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ORIGINAL ARTICLE

The effect of Verapamil in Malaria – A Prospective Randomized Double Blind Control Clinical Study

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ABSTRACT

Context: To reduce the drug resistance produced by malarial parasites to chloroquine and Verapamil, a chemosensitiser which has been tried in vivo.

Objectives: To find out whether verapamil facilitates the action of chloroquine in malaria and to find out the safety of using verapamil in malaria.

Study Design: A double blind randomized control study

Description of the Subjects: Sixty patients who were positive for malaria by the QBC test (vivax, falciparum) without any associated illness (hypertension, diabetes, anaemia, cardiac, renal diseases) were included. Informed consent was obtained from each patient.

Interventions: After thorough clinical examination, the patients were randomly allocated for two different treatments. Group A received standard chloroquine therapy (600 mg loading dose, 300 mg after 8 hrs, 24 hrs and 48 hrs). Group B received in addition to chloroquine therapy, verapamil 40 mg orally two hours after the administration of chloroquine. All the patients were evaluated, based on the time taken for the temperature to become normal, disappearance of rigor and chills (patients were evaluated at every 4^{th} hour) and the QBC test to become negative (test done at every 12^{th} hour)

Results: It was observed that patients in group B had earlier relief of symptoms and signs and QBC became negative early as compared to group A. Fever (Mean—18.53 hours for group A and 9.33 hours for group B, SD for group A is 7.68 hours and for group B is 3.53 hours)and rigor and chills (Mean for group A is 18.8 hours and group B is 9.7 hours, SD for group A is 7.94 hours and for group B is 3.53 hours) were reduced to normal within 24 hours in group B, whereas in group A, it became normal only in 36 hours. Parasitaemia was cleared in 36 hours in group B, but in group A, it was cleared only in 48 hours (Mean for group A is 28.4 hours and for group B is 19.7 hours, SD for group A is 7.68 hours and for group B is 6.81 hours). No one had hypotension or any other significant adverse effects. The results were analyzed by the Student's t test and they was considered to be significant ($p<0.001$).

Conclusion: Verapamil facilitates the action of chloroquine in malaria and it is safe.

Key Words: QBC test, Verapamil, chemosensitizer, Parasitaemia clearance

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Introduction

Malaria is one of the commonest parasitic diseases of the world which is prevalent throughout the tropics and subtropics [1]. The incidence of malaria worldwide is estimated to be 300- 500 million clinical cases every year [2]. In India, during the year 2001, there were 0.98million reported cases of malaria [3]. To bring down the incidence and morbidity, many national malarial programmes were implemented in India. In spite of these control measures and effective antimalarial treatment, there is still significant incidence and prevalence of malaria which is mainly due to treatment failure and vector resistance. One of the main causes for treatment failure is the development of resistance by the malarial parasites to many of the antimalarial drugs, especially to Chloroquine.

Hence, the management of drug resistance is an urgent need to decrease the incidence of malaria. Several commonly used drugs such as verapamil [4],[5],[6],[7],[8],[9],[10],[11],[12],[13] chlorpheniramine maleate [5], tricyclic antidepressants [5], desipramine [5],[7],[12],[14], cyproheptadine [5] and chlorpromazine [12) have been shown to reverse the resistance of P.falciparum to chloroquine in vitro. Mostly the antihypertensive, Verapamil has been proved as an effective chemosensitizer. Thus, although the first line antimalarial drug, chloroquine appears to lose its importance in most parts of the world, this inexpensive, rapid acting, well tolerated antimalarial may be still used with the same efficacy by combining it with effective resistance reversers.

Therefore, if chloroquine is combined with any one of the above resistance reversing drugs, its efficacy is expected to be retained in resistant malaria. Verapamil has been reported to reverse chloroquine resistance in several in vitro studies. Will verapamil have such action when used clinically? Will verapamil facilitate the action of chloroquine in sensitive malaria and bring out a synergistic effect? Thus, in order to find out the effect of verapamil in malaria, irrespective of the sensitivity status, the present study was undertaken. So, the purpose of the study was to find out the effect of verapamil in malaria, whether it has any facilitatory action when given along with chloroquine and whether it is safe.

Materials and Methods

It is a prospective, randomized double blind control study which was done in the Department of Pharmacology in collaboration with the Department of Medicine and the Department of Microbiology, Government Stanley Medical College, Chennai. The study was conducted only after getting the approval of the Institutional Ethics Committee.

Patients of both the sexes between 15- 60 years of age, who were diagnosed to have malaria by the QBC (Quantitative buffy coat) [15],[16],[17],[18],[19],[20],[21],[22],[23] method, were included in the study. Children < 15 years, pregnant and lactating mothers, those with known cardiac diseases (Hypertension, Coronary heart disease, Bradycardia, Conduction defects), Diabetes mellitus and other associated illnesses were excluded from the study.

