RETROSPECTIVE STUDY OF COMPARATIVE EFFECTIVENESS OF TWO ARTESUNATE COMBINATION DRUG REGIMENS IN UNCOMPPLICATED FALCIPARUM MALARIA IN CHILDREN

ANITA MEHTA, ABHA PANDIT*

Department of Pediatrics, BRD Medical College Gorakhpur, Uttar Pradesh,*Department of Medicine, Index Medical College Hospital & Research Centre, Indore, Madhya Pradesh. Email: drabhaindore@gmail.com
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ABSTRACT

Background: Malaria is a major cause of morbidity and mortality in children in developing world. Successful treatment and avoidance of resistance development to antimalarial drugs in endemic areas are important current concern. Method: Medical records of children under 14 year age treated for uncomplicated falciparum malaria with artesunate combination regimens were reviewed. Comparative efficacy of two artesunate combinations either with amodiaquin or sulfadoxine-pyrimethamine was evaluated. Fever clearance time, parasite clearance time and length of hospital stay were the studied parameters. Result and Conclusion: Study on modest sample of 55 cases, 34 treated with artesunate-amodiaquine (AS-AQ) and 21 cases treated with artesunate-sulfadoxine-pyrimethamine (AS-SP) regimens revealed both to be effective. AS-AQ regimen appeared to be superior to AS-SP regimen in regard to faster parasite clearance and shorter hospital stay.

Keywords: Falciparum malaria in children; antimalarial therapy; artesunate; amodiaquine; sulfadoxine-pyrimethamine.

INTRODUCTION

Resistance to antimalarial drug monotherapies has led WHO recommendation of artemisinine combination therapy (ACT) for malaria [1]. In principle, the combination therapy involves the use of two or more schizonticidal drugs targeting malaria parasite by independent mechanisms. ACT regimens are more effective than non-ACT in yielding rapid cure measured as parasite clearance, reduction in gametocyte carriage and lower risk of drug resistance of parasite [2]. Artemisinine rapidly reduces the biomass of drug-resistant parasites and high concentration of the combination partner drug helps elimination of residual parasites.

Amodiaquine derivatives are quite safe medications. These are well absorbed upon oral administration; are fast converted to the active metabolite, achieving peak concentration in 1 to 2 hours [3]. The half-lives are fairly short of 1 to 3 hours and they possess strong antimalarial efficacy [4]. Short half life mandates their use in combination therapy toward treatment success. Artesunate-amodiaquine (AS-AQ) combination is not expensive and well tolerated. It offers fast antimalarial effect; is able to prevent gametocyte formation and effective against drug-resistant strains [3]. Amodiaquine is like chloroquine, a 4-aminoquinoline derivative, generally effective against P.falciparum. It is more palatable and better tolerated than chloroquine [5].

Sulfadoxine-pyrimethamine (SP) is a fixed combination of long-acting sulfonamide and antifolate pyrimethamine. It is also inexpensive single dose therapy for malaria in areas of documented chloroquine resistance of parasite [5]. AS-SP combination treatment regimen is extensively studied and found effective in uncomplicated falciparum malaria. Sole SP treatment is accompanied by high recurrence rate [5].

The present retrospective study had the objective of comparing the efficacy of AS-AQ and AS-SP combination therapies employed in children admitted with uncomplicated falciparum malaria.

Patients and method

The review was conducted of medical records of children admitted to the pediatric ward of BRD medical college, Gorakhpur between October 2012 till March 2014, diagnosed as uncomplicated falciparum malaria. Those cases treated with AS-AQ and AS-SP were specifically picked up for study. Inclusion criteria were age under 14 years and bearing no other comorbid conditions. Uncomplicated falciparum malaria was diagnosed as symptomatic P.falciparum parasitemia <5%, with vital organ dysfunction, and managed on standard oral therapy. Children with a clinical picture of mixed infection, severe disease, and incomplete data were excluded.

Information about each case was collected on age, gender, clinical and laboratory profiles. Children were treated with the following combined drug regimens:

AS 4mg/kg/day for 3 days, combined with AQ 10 mg base/kg/day on first and 2nd day and 5mg base/kg/day on 3rd day. The alternative combination was a single dose of SP 1 to 1.5 mg/kg pyrimethamine on the first day. All the children also received 0.75mg/kg single dose of primaquine also.

