journal has forced us to rethink the use of these drugs in serious patients. Even the World Health Organization (WHO) has withdrawn this drug from its solidarity trials for COVID-19 worldwide. The present study was undertaken to describe the use of hydroxychloroquine (HCQ) in healthcare workers as a prophylactic therapy in combating the COVID-19 infection.

METHODS

Approval for this study from institutional ethics committee was obtained and a duly informed consent was also taken from all participants for their participation. The nasopharyngeal and oropharyngeal swabs of the suspected healthcare workers was tested at the Laboratory of Microbiology of the Institute using reverse transcriptase-polymerase chain reaction (RT PCR) techniques following ICMR guidelines. The study was conducted for a period of two months.

Hydroxychloroquine was prescribed as a prophylactic therapy to all the healthcare workers in India engaged in direct management of COVID-19, including the state of Rajasthan as per the advisory of National Task force for COVID-19 constituted by the Indian Council for Medical Research (ICMR), India; issued on 23 March 2020.[15] HCQ pre exposure prophylaxis was not given to participants who were known cases of hypersensitivity, retinopathy, glucose 6 phosphate dehydrogenase deficiency, or had a history of cardiomyopathy and arrhythmias. In this study, data of COVID-19 infection in health workers and its clinical manifestations were collected and analyzed. This observational, descriptive study also took into consideration the adverse drug reaction profile of HCQ among healthcare workers engaged in management of COVID-19 patients.

Following the protocol of ICMR advisory, all the healthcare workers of SMS Medical College and attached hospitals, Jaipur, India engaged in management of COVID-19 patients were prescribed HCQ in a dose of 400 mg to be taken twice a day on day 1, followed by 400 mg once weekly for next 7 weeks. Adverse drug reactions were monitored through self-reporting as recommended in pharmacovigilance program of India. Approximately 37,000 tablets were distributed among 6,000 health care workers by the hospital administration, unless there was any specific contraindication related to HCQ and information regarding consumption, adverse effects, hospitalization, contracted COVID-19 infection, and laboratory testing for COVID-19 was maintained.

RESULTS

Out of 6,000 healthcare workers who were provided HCQ tablets, record of 4,239 workers that consumed the tablets was available. 139 participants did not consume HCQ tablets as prescribed, details are summarized in figure 1.

As of 29th May 2020, a total of 93 health workers at SMS Medical College and attached hospitals, Jaipur, that were either doctors, nursing or paramedical personnel, contracted the COVID-19 infection, confirmed with RT-PCR test for SARS-CoV-2. Among infected 93 participants, majority (n=70) were infected with COVID-19 in first week of initiation of HCQ prophylactic therapy. Therefore, it can be inferred that these cases might be infected prior to onset of therapy. The remaining 15 participants were shown positive RT-PCR confirmatory test in second week of the preventive therapy, 6 in the third week, and only 2 participants were infected in the fourth week. Most of the infected participants (n=85) were asymptomatic while only a few (n=8) developed mild symptoms, although symptomatic manifestation was seen in early phase of initiation of HCQ prophylactic therapy especially five patients in first week and three patients in

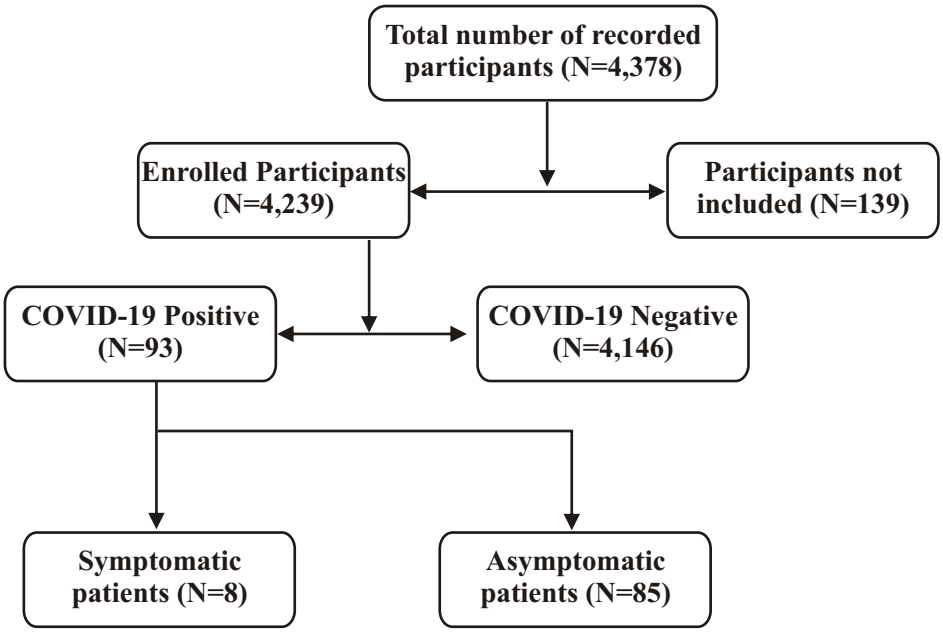

Figure 1: Flow chart showing the distribution of participants.

second week (Figure 2).

