Patient Adherence and Treatment Outcome in Uncomplicated *falciparum* Malaria Treated with Supervised versus Non-Supervised Artesunate - Sulphadoxine - Pyrimethamine Regimen

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ABSTRACT

BACKGROUND

Artemisinin Combination Therapy (ACT) is presently the recommended treatment of uncomplicated *falciparum* malaria in India but poor adherence and emerging resistance is a concern. We wanted to compare patient adherence and treatment outcome (efficacy and tolerability) of supervised versus non-supervised artesunate -sulphadoxine-pyrimethamine (AS-SP) therapy in uncomplicated *falciparum* malaria.

METHODS

Study participants were randomly distributed into supervised (S) and non-supervised (NS) treatment groups to receive a three day AS-SP plus single dose of primaquine (PMQ) on second day. They were followed up on the fourth day (Day 3) for adherence check (NS group) and on Day 3, (7 ± 1) and (28+2) day of study for efficacy and tolerability assessment (both S and NS groups). A total of 64 patients (33 in group NS and 31 in S) was enrolled in this 18-month study. Adherence was evaluated in the NS group by counting left-over tablets and oral interview.

RESULTS

Altogether 29 (87%) and 31 (100%) patients were treatment adherent in NS and S group respectively (p-0.114). Four subjects (12.1%) did not bring the empty strips i.e. non-adherent but on verbal interview confirmed medicine intake correctly. In spite of an increased total delay in dosing (0.61 ± 1.171 vs. 0.064 ± 0.250 hours, p-0.035) in group NS, no significant difference in (28+2 day) in clinical and parasitological (100% clearance in both groups), efficacy and safety parameters were found. One case of late clinical failure (Day 40) and another possibly re-infection case (Day 57) were successfully treated with the same drug regimen, both in group NS.

CONCLUSIONS

AS - SP combination possessed a very good adherence, efficacy, and tolerability profile, in both study groups and the supervised dosing didn't have any additional benefit over currently practiced non-supervised therapy.

KEYWORDS

Uncomplicated *falciparum* Malaria, Patient Adherence, Supervised, Non-Supervised, Artesunate-Sulphadoxine-Pyrimethamine

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BACKGROUND

Malaria remains a major public health problem in the tropics with India contributing about 70% of the total cases.[1] West Bengal including Kolkata is a highly malaria-stricken region in India.[2, 3, 4] Inappropriate use of antimalarial agents and consequent emergence of drug resistant *falciparum* malaria is a major concern. Thus, artesunate plus sulphadoxine pyrimethamine (AS-SP), has been used as the universal first-line drug for *falciparum* malaria in India since 2010 under the aegis of National Vector Borne Disease Control Programme (NVBDCP).[5,6,7]

Prevailing resistance to SP in India, and alarming clinical observations of failure of artemisinin combination therapies (ACT) in Thai-Cambodian border mandates regular monitoring of the responses to AS-SP combination as the efficacy and lifespan of ACT largely depend on the partner drug.[7,8,9,10] Moreover, treatment non-adherence resulting in subtherapeutic drug levels is a recognized factor contributing to antimalarial resistance, while good adherence to ACT fosters rapid clinical and parasitological cure.[11,12,13]

It is hypothesized, quick clinical and parasitological response of ACT and daily pill burden may predispose to poor compliance to the 3-day AS-SP treatment.[14] This encourages the risk of recurrent disease and the emergence of drug resistance as well. It seems this issue has not been adequately explored in India yet, although a few reports from other parts of the world have been published.[15,16] Under these circumstances, to determine the extent of adherence to AS-SP therapy in uncomplicated *falciparum* malaria and to investigate its impact on treatment outcome (efficacy and tolerability), a randomised controlled trial (Registered to Clinical Trial Registry of India, retrospectively, bearing registration no: CTRI/2014/10/005105) was conducted comparing AS-SP therapy, deployed as supervised versus non-supervised administration.

METHODS

This study was an open-label, parallel-arm, randomized controlled clinical trial. However, the intervention was supervised dosing of the existing AS-SP regimen i.e. process of care changes. The study commenced from May, 2012 after obtaining approval from Clinical Research Ethics Committee of the institute and continued for a span of 18 months. In this OPD-based study, the subjects were drawn from the patients attending the Malaria Clinic of our institute. This being primarily an effectiveness trial the inclusion-exclusion criteria were not stringent or rigid and as far as practicable was thus limited to logistic and feasibility considerations only.

