Azithromycin Pulse Therapy with Oral Doxycycline in the Treatment of Acne Vulgaris, a Randomized Group Study

C. Sadhana and N. S. Muthiah

1Department of Pharmacology, Sree Balaji Medical College & Hospital Affiliated to Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

Authors’ contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Acne vulgaris is a common dermatological problem. The choice of proper treatment is determined by the severity and extent of acne. Moderate to severe acne vulgaris cases respond well to systemic antibiotics. Antibiotics execute their anti-propionic bacterium effect by inhibiting the bacterial growth and colonization of pilosebaceous glands and thus further inflammation is prevented. The efficacy and possible side effects of various oral antibiotics has been the subject of numerous studies for at least the last twenty years in an effort to understand, which products are likely to produce better efficacy with least possible side effects. The new emerging problem is antibiotics resistance to propionic bacterium. There has been a constant increase in search of safe medications to overcome the side effects and resistance of existing formulations for the treatment of acne vulgaris. The study duration was 8 weeks. A total of 200 study participants of both sexes with complaints of acne vulgaris were included in the study and randomized into two groups. Group I (100 study subjects) – 500 mg Azithromycin once daily for three consecutive days in a week for 2 months and Group II (100 study subjects) –100 mg Doxycycline once daily for 2 months. After doing initial laboratory tests treatment was initiated. Three scheduled visits – Baseline, at the end 4th week and at the end of study were done and the response to treatment was evaluated. The
efficacy of the drugs was assessed by the change in grading of acne from baseline and at follow up visits. Doxycycline was found to be better than azithromycin pulse therapy in reducing acne severity. During the visits gastrointestinal, dermatological and other side effects were also noted and recorded. Adverse event profile of both the drugs showed that there was no non-compliance incidence due to adverse event. But the number of adverse events was higher in doxycycline group.

Keywords: Azithromycin pulse; oral doxycycline; acne vulgaris.

1. INTRODUCTION

Acne vulgaris a common chronic, inflammatory disease of pilosebaceous unit, usually manifests in adolescents with polymorphic lesions like comedones, papules, nodules and cysts. When the condition is not treated properly it can lead to scaring [1]. It is a multifactorial disease influenced by hormonal, genetic, microbiological and immunological factors. Though, it is highly prevalent among adolescent age group, it can affect all age groups [2]. Acne normally affects people during the onset of puberty [1]. Its severity generally increases with age and time. The inflammatory changes of acne may be quite chronic and may lead to severe residual scarring. It is more common and severe in males. The age of incidence is between 14 to 17 years in women and 16 to 19 years in men [1-2]. The racial difference is not well studied.

Genetic factors influence the susceptibility to acne [1]. The role of diet as a cause is unclear. Menstrual cycles and puberty, may chip in acne formation. Raise in androgens cause follicular glands to overgrow and produce more sebum [3]. Alike condition is seen in pregnancy, leading to increased sebum production. Smoking worsens acne in susceptible individuals [1,4]. Acne principally affects skin with a greater number of oil glands including the face, chest and back. Pathogenesis of acne is due to increased sebum secretion, follicular hyper keratinization, colonization of pilosebaceous glands by propionic bacterium and inflammation [5]. If not treated properly, acne might lead to complications like inflammatory lesions and nodules, cystic lesions, post inflammatory hyperpigmentation (PIH), nodular hypertrophic scars, exudative or hemorrhagic nodules and rarely sinus tract formation between the nodules. Lesions in severe acne vulgaris might be very painful, chronic, and refractory to treatment and even cause psychological complications.

Clinical presentation and individual patient needs are the key components to be considered in acne treatment. Many therapeutic options exist for treating acne. For mild cases topical agents such as benzoyl peroxide, antibiotics or retinoid can be used. Moderate to severe cases respond well to oral antibiotics, hormonal therapy or oral retinoid [6]. Antibiotic selection is mainly focused by its efficacy, adverse effect profiles and Propionibacterium acnes (P.acnes) resistance. In the past tetracycline and erythromycin were the commonly prescribed oral antibiotics. As the responsiveness of P.acnes to these drugs decreased, their usage was reduced. This led to increased use of doxycycline. However tetracycline group of drugs may be associated with a large number of undesirable side effects. In recent times, azithromycin - a macrolide methyl derivative of erythromycin gains importance in acne management. It is as effective as doxycycline [7]. Its extensive distribution in the tissue allow pulse dose regimen recommendation for increased compliance [8]. Due to its improved pharmacokinetic properties, high tolerability profile and efficacy against P.acnes, its rationale use in acne has been examined and it has been found to be effective in few clinical studies [7,9-10].