Sixty patients were included in the study. Both the control (Group A) and the test group (Group B) had an equal number of thirty patients. All the patients were found to belong to lower and lower middle class families. The mean age in the control group was 26 years and in the study group was 23 years. Even though malaria is common in all the age groups, our study group had only young adults.

Sixty patients with QBC positive malaria were enrolled in the study. All the 60 patients were admitted in the Medicine

ward. They were well informed about the study. Written consent was obtained from all of them. The patients' name, age, sex, residence, income and locality were noted. Then, the detailed history about the fever (duration, chills, rigor, whether continuous or intermittent), vomiting, abdominal pain, headache, and loss of appetite were recorded. General and systemic examinations were done. Temperature, pulse rate and blood pressure were recorded at every 4th hour. The patients were also examined for anaemia, Jaundice, splenomegaly and hepatomegaly. After the clinical examination, the following lab investigations were done.

Haematological investigations: Haemoglobin, Total Count, Differential Count, Erythrocyte Sedimentation Rate and Peripheral smear for Malarial Parasite

Urine examination: For Red Blood Cells (RBCs) along with the routine examination.
Other investigations: Electrocardiogram (ECG) and ophthalmic examination.

After the pre-trial investigations, each patient was randomly allocated by using lots, to either one of the 2 groups, namely A and B. Patients in-group A (control) received the standard chloroquine therapy (24,25) (600mg as first dose and after 8 hours 300mg, followed by 300 mg after 24 hours then another 300 mg after 48hours), along with symptomatic treatment. Patient in-group B (study) received in addition to chloroquine, 40mg of verapamil orally 2 hours after the administration of chloroquine. Since verapamil is an anti hypertensive drug, blood pressure and pulse rate were recorded at every 4th hour.

Each patient was examined at every 4th hour for the improvement in signs and symptoms like fever, chills and rigor, blood pressure, vomiting and abdominal pain .12th hourly QBC was done to know the rate of clearance of parasitaemia. In addition, all the patients were subjected to the same pre-trial investigations and any change in the results was suitably analyzed.

Statistical Methods

The data was analyzed by the independent Student's t test and p values < 0.05 were considered as significant.

Results

The mean age in the control group was 26 years and in the study group was 23 years. Among the 60 patients who were enrolled in the study, 51 were males and 9 were female patients. The clinical features of Group A and B were compared and they were not statistically significant ($p > 0.5$), as shown in [Table/Fig 1]**.** Pre trial investigations and their means and standard deviations are given in [Table/Fig 2]. Pre trial investigations for both group A and group B were statistically not significant ($p > 0.5$).

(Table/Fig 1) It shows the comparison of the clinical features.

		Group			
		Control (30)		Study (30)	
		Number of patients	%	Number of patients	%
Fever (F)	Present	30	100.0%	30	100.0%
F+ Rigor (R)	Absent	3	10.0%		
	Present	27	90.0%	30	100.0%
Vomiting (V)	Absent	16	53.3%	10	33.3%
	Present	14	46.7%	20	66.7%
F+R+V	Absent	16	53.3%	10	33.3%
	Present	14	46.7%	20	66.7%
Headache	Absent	19	63.3%	19	63.3%
	Present	11	36.7%	11	36.7%
Abdominal pain	Absent	24	80.0%	22	73.3%
	Present	6	20.0%	8	26.7%
Loss of appetite	Absent	25	83.3%	20	66.7%
	Present	5	16.7%	10	33.3%
Anemia	Absent	2	6.7%	6	20.0%
	Present	28	93.3%	24	80.0%
Splenic enlargement	Absent	15	50.0%	16	53.3%
	Present	15	50.0%	14	46.7%
Liver enlargement	Absent	24	96.0%	28	93.3%
	Present	1	4.0%	2	6.7%

(Table/Fig 2) Pre trial investigations done for both control and study groups

	Group	N	Mean	Std. Deviation
Hemoglobin	Control	30	9.9536	1.11272
	Study	30	10.5286	0.88270
Total count	Control	30	8126.6667	1191.32882
	Study	30	7103.3333	1062.36020
Polymorphs	Control	30	51.5667	4.74657
	Study	30	48.5000	5.02236
Lymphocytes	Control	30	46.1333	4.73966
	Study	30	47.8000	4.15559
Monocytes	Control	30	2.7000	0.95231
	Study	30	2.6333	0.88992
Eosinophills	Control	30	1.6000	1.03724
	Study	30	2.8667	1.43198
ESR1/2	Control	30	3.1667	1.17688
	Study	30	3.0000	0.90972
ESR1	Control	30	6.3333	2.35377
	Study	30	6.0000	1.81944
The values were analyzed by Independent Student t test and there was no statistical significance between the two groups (p>0.5).				