The mean age of the healthcare workers who got infected was 35.70±10.26 years. Gender based analysis showed that more males (n=57, 61%) were infected than females (n=36, 39%). The most common adverse effects were related to gastrointestinal system, with 20 participants reporting either gastritis (n=12), diarrhoea (n=3), nausea (n=2), vomiting (n=2), or mouth ulcers (n=1) due to HCQ consumption. Headache was another common side effect (n=10) with other uncommon effects like sweating, palpitation, tremors, vertigo, and breathing difficulty. Palpitation, mouth ulcer, and breathing problems were reported in one participant each (Table).

DISCUSSION

The pandemic of COVID-19 has created a huge burden on global health care system with no effective drug/vaccine available yet in market for its management. The available literature indicated that Chloroquine and Hydroxychloroquine possess antiviral properties that might be effective in the combat against COVID-19.[16] There is a paucity of data regarding antiviral effects of Chloroquine and Hydroxychloroquine due to lack of large sample studies on use of these drugs in COVID-19 patients.

The present study demonstrated that prophylactic HCQ therapy might have a role in deaccelerating infectivity and preventing severe infection in healthcare workers who closely participated in management of COVID-19 patients. Although a few health workers were reported positive for COVID-19 infection but mostly in initial two weeks of administering the prescribed dose of HCQ. This suggested that those patients while being actively involved in management of COVID-19 patients might have been exposed prior to onset of HCQ prophylactic therapy. The most important observation was that no mortality related to COVID-19 was reported among healthcare workers who consumed HCQ. Milder adverse drug reaction profile might have been due to antiviral, immunomodulatory, and anti-inflammatory properties of HCQ.[17]

The rapid progression of COVID-19 patients with subsequent poor outcome has been linked to the associated cytokine storm.[18] HCQ might prevent this storm by attenuation of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1(IL-1), interleukin-6 (IL-6) in addition to its antioxidant activities, that has been observed in autoimmune diseases.[17,19] For this, IL-6 antibody blocker, transfusion of convalescent plasma, and other therapies have been applied to counteract the cytokine storm.[20-21] The protective effect of HCQ pre exposure prophylaxis against COVID-19 is also evident by ability of HCQ in a version of new infection in South Korea's long-term care facility, after a large exposure.[22]

A recent large sample study has demonstrated the protective effects of HCQ against COVID-19 in four or

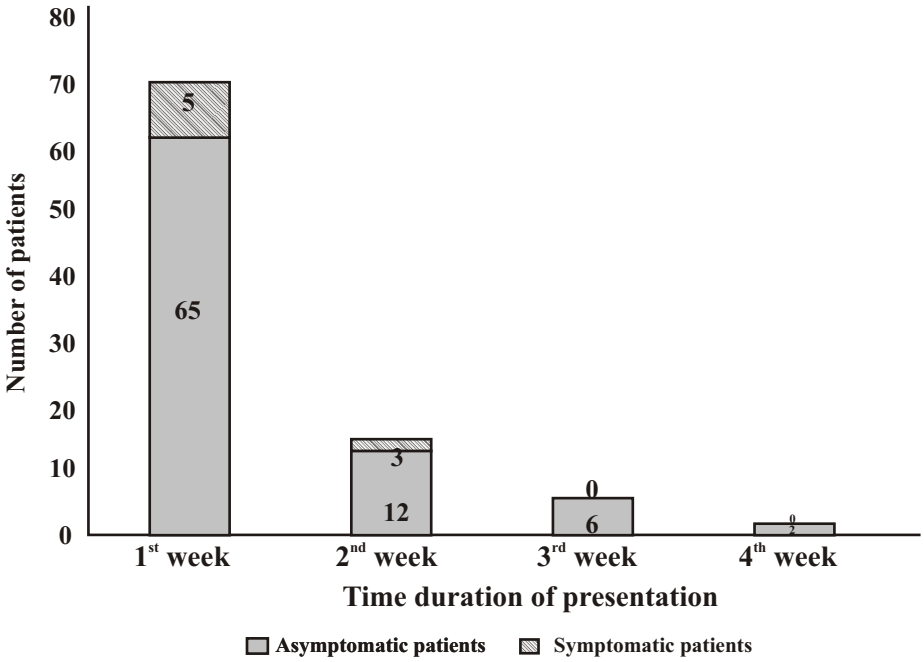

Figure 2: Incidences of COVID-19 infections among healthcare workers that were on HCQ prophylaxis therapy.

