

differ from the original vacuum spaces by inclusion of a topological defect, a global monopole charge.

Note that the characterization of empty space and its dual is by the covariant equations. Earlier the dual spacetimes^{1,13} were obtained by modifying the vacuum equation, so as to break the invariance relative to the electrogravity duality transformation, in a rather ad-hoc manner. Now the effective vacuum equation has the direct physical meaning in terms of the energy and convergence density. This characterization could as well be applied in lower and higher dimensions to find new dual spaces. For example, in three-dimensional gravity the dual space represents a new class of black hole spaces¹⁴ with a string dust matter field. For higher dimensions, the method would simply go through without any change for n -dimensional spherically symmetric space and the dual space would represent a corresponding Schwarzschild black hole with a global monopole charge. It can be further shown that a global monopole field in the Kaluza-Klein space can be constructed similarly¹⁵ as dual to the vacuum solution¹⁶. It is thus an interesting characterization of empty space which leads to new spaces dual to corresponding empty spaces.

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Comparative efficacy of Ayush-64 vs chloroquine in vivax malaria

Neena Valecha^{†,‡}, C. Usha Devi[†], Hema Joshi[†], V. K. Shahi^{*}, V. P. Sharma and Shiv Lal^{**}

[†]Malaria Research Centre, 22 Sham Nath Marg, Delhi 110 054, India

^{*}Central Council for Research in Ayurveda and Siddha, Anusandhan Bhavan, 61-65 Institutional Area, Opp. D-Block, Janakpuri, Delhi 110 058, India

^{**}National Anti Malaria Programme, 22 Sham Nath Marg, Delhi 110 054, India

A phase II prospective comparative randomized clinical trial was conducted in patients of vivax malaria to compare the efficacy of Ayush-64 vs chloroquine. Ayush-64, a herbal formulation patented by Council of Ayurveda and Siddha was compared with chloroquine. Patients received an oral dose of either 1 g Ayush-64, three times a day for 5-7 days or a total dose of 1500 mg chloroquine over 3 days. Peripheral smears were examined everyday for 3 days or till they were negative and then weekly up to 28 days.

The results of the study showed that at day 28, only 23 of 47 (48.9%) patients in the Ayush group and all the 41 in the chloroquine group were cured ($p < 0.05$). Even in these 23 patients in the Ayush group parasite clearance time was longer than chloroquine (3.16 vs 1.5 days). Both regimens were generally well tolerated. In conclusion, Ayush-64 in a dose of 1 g three times a day for 5-7 days is not as effective for treatment of vivax malaria, as standard chloroquine therapy.

MALARIA is a major health problem in India. The annual incidence was between 2 and 3 million during the last decade¹. The problem of drug resistance and treatment failures in *P. falciparum*² and recently in *P. vivax*^{3,4} malaria using chloroquine has focused interest on new drugs/drug combinations/indigenous drugs or remedies.

Ayush-64 is a combination of four Ayurvedic drugs namely *Alstonia scholaris* R. Br. (aqueous extract of the bark - 1 part), *Picrorhiza kurroa* Royle (aqueous extract of the rhizome - 1 part), *Swertia chirata* Buch-Ham (aqueous extract of the whole plant - 1 part) and *Caesalpinia crista* Linn (fine powder of seed pulp - 3 parts)⁵. The ingredients after mixing are formulated into tablets of 500 mg each. The drug/formulation is patented and registered by Central Council for Research in Ayurveda and Siddha (CCRAS) and was reported to cure malaria^{5,6}. Since the studies were conducted more than 15 years ago and susceptibility of parasites to drugs keeps changing, it was considered essential to evaluate the efficacy of the drug before introduction in the national programme. Moreover, in these studies, patients were included on the basis of clinical diagnosis of malaria and assessment criteria were not uniform⁵, therefore the present comparative

[‡]For correspondence. (e-mail: valecha@del3.vsnl.net.in)

study was designed to confirm the antimalarial activity of Ayush-64.

The study was conducted at Malaria Research Centre (MRC), Delhi. The clinics at MRC and the National Anti Malaria Programme (NAMP) were selected for the study. Patients from 4 to 5 peri-urban villages and resettlement colonies visit these clinics. They belong to the low socio-economic status. It was a prospective comparative, open and randomized study. The randomization was done by using a simple random sampling table. Proven cases of vivax malaria seeking treatment at the clinics of MRC and NAMP were asked to volunteer for the study if they were 18–60 years of age, had asexual parasitaemia $< 50,000/\mu\text{l}$, were febrile or had recent history of fever within the last 48 h. Pregnant and lactating females and G-6 PD deficient subjects were not included in the study. Patients who had taken antimalarials within 7 days prior to enrollment in the study were also not included.