Treatment efficacy was evaluated by fever clearance time, parasite clearance time and length of hospital stay. Parasite clearance time was time since drug administration till disappearance of asexual P.falciparum from patients blood samples evaluated every 24 hours for 3 consecutive days. Semi-quantitative thick smear parasite counts were interpreted as follows:+, 1 to 10 asexual parasites per 100 high-power field. ++ 11 to 100 asexual parasites per 100 high-power fields. +++ 1 to 10 asexual parasites per single high power field and ++++ >10 asexual parasites per high power field.

Fever clearance time was defined as the time between the antimalarial drug administration and attaining afebrile state. The length of hospital stay was as ambulatory patients from admission to discharge. Daily treatment record was examined for record of any adverse event. Comparative effectiveness of two treatments was assessed by independent t test. Observation and results

In all 171 case records were screened and 55 case records contained adequate recorded information’s to meet eligibility for inclusion.34 patients were recipients of AS-AQ combination daily. Rest 21 cases received AS-SP combination.

Baseline characteristics of the patients are presented in table.1.
Table 1: Characteristics of children with uncomplicated falciparum malaria.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AS-AQ Treated</th>
<th>AS-SP Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean ±SD)</td>
<td>6.7 ±3.57</td>
<td>7.2 ±3.82</td>
</tr>
<tr>
<td>Males/Females</td>
<td>20/14</td>
<td>15/6</td>
</tr>
<tr>
<td>Clinical Symptoms (N cases &amp; %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>34 (100)</td>
<td>21 (100)</td>
</tr>
<tr>
<td>Shivering</td>
<td>25 (73.5)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Simple febrile seizures</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb g/dl (Mean ±SD)</td>
<td>10.27 ±2.41</td>
<td>10.73 ±1.8</td>
</tr>
<tr>
<td>WBC count/mm³ (Mean ±SD)</td>
<td>6584 (5368)</td>
<td>5585 (2316)</td>
</tr>
<tr>
<td>Platelet count/mm³ (Mean ±SD)</td>
<td>136922 (90242)</td>
<td>129270 (9160)</td>
</tr>
</tbody>
</table>

Observed outcomes of studied two combination regimens are summarized in table 2.

Table 2: Outcome measures of two artemesunate combination treatment regimens.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AS-AQ (n=34)</th>
<th>AS-SP (n=21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasite clearance time (days; Mean ±SD)</td>
<td>1.38 ±0.68</td>
<td>1.9 ±0.93</td>
<td></td>
</tr>
<tr>
<td>Fever clearance time (days; Mean ±SD)</td>
<td>1.42 ±0.94</td>
<td>1.54 ±0.83</td>
<td></td>
</tr>
<tr>
<td>Length of Hospital stay days (Mean ±SD)</td>
<td>5.1 ±1.21</td>
<td>6.2 ±0.96</td>
<td></td>
</tr>
</tbody>
</table>

*Indicates statistically significant difference

As seen in the table 1, there were no significant differences in baseline characteristics including clinical and laboratory findings in groups of patients that received separate artemesunate combination antimalarial therapy. Further as depicted in table 2, patients receiving AS-AQ regimen had significantly shorter mean parasite clearance time and shorter length of hospital stay. There was no significant difference in time of fever clearance in the two groups.

DISCUSSION

The results show both the studied treatment regimens to be effective in treating uncomplicated falciparum malaria in children. The clinical efficacy of AS-SP combination was lower than AS-AQ combination. The observation is consistent with other reports [5, 7]. The efficacy of AS-AQ and AS-SP was found to be 100% and recrudescence less than 5% in the referred study. Artesunate is documented for fast parasite clearing effect [8]. No significant difference in fever clearance time of AS-AQ and AS-SP regimens was found. Another study on AS-AQ treatment reported fever disappearance in 86% of cases on the first day and 97% by the second day [9]. Faster fever clearance is reported by AS-AQ compared to chloroquine treatment alone [10]. A faster disappearance of fever with AS-SP combination compared to SP treatment alone is also similarly reported [11]. This study reveals ACT regimens in uncomplicated P. falciparum malaria, to clear fever within two days.

Parasite clearance time indicates treatment efficacy. Faster parasite clearance with ACT compared to non-ACT treatment regimens is documented [12]. Another study comparing the same ACT regimens as herein also reported similar observations for parasite clearance time [9]. No significant difference in fever and parasite clearance time in uncomplicated falciparum malaria with the same compared ACT regimens has however been reported in a study in South Africa [13]. The relative efficacy of artemesunate combination treatment may vary regionally due to variations in epidemiological determinants. The present study suggests such inference.

CONCLUSION

Preference of AS-AQ regimen over AS-SP whenever feasible is advocated.

Conflict of interest statement

There is no conflict of interest.

REFERENCES