Inclusion Criteria

- Presence of acute symptomatic uncomplicated malaria confirmed by blood smear positivity with asexual forms of *P. falciparum* parasites only (without mixed infection).
- Only those of the above patients considered eligible by the physician at the Malaria Clinic, for dispensation of AS-SP plus primaquine treatment as per the national guidelines (NVBDCP).
- Adult patients (age >18 years) - both sexes. No upper age limit was fixed conforming to the usual clinical practice for adult patients at our OPD.
- Patients willing to give informed consent.
- Patients considered able to comply with the study protocol for the duration of the study.
- Patients residing within a reasonable distance of the site, so that attendance of all study visits and follow-up by medical staff are logistically feasible.

Exclusion Criteria

- Mixed infection with another *Plasmodium* species at the time of presentation (including *P. vivax, P. ovale and P. malariae*)
- Known allergy to artesunate, artemisinin derived products, sulphadoxine, pyrimethamine, primaquine or any other related drugs.
- G6PD deficiency as investigated by the G6PD test.[17]

Adult patient of both sexes, fulfilling the above-mentioned inclusion and exclusion criteria were considered for enrolment in the study after obtaining duly signed informed consent.

Patients were randomly assigned into two study groups namely supervised (S) and non-supervised (NS) treatment groups. Both of the groups received the same ACT antimalarial regimen - AS-SP as recommended in the NVBDCP of India[6] i.e. tablet artesunate (AS) 50 mg - 4 tabs daily for 3 days (on day 0, 1, and 2) and tablet sulphadoxine 500 mg + pyrimethamine 25 mg (SP) - 3 tabs on day 0. Additionally, primaquine at a dose of (0.75 mg/kg body weight) i.e. 6 tablets of primaquine phosphate 7.5 mg base were administered on day 2 encompassing a total dose of 45 mg base. In group S the study subjects were asked to attend the study site daily on days 0, 1 and 2 when the study medications were administered under direct supervision. In group NS, in strict accordance to routine practice at Malaria Clinic, the study medications were dispensed to the subjects with proper direction of intake. In case of vomiting within 30 minutes after receiving any study medication in group S on any of the dosing days, the patient was administered a second full dose. However, generally redosing was not performed in the NS group. A single dose of paracetamol (≤1g) was prescribed concomitantly to relieve fever, general body aches and ondansetron for nausea and vomiting, at necessary.

The study was designed as standard superiority design. With a predicted adherence of 100% in the group S and 80% in group NS, total 64 patients (each group comprising of 32) were required to have 80% chance of detecting the difference of adherence at the significance level of $p<0.05$.

Further allowing a drop-out rate of 20%, to get the full data of 64 patients the total number of patients to be enrolled was calculated as 80 with each group comprising of 40 patients (using standard statistical software: www.sealedenvelop.com). Although we did not perform any pilot study and no published data was available in West Bengal, 80% figure for non-supervised adherence was taken on the basis of general experience with patients in our setting. For logistic reasons, initially only patients attending the Malaria Clinic on two days (Monday and Tuesday) every week were approached. Subsequently as the study advanced, we extended the patient recruitment over more days in a week as per the situation.

The screen-eligible subjects were randomized using a computer-generated random number table, by balanced block randomization in blocks of 4, into either Group S or Group NS till the desired number of subject's data are accumulated in two groups.

Assessment Parameters

Demographic parameters – Patient's age, sex, bodyweight, address, race, marital status, educational level, occupation etc., were recorded at screening (Day 0) only.

For Assessment of Adherence

In Group NS, the study participants were asked to attend the study site on day 3 carrying back the empty strips of medications as dispensed. Adherence to therapy in patients of group NS was assessed on day 3 by a mix of the following:

- checking the blister packs for remaining left-over tablets.
- checking the medication compliance through oral interview.
- subject's self-reported compliance.

Medication adherence was not checked with the medication compliance card or medication diary in the NS group in order to not interfering with the current treatment practice as followed in the malaria clinic. Patients were classified as non-adherent if tablets remained in the blister pack or when reporting inadequate intake of dose and/or timing of tablets. In case of non-adherence, attempts were made to find the reasons for such non-adherence. Patients were classified as adherent when all the doses of study medications were taken at the correct time on the correct day and in the correct amount.