The time taken for the reduction in temperature [Table/Fig 3], chills and rigor [Table/Fig 4] and parasitaemia [Table/Fig 5] were also analyzed. It was observed that patients in group B (Study group) had earlier relief of symptoms and signs and QBC became negative early as compared to group A (control group). Fever (Mean—18.53 hours for group A and 9.33 hours for group B, SD for group A is 7.68 hours and for group B is 3.53 hours) was reduced to normal within 24 hours in group B, whereas in group A, it was only reduced in 36 hours. The results were analyzed by the Student's t test and they were considered to be significant ($p < 0.001$). Rigor and chills (Mean for group A is 18.8 hours and group B is 9.7 hours, SD for group A is 7.94 hours and for group B is 3.53 hours) was reduced to normal within 24 hours in group B, whereas in group A, it was reduced only in 36 hours. The results were analyzed by the independent Student's t test and they were considered to be significant ($p < 0.001$). Parasitaemia was cleared in 36 hours in group B, but in group A, it was cleared only in 48 hours (Mean for group A is 28.4 hours and for group B is 19.7 hours, SD for group A is 7.68 hours and for group B is 6.81 hours). The results were analyzed by the Student's t test and they were considered to be significant ($p < 0.001$).

(Table/Fig 3)It shows the reduction in temperature in both control and study group for every 12 hours

Time taken for normalization of temperature (in hrs)	Group			
	Control n=30		Study n=30	
	Number of patients	%	Number of patients	%
12	9	30.0	28	93.3*
24	18	85.7	2	100.0
36	3	100.0	0	100
48	0	100	0	100
It was observed that patients in group B (Study group), had earlier relief of symptoms and signs and QBC became negative early compared to group A (control group). Fever (Mean—18.53 for group A & 9.33 for group B, SD for group A is 7.68 & for group B is 3.53) was reduced to normal within 24 hours in group B, whereas in group A, it was 36 hours. The results were analyzed by Student t test and it was considered significant (p<0.001).				

(Table/Fig 4) Chart Showing the reduction in Chills & Rigor in both control and study group for every 12 hours

Time taken for normalization of chills and rigor (in hrs)	Group			
	Control n=30		Study n=30	
	Number of patients	%	Number of patients	%
12	9	30.0	28	93.3*
24	16	76.2	2	100.0
36	5	100.0	0	100
48	0	100	0	100
It was observed that patients in group B (Study group), had earlier relief of symptoms and signs and QBC became negative early compared to group A (control group. Rigor & chills (Mean for group A is 18.8 & group B is 9.7, SD for group A is 7.94 & for group B is 3.53) was reduced to normal within 24 hours in group B, whereas in group A, it was 36 hours. The results were analyzed by Student t test and it was considered significant (p<0.001).				

(Table/Fig 5) Chart Showing the Parasitemia clearance in both control and study group for every 12 hours

Time taken for Parasitemia clearance (in hours, by QBC method)	Group			
	Control n=30		Study n=30	
	Number of patients	%	Number of patients	%
12	3	10.0	18	60.0
24	16	59.3	11	91.7*
36	8	72.7	1	100.0
48	3	100.0	0	100
It was observed that patients in group B (Study group), had earlier relief of symptoms and signs and QBC became negative early compared to group A (control group. Parasitemia was cleared in 36 hours in group B, but in group A, it was 48 hours (Mean for group A is 28.4 & for group B is 19.7, SD for group A is 7.68 & for group B is 6.81). The results were analyzed by Student t test and it was considered significant (p<0.001).				

Post trial investigations along their means and standard deviations are given in [Table/Fig 6.] Post trial investigations for both group A and group B were statistically not significant ($p > 0.5$). The difference between the control group and the study group was not statistically significant in both pre trial and post trial laboratory investigations.

(Table/Fig 6) Post trial investigations done for both control and study groups

	Group	N	Mean	Std. Deviation
Hemoglobin	Control	30	9.7238	1.11354
	Study	30	10.5151	0.87525
Total count	Control	30	9214.4500	1185.35822
	Study	30	7600.4853	1075.35869
Polymorphs	Control	30	49.5847	4.78569
	Study	30	50.4153	5.14524
Lymphocytes	Control	30	48.4583	4.79874
	Study	30	45.4200	4.16584
Monocytes	Control	30	2.7124	0.87431
	Study	30	2.6752	0.92452
Eosinophills	Control	30	1.4658	1.25844
	Study	30	2.2547	1.25848
ESR1/2	Control	30	3.1547	1.45878
	Study	30	3.2540	0.924582
ESR1	Control	30	6.4751	2.87574
	Study	30	6.2541	1.95784
The values were analyzed by Students t test and there was no statistical significance between the two groups (p>0.5).				