The study was approved by an ethical committee of MRC. Patients satisfying the inclusion criteria were enrolled after obtaining an informed written consent. Patients were randomly allocated to receive one of the two treatment regimens. One group received a total dose of 1500 mg chloroquine over 3 days followed by 15 mg primaquine daily for 5 days as standard therapy for vivax malaria. The other group received Ayush-64, 2 tablets of 500 mg each three times a day for 5 days. The patients in the Ayush group who did not respond, as evidenced by the presence of parasites in the peripheral smear, were given treatment for further 2 days and labelled as treatment failures if they remained positive. This dose was as per recommendation by NAMP and in accordance with the doses used in earlier studies^{5,6}.

Patients were observed for at least 2 h after drug administration for vomiting. They were then followed-up as out-patients on day 1, 2, 3, 7, 14, 21 and 28 for clinical and parasitological cure. All the patients who became positive after smear being negative at day 7 were labelled as recrudescences. Haematology and blood chemistry were done on day 0 and day 7. A slide was considered negative only after 200 fields had been examined without finding a parasite. The antimalarial efficacy in both groups was compared using parasite clearance time (PCT), cure rate at day 28 and recrudescence rate as parameters. The technician involved in investigations was not aware of the treatment regimen of the patients. The statistical method used for comparing PCT was the *t*-test and the *z*-test was used for cure rate and recrudescence rate in the two groups.

Fifty-four cases of *P. vivax* were enrolled in the Ayush-64 group and fifty in the chloroquine group. Seven cases in the former (age 19–50 years) and nine in the latter (age 18–40 years) group were lost to follow-up before they had completed the 28-day observation period. Although the drop-out rate was similar in both groups, the reasons were different. In chloroquine group the drop-out was because

patients left the study area after being smear negative and the 28-day follow-up could not be completed. In the Ayush group, 4 cases dropped out as they did not want to continue therapy after the third day while 3 left the study area. Patients randomized to the Ayush-64 and chloroquine groups had comparable baseline characteristics with respect to age, sex, duration of illness, initial parasite counts, clinical symptoms, etc. (Table 1).

In the chloroquine group ($n = 41$) mean parasite clearance time was 1.5 ± 0.5 days compared to 3.16 ± 2.4 days in the Ayush-64 group ($n = 31$ including recrudescence cases). The values were significantly different with $p < 0.05$ (*t*-test). Similarly cure rate of 100% vs 48.9% in the chloroquine and Ayush groups, respectively was significantly different ($p < 0.05$) from each other. Recrudescence rate in the chloroquine group was 0% as against 17% in the Ayush group ($p < 0.05$).

In addition, clinical recovery was also slow in the Ayush group and general acceptability of the drug was poor. The patients complained about frequency and duration of dosing and size and quality of the tablet formulation. The course of parasitaemia in the two treatment groups is shown in Figure 1. Out of the 16 cases who were labelled as treatment failures in the Ayush group, three had to be referred to hospital due to deterioration of clinical condition and all responded to chloroquine therapy.

Both treatment regimens were generally well tolerated. There was no significant difference in pre- and post-treatment haematological or biochemical findings in both treatment groups. One patient of the Ayush group had generalized oedema and proteinuria but causality relationship could not be established since the patient was lost to follow-up. Three patients in the Ayush group complained of gastrointestinal disturbances, viz. nausea and diarrhoea.

In the recent past efforts are being made to revive indigenous systems of medicine. Ayush-64 has been previously shown to be effective as an antimalarial in animal experiments and clinical studies conducted by the CCRAS^{5,6}. However, in experimental studies in rodent models, increase in survival time and not the parasite clearance was observed in the dose of 3 g per day for 4

Table 1. Curative efficacy of Ayush-64 and chloroquine

Parameter	Treatment groups	
	Ayush	Chloroquine
Total cases enrolled	54 (46 M + 8 F)	50 (35 M + 15 F)
Age	29.40 ± 9.04 years	30.46 ± 10.25 years
Parasitaemia on day 0	$0.25 \pm 0.26\%$	$0.31 \pm 0.32\%$
Dose of drug used	1 g tds \times 5–7 days	1.5 g (base) over 3 days
Total cases completing 28 days	47	41
Cure rate	48.9%	100%
Recrudescence rate	17%	0
Parasite clearance time	3.16 ± 2.4 days	1.5 ± 0.5 days
Clinical recovery	Slow	Rapid