For Assessment of Efficacy and Tolerability

All relevant information had been duly captured on day 0 and day 3 through patient interview and clinical (including vital signs and axillary temperature) and parasitological evaluation for efficacy assessment, 12 lead ECG and relevant laboratory tests for safety evaluation (Table 1). Study participants were asked to attend the study site again on day 7(± 1 day) and day 28 (+2 days) for follow-up to evaluate treatment outcome by history taking, clinical and parasitological examination in the post treatment period.

Patients attending the malaria clinic on two days (Monday and Tuesday) every week, and considered eligible by the physician at the clinic, for dispensation of AS-SP plus primaquine treatment as per the national guidelines (NVBDCP), subjected to screen		
Day 0	SCREEN (inclusion-exclusion criteria) - Informed consent process - Screen-eligible and willing subjects – Randomisation Baseline assessment of efficacy and safety parameters: history, clinical and parasitological (including gametocyte) examination, ECG, lab tests*	
Day 0	Group S Advising† and implementing Supervised (at Clinic) administration of AS-SP	Group NS Advising administration (at home) of AS-SP for 3 days plus single dose of PMQ on Day 1 Non-supervised intake (at home) AS-SP
Day 1	Supervised (at Clinic) administration of AS-SP and PMQ	Non-supervised intake (at home) AS-SP and PMQ
Day 2	Supervised (at Clinic) administration of AS-SP	Non-supervised intake (at home) AS-SP
Day 3 Follow up (Assessment) Visit 1	Efficacy - clinical and parasitological (including gametocyte clearance), Tolerability - history, clinical examination, ECG, lab tests	Compliance - Pill count, Interview, Efficacy - clinical and parasitological (including gametocyte clearance), Tolerability - history, clinical examination, ECG, lab tests
Day 7 (± 1 day) Follow up (Assessment) Visit 2	Efficacy - clinical and parasitological (including gametocyte clearance), Tolerability - history, clinical examination	Efficacy - clinical and parasitological (including gametocyte clearance), Tolerability - history, clinical examination
Day 28 (+ 2 days) Follow up (Assessment) Visit 3	Efficacy - clinical and parasitological (including gametocyte clearance)	Efficacy - clinical and parasitological (including gametocyte clearance)

Table 1. Study Techniques - Different Study Related Activities and Timelines

*Lab Tests: Laboratory evaluations for safety (haematology, biochemistry and urinalysis (dipstick)) will be performed at screening and on the Day 3 and on any other day if a patient spontaneously returns with fever. Haematology- Haemoglobin, haematocrit, TLC, DLC, platelet count Biochemistry - Glucose, urea, creatinine, liver function tests (bilirubin, AST, ALT, ALP). Urinalysis - Specific gravity, pH, glucose, protein, ketones, leukocytes (microscopic examination in case of abnormalities)
A total of 5 ml of blood will be drawn from anterior cubital vein on day 3 to study the haematological and biochemical parameters.

†For ethical reasons, the patients of Group S shall also be dispensed with the Day 1 and Day 2 quota of AS-SP and PMQ tablets as in the case of the NS Group. But they will be counselled to return on Day 1 and Day 2 for supervised administration. This is done to avoid any potential non-attendance of the patients of Group S on Day 1 and/or Day 2 which may eventually lead to fatal outcome. In case the patient is unable to turn up, he or she would be advised over telephone to take the medications at home, though not directly observed. These data would also be appropriately considered for analysis.
NVBDCP: national vector borne disease control programme, AS-SP: artesunate / sulphadoxine-pyrimethamine, ECG: electrocardiogram, PMQ: primaquine, TLC: total leucocyte count, DLC: differential leucocyte count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, pH: potential of hydrogen, S: supervised, NS: non-supervised

Parasitological Study[18]

- Both thick (for counting number of parasites) and thin (for species identification) peripheral smears had been prepared and stained properly.
- Asexual parasites and gametocytes were counted against 200 white blood cells and converted to parasites/µL by assuming a density of 8000 white blood cells/µL blood.