Various doses and regimens of azithromycin have been studied for acne treatment but still, data about the optimum dose of azithromycin is lacking. On this basis, the present study is specifically undertaken to compare the efficacy and safety of oral azithromycin pulse therapy - 500 mg once daily for three consecutive days in a week with oral doxycycline 100 mg daily for 2 months.

2. MATERIALS AND METHODS

This study is an open label, prospective, randomized, single centre, parallel group study conducted to evaluate the efficacy of oral Azithromycin Pulse Therapy and oral Doxycycline Therapy in patients with acne vulgaris (Ref. No. 002/SBMC/IHEC/2017/879).
Patients, who visited the Department of Dermatology, at Sree Balaji Medical College and Hospital, Chennai - Tamil Nadu, with the complaints of pimples (acne), were the source of samples in the present study. The study duration was for 2 months and study period was from March 2016 to March 2017.

2.1 Drug Dosage

Group I (100 patients): Drug Azithromycin - 500 mg Azithromycin is given orally once daily for three consecutive days in a week for 2 months.

Group II (100 patients): Drug Doxycycline - 100 mg Doxycycline is given orally once daily for 2 months. Study subjects were also instructed not to apply any topical medicaments or to undergo any beauty procedures such as chemical peels, facials, bleaches etc during the study period. Parallel assignment of drug was used in both the groups.

Three scheduled visits were carried out during the study period– Baseline visit, at the end 4th week and visit at the end of 8th week (end of study). The response to treatment was evaluated during each follow up visit. During visits gastrointestinal, dermatological and other side effects were also noted and recorded. The following laboratory investigations were done during screening i.e. baseline visit ('0'weeks), at 4th week and at 8th week. Blood Biochemistry, Complete blood count, Random blood sugar, Renal function test and Liver function test.

2.2 Statistical Analysis

Data analysis was done using Statistical Package for the Social Sciences (SPSS) version 23. All continuous variables were compared using t-test and Qualitative variables were compared using chi-2 test.

3. RESULTS AND DISCUSSION

A total of 248 patients were screened for this study, out of which 48 patients were excluded. Among the 48 patients, 10 patients refused to participate and 38 patients didn’t meet the inclusion criteria of our study. The selected 200 patients were randomized into two groups and the treatment was started as and when they reported to the hospital. All of them continued the study, and there was no discontinuation or withdrawal due to adverse events. All statistical analysis was done in SPSS version 23 and intent to treat principle is employed for analysis. Results were distributed in age, sex, treatment comparison and adverse event profile.

The overall results of this study is shown below: p value (Probability that the result is true) of < 0.05 was considered as statistically significant after assuming all the rules of statistical tests. Regarding demographic characteristics there is no significant difference between the two treatment groups.

Distribution of different grades of disease at baseline and at the end of first and second month for both azithromycin and doxycycline is documented in Table-3. At the follow up visits the acne grades were significantly reduced in both the groups compared to the baseline indicating that both drugs are able to reduce acne vulgaris. Towards the end of the study, presence of more grade III and grade IV patients in azithromycin group compared to the doxycycline group indicates that doxycycline is better in reducing the severity of the acne compared to azithromycin.

Further comparison of response in both azithromycin and doxycycline groups also showed that the doxycycline is better in achieving good improvement Table-4. The difference in the response of these treatments is statistically significant (p value = 0.004).

3.1 Gastro-intestinal Side Effects

Vomiting, nausea, gastritis and diarrhea are the common gastro-intestinal side effects observed during the trial period. The side effects were mild and manageable in both the groups. Overall gastrointestinal side effects in azithromycin and doxycycline groups are 20% and 46% respectively. Comparison of gastro-intestinal side effects between azithromycin and doxycycline treatment groups showed that the doxycycline caused more gastrointestinal side effects compared to the azithromycin treatment (p value = 0.001).

Analysis of complete blood count (CBC) at baseline and the end of first month and second month revealed that there are no major changes in the CBC of the patients. However in the doxycycline group about 7% of the patients show abnormal liver function. The azithromycin
The treatment group has not shown any abnormality in the liver function.