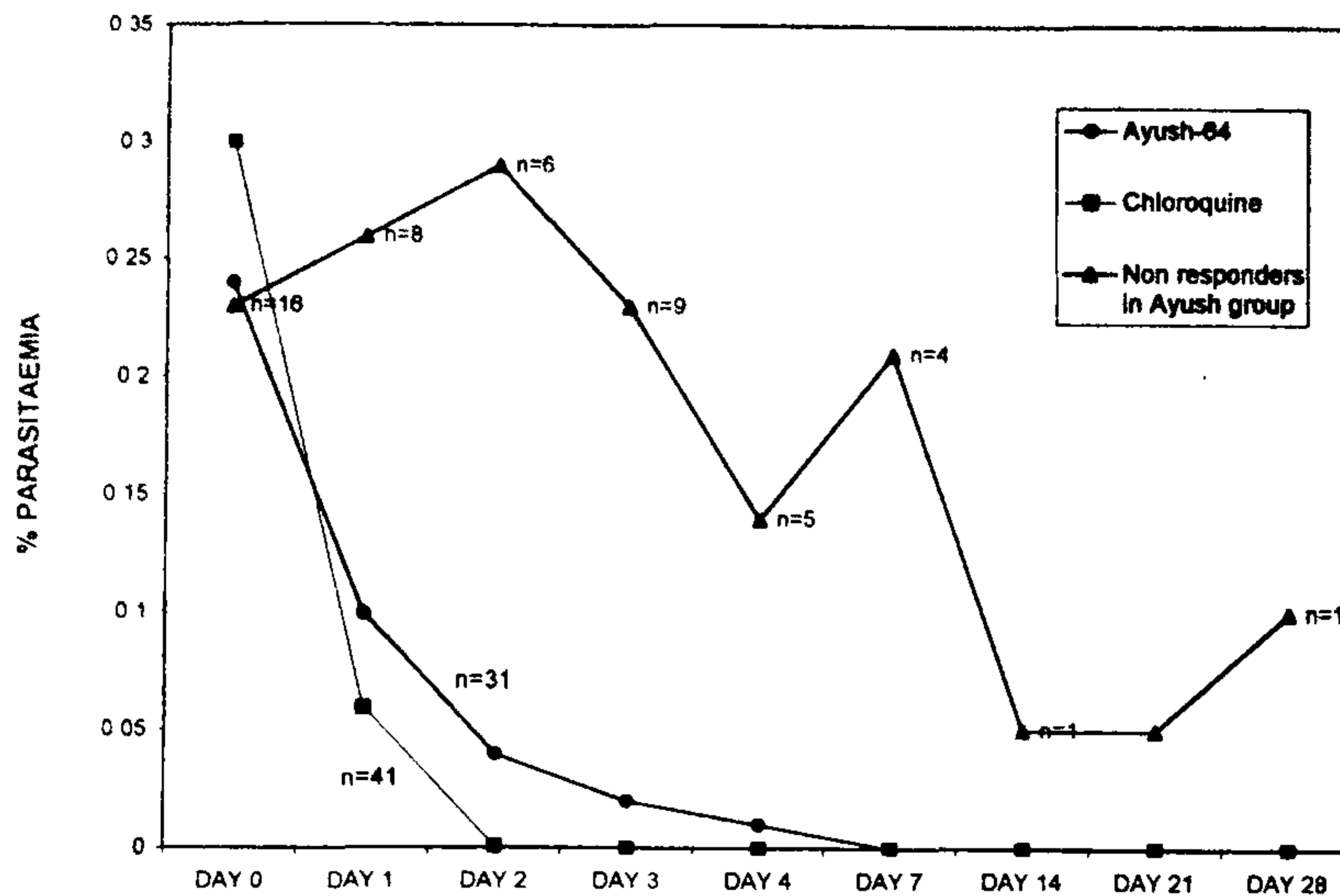


Figure 1. Course of parasitaemia in the two treatment groups. Data are arithmetic mean of parasitaemia.

days. In clinical studies an efficacy of 72–90% in vivax malaria was reported with the dose of 3 g/day for 4–5 days. However, some of the cases were included on the basis of clinical diagnosis only.

Similarly Sharma *et al.*⁶ have shown the efficacy of Ayush-64 with variable dose and duration of treatment to be 70%. In all the studies the total dose of drug has varied from 9 to 37 g. The frequency of administration varied from patient to patient. However, the total daily dose was not more than 3 g in any case.

In the present study a uniform dose schedule of 3 g per day for 5 days (15 g) extending to 7 days if needed (21 g) has been used.

A cure rate of less than 50% has been observed with Ayush-64 as against 100% with chloroquine. The latter drug was administered once a day only for 3 days and is therefore more acceptable and cost effective. It is evident from the present study that Ayush-64 does not have specific schizonticidal or gametocytocidal activity. Our results are supported by lack of antimalarial action in rodent and simian models even at dose of 3 g/kg (ref. 7). One of the ingredients of Ayush-64, i.e. *Alstonia scholaris* has also been shown to be devoid of specific antiplasmodial action⁸.

The drug does not appear promising as a primary drug for treatment of malaria in the present dose regimen. In addition to increasing morbidity, slow parasite clearance

poses a threat of continuing transmission of the disease. And this, therefore, is unlikely to be an alternative for chloroquine in vivax malaria. Considering the poor efficacy of the drug and risk of complications in falciparum malaria, further study in *P. falciparum* cases was not conducted.

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