Tolerability Assessment

For grading the adverse events Common Terminology Criteria for Adverse Events V3.0 (CTCAE) was followed.[19] Treatment emergent clinical adverse events were documented. Intensity of the adverse events was determined by following generally accepted criteria: Mild – No disruption of daily activities and requiring no specific treatment. Moderate – Some disruption of daily activities or requiring specific treatment and Severe – Definite disruption of daily activities and requiring specific treatment. Causality

assessment was done using World Health Organisation (WHO) - Uppsala Monitoring Centre Causality Assessment criteria.[20]

12-Lead ECG[21,22]

- Performed at screening Day 0 and on day 3 in both groups and on any other day if a patient spontaneously returned with fever.
- QTc interval was calculated 'manually' using Fridericia's formula.
- Any increase in QTc interval of >60 msec from the baseline or any recorded absolute value of ≥500 msec was recorded as QT_C prolongation.

Owing to logistic constraints the follow up visits of study subjects was restricted to three visits only - on day 3, day 7 (±1 day) and day 28 (+2 days). Different study related activities are depicted in a tabular form as shown in the Table 1.

RESULTS

A total of 82 patients were randomized to two study groups (NS and S) equally i.e. 41 in each group. Eighteen (18) study subjects were lost in follow-up, 10 in group NS and 8 in group S (Chart 1). Final analysis was done for 64 (78.04%) patients (33 in group NS and 31 in group S).

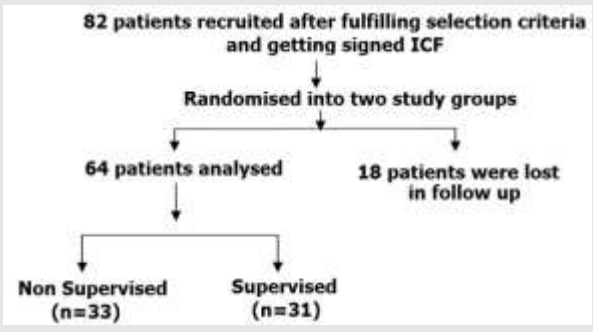

Chart 1. Flow of Participants in the Study

Efficacy and safety analysis for the 64 subjects was done on the basis of modified intention to treat analysis. Pre- and post-treatment laboratory data were obtained from subjects who had come for at least the 1st follow up visit, i.e. when the post-baseline laboratory data was assessed. Missing values were dealt with the last observation carried forward strategy. Data was analysed keeping a two tailed significance level at $p<0.05$ with standard statistical software like Microsoft Excel, SPSS version 11.5/ GraphPad prism version 5 etc. Beforehand, for numerical variables a test of normalcy like Kolmogorov-Smirnov test was used.

All study subjects were recruited on an ambulatory (outpatient) basis, all of them were male, in their forties in average, indicating a preponderance of young adults (Table 2). Study subjects in both groups were comparable in respect to age, sex, body weight, religion, occupation, literacy and G6PD status. Majority were from the urban locality surrounding the study site.

Category	Non-Supervised Group (n= 33)	Supervised Group (n=31)	P Value (between Groups)
Age (in years)			
Range	19-46	19-65	
Mean ± SD (Standard Deviation)	37.6 ± 13.37	40.5 ± 13.46	0.384
Median ± IQR (Inter Quartile Range)	40.0 (25.5, 47.0)	40 (30.0, 52.0)	
Sex			
Male	33 (100%)	31 (100%)	
Female	0	0	–
Body weight (in kg)			
Range	60.84 ± 8.119	57.29 ± 7.450	0.073
Mean ± SD	45.4-84.0	44.0-69.9	
Residence			
Urban	32 (96.97%)	30 (96.77%)	1.000
Rural	1 (3.03%)	1 (3.23%)	
Literacy no (%)			
Illiterate	17(51.52%)	19 (61.29%)	
Primary	2 (6.06%)	2 (6.45%)	
Secondary	9 (27.27%)	8 (25.81%)	0.706
Higher Secondary and above	5 (15.15%)	2 (6.45%)	
Religion no (%)			
Hindu	9 (27.3%)	8 (25.8%)	0.894
Muslim	24 (72.7%)	23 (74.2%)	
Occupation no (%)			
Manual worker	4 (12.12%)	11 (35.48%)	
Business	15 (45.45%)	12 (38.71%)	
Service	8 (24.24%)	4 (12.90%)	0.142
Self-employed	2 (6.06%)	3 (9.68%)	
Student	4 (12.12%)	1 (3.03%)	
G6PD Status			
Normal	33 (100%)	31 (100%)	
Abnormal	0 (0.00%)	(0.00%)	–