Disucssion

Though alternative drugs are available for the treatment of chloroquine resistant malaria, the resistance to these drugs (Quinine, Pyremethamine- Sulfonamide, Artemisinin compounds and Halofantrine) is also emerging and multidrug resistant malaria is prevalent in many parts of the world.

Whenever the organisms become resistant to the available drugs, two modalities of treatment can be followed. One is, to select a new drug; if a new drug is not available, the existing drug can be used along with another drug which has the property of reversing the resistance. As chloroquine, which has been effective for more than fifty years has recently developed resistance and when drugs which can reverse chloroquine resistance have been reported, it would be economical to use chloroquine along with any one of these resistance reversers rather than finding out a new drug, which would be very expensive and time consuming.

Hence, it would be appropriate to study the effect of chloroquine resistant reversers. The calcium channel blocker, verapamil, has been reported to be an effective resistant reverser by many in-vitro studies [4],[5],[6],[7],[8],[9],[10],[11],[12],[13]. But its effect in sensitive malaria is unknown. It works by the mechanism of preventing the efflux of chloroquine from the parasite by inhibiting the P-glycoprotein [8], [13], [24]. Whether a multidrug resistant protein, (which increases the efflux of the drug) or inhibition of the Calcium channel (which is necessary for drug influx), would facilitate and prolong the action of chloroquine, has to be studied. Therefore, in order to find out its effect in both sensitive and resistant malaria, the present study was undertaken.

Among the 60 patients who were enrolled in the study, 51 were males and 9 were female patients. Even in random allocation, the number of male patients who entered the study was high in both the groups. The male preponderance may be due to the outdoor sleeping habit of the male workers.
46.7% of the patients in the control group and 66.7% of the patients in the study group complained of vomiting before treatment. Vomiting is attributed to the high concentration of parasites and toxaemia. After the treatment was started, the number of patients with vomiting was reduced, which may be due to the clearance of parasitaemia and toxaemia. Very few patients complained of vomiting even after treatment, which could be due to the drug effect. In the study group, vomiting was relieved within 12 hours as compared to the control group.

Similarly, fever and rigor subsided 12 hours earlier in the study group. It was due to the early clearance of parasitaemia. Loss of appetite was present in 16.7% of the control group patients and 33.3% of the study group patients, which improved within 36 hours of the treatment. Reduction in temperature is an important clinical sign, denoting improvement. It was reduced to normal in all the patients in-group A within 36 hours, whereas in-group B, it was reduced within 24 hrs of drug administration (12 hours earlier than the control group), which is found to be statistically very significant.

All the patients in the control group had relief from symptoms and signs within 48 hours, but the rate of clearance was found to be slower than in the study group. Thus, the study has shown that, all the patients in the

study group who were treated with chloroquine and verapamil, had complete relief of signs and symptoms within 36 hours. The duration of temperature, relief from chills and rigor and the clearance of parasitaemia were significantly earlier (12 hours) than in the control group.

The difference between the two groups was found to be statistically significant, indicating that verapamil had facilitated the action of chloroquine. Though it is reported that in malaria there will be increased leucocyte count, increased monocytes, increased ESR and decreased neutrophils, this picture was not seen in this study. Anaemia was found in 93.3% of the control group patients and in 80% of the study group patients. The increased incidence of anaemia could be due to the extensive destruction of RBCs in patients who were treated with chloroquine alone [26].

Verapamil, a calcium channel blocker, is known to cause bradycardia, hypo tension and constipation due to its inhibitory effect on the heart and the gastrointestinal tract [11]. But none of our patients suffered from hypotension or bradycardia. When verapamil is used either as an antihypertansive or antiarrhythmic, the duration of therapy is long, whereas in malaria, it was used only for three days and the maximum dosage administered was only 160 mgm. Hence, at this dosage, verapamil did not produce any side effects and it was found to be very safe. The number of days of stay in the hospital was reduced to two because of the earlier relief of symptoms. This has reduced the cost on hospitalization and helped the patients to resume duty at an early date [27],[28].

The beneficial effect of verapamil is as discussed earlier, due to its action on chloroquine efflux, leading to the increased concentration of chloroquine in the parasite, causing early death of the parasites and thus resulting in the early relief of signs and symptoms.

Conclusion:

It can be concluded from the present study, that verapamil is effective in malaria, it has a synergistic action when given with chloroquine in malaria and it is safe. Hence, it can be used along with chloroquine in malaria for better efficacy and early recovery.

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