more maintenance doses while six or more prophylactic doses of HCQ significantly reduced the odds of SARS-CoV-2 infection in healthcare worker.[23] This finding supports the observation of the present study. Due to beneficial effects of HCQ pre exposure prophylaxis against SARS-CoV-2, a revised advisory from National Task Force of ICMR, India issued in supersession of the previous one has also included other frontline workers at risk of COVID-19 infection such as surveillance workers, paramilitary, and police personnel.[24]

Use of HCQs as post exposure prophylaxis had variable impact on outcome. Boulware et al[25] in their study suggest that after high-risk or moderate-risk exposure to COVID-19, Hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure. The present study based on pre-exposure prophylaxis support the beneficial effect of HCQs as prophylaxis for COVID-19. Cortegiani et al[26] in their study suggest that patients with COVID-19 should be treated with HCQs only if monitored and within the context of high-quality randomized control trials. So, pre exposure prophylaxis of HCQs in the present study might be taken as preventive measure for COVID-19.

Serious adverse effects of Chloroquine and HCQ, especially cardiac, ophthalmological, and hematological manifestations have hindered its therapeutic use in COVID-19.[27] The chances of HCQ causing cardiovascular toxicity of electrical instability due to hERG potassium channel blockade clinically characterized by QTc elongation and torsades de pointes are rare but co-prescription of other drugs like Azithromycin or other co-morbid condition have the potential to amplify the risk.[28] However, it would be pertinent to add that rheumatologists have been using HCQ for millions of patients globally for years and hardly have they ever come across this complication, though long term use of HCQ has been documented to cause eye toxicity. In this aspect it would be relevant to add that cardiac toxicity of short-term use of HCQ is least likely, though HCQ needs to be used with caution in COVID-19 positive patients with co-existing co-morbid cardiac complications as it could very well add fuel to already flagrant fire, especially because of relatively high loading dose used in COVID-19. On the basis of the findings of the present study together with the available literature on HCQ, it can be concluded that HCQ pre exposure prophylaxis is safe and effective in standard dosage against COVID-19 infection due to its antiviral and anti-inflammatory actions. National Task Force (NTF) for

Table: Adverse effects of HCQ reported and its frequency

Name of Department	Adverse effects	Frequency
Microbiology	Diarrhoea	3
	Headache	1
	Palpitation	1
	Sweating	2
	Nausea	2
	Gastritis	8
ENT	Gastritis	4
	Headache	1
Nursing	Headache and vomiting	2
	Headache and vertigo	1
	Headache, tremors, and vertigo	1
	Mouth ulcers and headache	1
	Headache and diarrhoea	1
	Headache and body ache	1
	Headache and tremor	1
	Breathing difficulty (h/o CABG)	1
Chest and TB	Headache	1

COVID-19 constituted by ICMR, India reviewed the use of HCQ for pre exposure prophylaxis of SARS-CoV-2 infection for high risk population especially healthcare workers engaged in management of COVID-19. The NTF reviewed the data on in vitro and in vivo testing of HCQ for antiviral efficacy against SARS-CoV-2 and concluded that prophylactic HCQ had been found to reduce viral load in high risk group and prompt to hampered complications of COVID-19 infection.[24]

CONCLUSION

Prophylactic HCQ therapy might have a role in deaccelerating infectivity and preventing severe infection in healthcare workers who closely participated in management of COVID-19 patients. For validity of HCQ as pre exposure prophylaxis and safety profile require further research with bigger cohorts. Moreover, their use in treatment of severe COVID-19 disease and in patients with known cases of cardiovascular disease needs further validation.

Limitations: This study is purely based on oral questionnaires from participants and did not allow continuous monitoring of patients for compliance of medicine. This study did not allow consistent proof of exposure to SARS-CoV-2. The sensitivity of RT-PCR for COVID-19 is low, so it is hard to be certain that how many participants in the study actually had COVID-19. This study does not include control group, so definitive outcome could not be concluded.

Funding: The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not for profit sectors.