Table 2. Baseline Demographic Profile of the Two Groups of Study Subjects

G6PD: Glucose 6 phosphate dehydrogenase
p values for body weight, age are from Student's unpaired t test, for religion, literacy and occupation from Chi-square test and for residence from Fisher's exact test,

Category	Non-Supervised Group (n= 33)	Supervised Group (n=31)	P Value (Between Groups)
Adherence to dosing regimen no. (%)			
Nonadherent	4 (12.1%)	0	0.114
Adherent	29 (87.9%)	31 (100.0%)	
Delay (in hours) on Day-1(2nd day) of AS (Artesunate) intake			
Mean ± SD	0.27 ± 0.574	0.00 ± 0.00	
Range	0-2	0-0	0.007 *
Median	0.00	0.00	
Delay (in hours)on Day-2 (3rd day)of AS (Artesunate) intake			
Mean ± SD	0.33 ± 0.645	0.06 ± 0.250	
Range	0-2	0-1	0.045 †
Median	0.00	0.00	
Total delay (in hours) between 3 doses of AS (Artesunate)			
Mean ± SD	0.61 ± 1.171	0.064 ± 0.250	
Range	0-4	0-1	0.035 †
Median	0.00	0.00	

Table 3. Medication Adherence Profile of the Two Groups of Study Subjects

p values for dosing adherence is from Fisher's exact test and for dosing delay from Mann-Whitney U test(* denotes p<0.01, † denotes p<0.05)

Assessment of Treatment Adherence

Consumption of scheduled medications were confirmed by the returned empty strips. The patients who did not return any of the two empty blister packs were considered as nonadherent. Delay was defined as more than one-hour time interval between recommended time and actual time of drug intake. From the time record maintained by the subject the delay time was noted. Thus, if medicine was taken within one hour of the recommended clock time no delay was

considered to have occurred for that subject. Beyond that point any delay was considered rounding up to nearest half an hour. The delay of intake of 2nd and 3rd dosage of AS was calculated by interviewing the patients and documented as Day 1 (2nd Day) delay and Day 2 (3rd day) delay. Then total delay was calculated by simply adding the two measurements.

Table 3 shows that 4 patients (12.1%) in the NS group were nonadherent to treatment regimen as they did not bring all of the empty blister packs. But, on verbal interview and patient's self-reported compliance, they all confirmed the intake of all of the scheduled dosage of the medications. It is also evident that 'delay' in group NS is significantly more than group S both in terms of delay on Day 1 ($p<0.01$) and Day 2 and total delay ($p<0.05$) of intake of AS.

Efficacy Parameters

Primary efficacy variables were clinical efficacy parameters (Table 4) and parasite (both asexual and gametocyte) clearance (Table 5)

Parameters	Non-Supervised Group (n= 33), no (%)	Supervised Group (n=31), no (%)	P Value (between Groups)
Fever			
Day-0	33 (100%)	31 (100%)	
Day 3	0*	0*	
Day 7	1 (3%)*	0*	1.000
Day 28	0*	0*	
Nausea			
Day-0	10 (30.3%)	10 (32.3%)	0.866
Day 3	6(18.2%)	1 (3.2%)†	0.105
Day 7	0 (0.0%)†	0 (0.0%)†	_
Day 28	0 (0.0%)†	0 (0.0%)†	_
Vomiting			
Day-0	8 (24.2%)	5 (16.1%)	
Day 3	1 (3.0%)‡,	0 (0.0%)‡,	0.420
Day 7	0 (0.0%)†	0 (0.0%)‡,	1.000
Day 28	0 (0.0%)†	0 (0.0%)‡,	
Anorexia			
Day-0	25 (75.8%)	21 (67.7%)	0.476
Day 3	22 (66.7%)	11 (35.5%)†	0.013
Day 7	8 (24.2%)*	3 (9.7%)*	0.123
Day 28	0 (0.0%)*	2 (6.5%)*	0.231
Headache			
Day-0	26 (78.8%)	26 (83.9%)	0.603
Day 3	21 (63.6%)	17 (54.8%)†	0.474
Day 7	6 (18.2%)*	9 (29.0%)*	0.306
Day 28	1 (3.0%)*	2 (6.5%)*	0.607
Fatigue			
Day-0	27 (81.8%)	28 (90.3%)	0.476
Day 3	24 (72.7%)	27 (87.1%)	0.153
Day 7	19 (57.6%)‡,	22 (71.0%)‡,	0.264
Day 28	5 (15.2%)*	8 (25.8%)*	0.290
Myalgia			
Day-0	29 (87.9%)	24 (77.4%)	0.268
Day 3	11 (33.3%)*	6 (19.4%)*	0.206
Day 7	3 (9.1%)*	2 (6.5%)*	1.000
Day 28	0 (0.0%)*	0 (0.0)*	_