In the current study which included 200 patients, the minimum age of the study population was 15 and the maximum age was 40. The maximum numbers of patients were in the adolescent age group 26-30 years which similar to other acne study of Kane et al, 2007 [11]. In our study, 44% were males and 56% were females which shows increased incidence of the disease among females. This is similar to other acne studies conducted by Balaji Adityan and Devinder Mohan Thappa, 2004 [12]. Doxycycline is a long acting tetracycline derivative. When compared to tetracycline, the absorption of doxycycline is less affected by food with better efficacy. Both inflammatory and non-inflammatory acnes lesions respond well to doxycycline. 50 to 100 mg doxycycline daily for three months treatment could able to reduce 14% and 50% for non-inflammatory lesions, and between 30% and 75% for inflammatory lesions [11,13]. In a study conducted by Moore et al, they concluded that a sub-antimicrobial dosage of oral doxycycline 20 mg when given twice daily for six months exerts considerable reduction in both inflammatory and non-inflammatory lesions [14]. Azithromycin belongs to the antibiotic class- Macrolides. It has a long half-life of 68 hours and therefore can be given three times a week to have better patient compliance. Various oral azithromycin regimens were found to be effective in reducing both inflammatory and non-inflammatory lesions in patients with moderate to severe acne [15-17].

The results of previous studies indicated that both drugs has good therapeutic efficacy. However, both azithromycin and doxycycline treatments showed adverse effects and their prolonged use associated with the resistance. Therefore comparison of the results of efficacy and side effects between these two drugs may help in optimizing the acne therapy in our patients.

**Table 1. Distribution of participants based on age**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 Azithromycin (n=100) Mean ± SD</th>
<th>Group 2 Doxycycline (n=100) Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.5 ± 5.6 yrs</td>
<td>26.9 ± 6.8 yrs</td>
<td>0.557</td>
</tr>
</tbody>
</table>

*The mean age of the study subjects is 26.7 ± 6.2 yrs*

**Table 2. Comparison of the clinical grades of patient at baseline, first and second month**

<table>
<thead>
<tr>
<th>Azithromycin</th>
<th>Doxycycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4th week</td>
</tr>
<tr>
<td>Grade 1</td>
<td>20</td>
</tr>
<tr>
<td>Grade 2</td>
<td>26</td>
</tr>
<tr>
<td>Grade 3</td>
<td>27</td>
</tr>
<tr>
<td>Grade 4</td>
<td>27</td>
</tr>
</tbody>
</table>

**Table 3. Frequency of gastro-intestinal side effects in study**

<table>
<thead>
<tr>
<th></th>
<th>No side effects</th>
<th>GIT side effects</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (100 patients)</td>
<td>80</td>
<td>20 (20%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Doxycycline (100 patients)</td>
<td>54</td>
<td>46 (46%)</td>
<td></td>
</tr>
</tbody>
</table>

*p value - significant*

**Table 4. Type of gastro-intestinal side effects identified in study subjects**

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin (100)</th>
<th>Doxycycline (100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0%)</td>
<td>7 (7%)</td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>11 (11%)</td>
<td>17 (17%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9 (9%)</td>
<td>19(19%)</td>
<td></td>
</tr>
</tbody>
</table>
The results of our study are based on the acne patients whose demographic characteristics and grading at baseline are not statistically significant between the two groups, therefore comparison of the results between the two groups was more precises. At the follow up visits the acne grades were significantly reduced in both the groups compared to the baseline indicates that both drugs are effective in treating acne vulgaris. However towards the end of the study, presence of more grade III (34%) and grade IV (7%) patients in azithromycin group compared to grade (14%) and grade IV (2%) the doxycycline group indicates that doxycycline is more efficient in reducing the severity of the acne compared to azithromycin. This is similar to the study results of Ghafoor Ullah et al., 2014, where azithromycin was given for four consecutive days.

In the present study comparison of azithromycin and doxycycline treatments in acne patients revealed that the doxycycline treatment was more effective than azithromycin. This is assessed by the comparison of response levels.
for both study drugs at the end of the study. Among the 100 patients in azithromycin group -no response (12 %) mild response (21%), moderate response (29%), good response (28%), and excellent response (10%). Among the 100 patients in doxycycline group-no response (6%), mild response (10%), moderate response (19%), good response (52%), and excellent response (13%). On comparing of the response levels at the end, doxycycline group shows statistically significant reduction (p-value < 0.004).