Acknowledgments: I would like to thank the anonymous referees for their useful suggestion. I would like to thank my professionals Dr. Abhishek Agrawal, Dr. C. L. Nawal, Dr. S. Banerjee, Dr. Prakash Keswani, Dr. Sunil Mahavar, Dr. R S Chejara, Dr. Vidyadhar Singh, Dr. Kapil, Dr. Shivankan, Dr. Dileep Wadhawani and team of Department of General Medicine, SMS Medical college and attached group of Hospitals, Jaipur for their valuable support and Department of Radiodiagnosis for providing radiological information of COVID-19 patients.

REFERENCES

1. Centers for Disease Control and Prevention (CDC) Coronavirus Disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms. html.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
3. World Health Organization (WHO) Coronavirus Disease

(COVID-19) Dashboard. https://covid19.who.int/.

4. Ministry of Health and Family Welfare. https://www.mohfw.gov.in/
5. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Seminars in Arthritis and Rheumatism*. 1993;23(2):82-91. doi:10.1016/s0049-0172(10)80012-15.
6. Biot C, Daher W, Chavain N, Fandeur T, Khalife J, Dive D. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem*. 2006; 49:2845-49.
7. Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. *Lancet Infect Dis*. 2020; published online April 17. doi:10.1016/S1473-3099(20)30296-6.
8. Perricone C, Triggianese P, Bartoloni E, Cafaro G, Bonifacio AF, Bursi R et al. The anti-viral facet of anti-rheumatic drugs: Lessons from COVID-19. *J Autoimmun*. 2020;111:102468.
9. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16.
10. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020; published online March 12. *doi*:10.1016/j.ijantimicag.2020.105938.
11. Hashem AM, Alghamdi BS, Algaissi AA, Alshehri FS, Bukhari A, Alfaleh MA et al. Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review. *Travel Med Infect Dis*. 2020. doi:10.1016/j.tmaid.2020.101735.
12. Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. *Pharmacol Res Perspect*. 2017;5:e00293.
13. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*. 2020;71(15):732-39.
14. Popert AJ. Choloroquine: a review. *Rheumatology.*1976; 15:235-38.
15. National Taskforce for COVID-19. Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. Dated 23rd March 2020.
16. Biot C, Daher W, Chavain N, Fandeur T, Khalife J, Dive D. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem*. 2006; 49:2845-49.
17. Al-Bari MA. Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. *J Antimicrob Chemother*. 2015;70(6):1608-21.doi:10.1093/ jac/dkv018.
18. Jing Liu, Sumeng Li, Jia Liu, Boyun Liang, Xiaobei Wang, Hua Wang et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *MedRxiv*.2020.doi:https://doi.org/10.1101/2020.02.16.20023671.
19. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. *Inflammopharmacology.* 2015;23(5):231-69. doi:10.1007/s10787-015-0239-y.
20. P Conti, G Ronconi, A Caraffa, C Gallenga, R Ross, I Frydas et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies.*J Biol Regul Homeost Agents*. 2020;34(2):327-331. doi:10.23812/CONTI-E.
21. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19 [published online ahead of print, 2020 Feb 27]. *Lancet Infect Dis*. 2020;20(4):395-400. doi:10.1016/S 1473-3099(20)30141-9.
22. Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? *Int J Antimicrob Agents*. 2020. doi: 10.1016/j.ijantimicag.2020.105988.
23. Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S et al. Healthcare workers and SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. *Indian J Med Res* 2020, Epub ahead of print doi:10.4103/ijmr.2234_20.
24. Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for COVID-19 infection. Dated 22nd May 2020. Available at: https://www.mohfw. gov.in/pdf Revised advisory on the use of hydroxychloroquine as prophylaxis for SARS COVID-19 infection.pdf.
25. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC. A randomized trial of Hydroxy-

chloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med*. 2020;383(6):517-525.

26. Cortegiani A, Ippolito M, Ingoglia G, Iozzo P, Giarratano A, Einav S. Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. *Journal of Critical Care.* 2020;59:176-90.

27. Me´ garbane B. Chloroquine and hydroxychloroquine to treat COVID-19: between hope and caution. *Clin Toxicol*. 2020;2:1-2. doi:10.1080/15563650. 2020.1748194.

28. Traebert M, Dumotier B, Meister L, Hoffmann P, Dominguez-Estevez M, Suter W. Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells. *Eur J Pharmacol*. 2004;484(1): 41-48.

Corresponding Author

Dr Govind Rankawat, SMS Medical College and Associated Group of Hospitals, Jaipur, Rajasthan, India.

email: govindrankawat@gmail.com