Table 4. Changes in Clinical Efficacy Parameters in the Two Treatment Groups

p values in comparison between supervised and non-supervised groups are from Chi-square test
*, †, ‡ denote <0.001,<0.01 and p <0.05 respectively when compared within groups in comparison to Day 0 value (McNemar's test)

As per Table 4, there was no significant difference on clinical efficacy parameters between the two treatment groups except for anorexia which was significantly more pronounced ($p<0.05$) in non-supervised group than supervised group on Day 3 visit. However, it was evident that all clinical efficacy parameters significantly improved from Day 0 values in both supervised and non-supervised treatment groups, during subsequent follow-up visits, as the study advanced.

Parasite Clearance

As per Table 5, complete clearance of asexual parasite was achieved in both S and NS group right from the Day 3, and that had been maintained till the end (Day 28) of the study.

Parasite Form	Non-Supervised Group (n= 33) Persons Positive: no (%)	Supervised Group (n=31) Persons Positive: no (%)	P Value (between Groups)
Asexual Parasite			
Day 0	33 (100%)	31 (100%)	
Day 3	0 (0.00%)*	0 (0.00%)*	
Day 7	0 (0.00%)*	0 (0.00%)*	
Day 28	0 (0.00%)*	0 (0.00%)*	
Gametocyte			
Day 0	5 (15.2%)	3 (9.7%)	
Day 3	0 (0.00%)	3 (9.7%)	
Day 7	0 (0.00%)	0 (0.00%)	0.108
Day 28	0 (0.00%)	0 (0.00%)	
Before-after p value			
Day 3	0.063	1.000	
Day 7	0.063	0.250	
Day 28	0.063		

Table 5. Comparison of Parasite Clearance between the Treatment Groups

Between non-supervised and supervised groups, p value is from Fisher's exact test. *denotes p<0.001 in comparison to Day 0 value when compared within group (McNemar's test).

There was also no significant difference regarding gametocyte clearance in the two study groups in spite of incomplete clearance among the lone three gametocyte positive patients in the group S on Day 3.

Measures of Tolerability

The safety measures considered were haematological and biochemical tests and treatment emergent adverse events spontaneously reported by the patients.

Laboratory Parameters for Safety Assessment

There was no significant difference on all of the measured haematological parameters and urinary parameters. However, significant reduction in total leucocyte count and neutrophil count was evident in Day 3 in comparison to Day 0, in group NS, mean value 8492.42 ± 4517.53 (Day 0) and 6340.91 ± 3449.30 9 (Day 3), p=0.011. There was also no significant difference on liver function, renal function parameters and random blood glucose levels between the study groups. However, a significant reduction in serum total protein, mean 7.68 ± 1.14 (Day 0) and 7.30 ± 0.88(Day 3), p= 0.040 and significant increase in serum urea value, mean 20.60 ± 7.95 (Day 0) and 25.18 ± 13.97 (Day3), p= 0.038 was observed in the group S on Day 3. (Table not produced).

Treatment Emergent Clinical Adverse Events

There was no significant difference on number of adverse events in the two study groups (25 in Group S and 19 in

group NS) (Table 6). All of the adverse events reported were mild to moderate in intensity, none was serious, and all resolved during study period. Majority of the adverse events were possible or probable, few came out as unlikely (WHO-UMC causality assessment criteria). All adverse events resolved during the study period. None warranted discontinuation of the study medications.

Altogether three cases of QTc prolongation were documented during the study – one in group NS (84 msec on Day 3) and other two in the group S (67 msec on Day 2 and 65 msec on Day 3) all from Day 0 respectively. In later two cases QTc interval came to baseline level in the next visit (Day 7) and in the first case it persisted even up to 28 days.

Adverse Events	Non-Supervised Group (n= 33)	Supervised Group (n=31)	P Value (between Groups)
Dyspepsia	08	09	0.665
Rash	02	00	0.493
Itching	01	02	0.607
Diarrhoea	02	01	1.000
Constipation	01	00	1.000
Headache	03	0	0.239
Vertigo	00	03	0.108
Palpitation	00	01	0.484
Alteration of taste	01	01	1.000
Sinus bradycardia	00	01	0.484
Vomiting	01	00	1.000
Nasal block	01	00	1.000
Oral ulcer	00	01	0.484
Neck pain	01	00	1.000
Loss of appetite	01	00	1.000
Syncope	01	00	1.000
Enlarged lymph node	01	00	1.000
Fever	01	00	1.000
QTc prolongation cases	01	02	0.607

Table 6. Treatment Related Adverse Events in the Two Study Groups

QTc: Corrected QT interval
The numbers represent counts in individual groups.
p values are from fisher's exact test except in dyspepsia where it is from chi square test

DISCUSSION

The two study groups were comparable at baseline regarding age, sex, body weight, residence, education and occupation. The study showed that most of the patients were in their forties and quite young and all men. Female patients, lesser in number than male, did not agree with multiple follow-up visits as they were engaged in the regular household works. This might appear as a limitation of the study because of losing the scope to study the gender variation on adherence vis-à-vis treatment outcome. Most of the study participants were economically poor, Muslim by religion, migrated from other places, having no formal education. They lived in very unhealthy condition and mostly in open places, making them vulnerable to mosquito bites.

Regarding adherence to dosage regimen, the non-supervised group showed good adherence and was not significantly different from the supervised group. Only 4 (12.1%) patients showed nonadherence because of not returning the empty strips. They forgot to bring those strips and confirmed the intake of scheduled medications in time.

Our study result also conforms with the findings from other studies in India and abroad showing good adherence to AS-SP / other AS combinations.[10,15,16] The short duration of therapy and the disease with potentially serious consequences might made them a bit more adherent. Another point needs to be mentioned that according to many published literatures proper communication also improves treatment adherence.[23] One patient in group NS dialled the investigator about vomiting within half an hour of intake of artesunate and re-dosing was advised on ethical ground. Noteworthy, a modest delay (up to 2 hrs.) of AS intake in Group NS ($p<0.05$), did not make any significant difference, in terms of clinical and parasitological efficacy i.e. treatment outcome, with group S. (Table-3) Fever was earliest to disappear in both groups, remitting mostly on Day 3 and did not reappear till Day 28th. But fatigue, headache and myalgia continued to up to Day 28 in many subjects. One patient returned back with fever and *P. falciparum* parasitaemia, on Day 40 and another on Day 57 of the study respectively. They neither had any parasitaemia nor residual symptoms on Day 28. They again treated with AS-SP as per NVBDCP guideline and were clinically and parasitologically cured. The former patient was nonadherent in the study as he did not bring the empty strips but on self-reported compliance, he confirmed the intake of all of the study drugs at scheduled hours. This patient also qualified to be a case of late clinical failure (LCF).[6] But, there is a probability of re-infection or recrudescence in this particular patient. In the other case the probability of re-infection is more. Only genomic study of the parasite could confirm, but could not be done due to logistic reasons.

Study drugs had good tolerability profile in both groups not warranting withdrawal in any patient. A study on artemether-lumefantrine in uncomplicated *falciparum* malaria in Bangladesh, showed no advantage of directly observed therapy over non-supervised therapy where adherence was high, and efficacy was similar in both groups.[15]

Similarly, our study also demonstrated high medication adherence and cure rate with both the supervised and non-supervised AS-SP regimen in small cohorts of uncomplicated *falciparum* malaria patients. This issue had not been investigated in India earlier through an intervention study.

CONCLUSIONS

Non-supervised AS-SP regimen could demonstrate satisfactory adherence and treatment outcome in terms of clinical and parasitological cure rate and tolerability (as revealed in the small study population in Kolkata) thus does not necessitate supervised dosing. But, in few patients, reappearance of malaria after 28 days provides signal towards continuous monitoring on long term basis to detect the treatment failure cases at the earliest.

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