Doxycycline group showed (46%) gastrointestinal and (24%) dermatological side effects while azithromycin regime showed (20%) gastrointestinal and (0%) dermatological side. Hence compared to azithromycin, doxycycline showed more side effects and the values were also statistically significant. Further abnormal liver function was noted in about 7% of patients in doxycycline treated group.

Several studies have evaluated the efficacy and side effects of azithromycin and doxycycline for the treatment of acne. In a study done by Gruber et all in Croatian patients, they concluded that acne vulgaris when treated with azithromycin and minocycline showed satisfactory clinical response. There is no significant differences in their clinical efficacy and tolerability [18]. Oral doses of 250 mg of azithromycin per day for 3 days in a week for 4 weeks showed good response in reducing the acne lesions compared to other antibiotics such as doxycycline, tetracycline and minocycline [7]. In an acne study done among Pakistani patients about 82.9% patients showed remarkable improvement with azithromycin 500 mg thrice weekly for 12 weeks. However, heartburn and nausea, were reported in 11.4% of patients [19]. Comparison of three dosage regimens for assessing the efficacy and safety of azithromycin treatment revealed that 6.0 g of Azithromycin in 10 weeks seems to be a promising agent with few side effects and good patient compliance in Croatians [20].

An open-label, non-comparative study was conducted in Italian acne patients to assess azithromycin’s safety and efficacy. In that 500mg azithromycin was given thrice weekly for 8 weeks. The results were promising with excellent patient compliance [9]. Another study in Italian acne patients showed that moderate acne vulgaris responded well to azithromycin, 500 mg thrice weekly for 12 weeks. The drug was safe and effective treatment for with good patient compliance [15]. Diarrhoea and abdominal pain are the few side effects observed in this study [15]. Among Brazilian acne patients - an open, multicentric, non- comparative study was conducted by giving three monthly pulses of azithromycin 500mg for 3 consecutive days . Finally in that study it was concluded that azithromycin was safe, well tolerated, with good patient adhesion to the treatment. Their study reported gastrointestinal and central nervous systems adverse events [10]. In the present study gastrointestinal and dermatological side effects were found in doxycycline group, but in azithromycin group only gastrointestinal side effects were noted.

Comparison of azithromycin monthly pulse therapy and daily doxycycline treatment in Chandigarh patients with acne vulgaris, revealed that the monthly dose of azithromycin was more effective than the daily doxycycline doses [21]. But in our study doxycycline showed better results. When a combination of azithromycin and topical erythromycin was compared with doxycycline and topical erythromycin in treatment of inflammatory acne vulgaris patients from Jodhpur the results were very promising for macrolide combination. The difference was statistically significant [22]. Turkish acne patients treated with the azithromycin and doxycycline antibiotics revealed that there is no significant difference in the efficacy between these treatment groups. However, both treatment groups showed some side effects. The side effects of Azithromycin and doxycycline are diarrhea and photosensitivity respectively [23]. A randomized, investigator -blind, clinical trial carried out in Iran revealed that both azithromycin and tetracycline antibiotics were effective in improving acne. However, Azithromycin produced a slightly higher percentage of improvement compared with tetracycline [24].

By keeping age as an influencing parameter, a study was done to compare the efficacy and safety of oral azithromycin and doxycycline in Iran. Patients with age more than 18 were included in the study. In the end of that study it was found that doxycycline was significantly more effective in acne [13]. To evaluate the efficacy and safety of azithromycin and doxycycline for the treatment of moderate acne vulgaris patients, a study was conducted in Polish. The study results revealed that azithromycin is as good as doxycycline in acne.
Fig. 3. Distribution of normal and abnormal liver function tests in Azithromycin and Doxycycline treatment group

management. Further, the incidence of adverse events did not differ between the two treatment groups [16]. Comparison of the efficacy of oral azithromycin with oral doxycycline in the treatment of acne vulgaris patients from Afghanistan revealed that the doxycycline is a better option for treatment of acne vulgaris as compared to azithromycin [8].

Several lines of evidence revealed that the doxycycline is associated with an array of side effects [25]. Conventional acne treatment with doxycycline has triggered the development of characteristic lesions of AF represents a subtype called “pseudo-AF” [26]. Doxycycline – induced acute pancreatitis (DIAP) was reported in an Indian adult female acne vulgaris patient who received the usual therapeutic dose for a week [27]. When safety and efficacy of sub antimicrobial modified-release doxycycline (MR- DC) 40 mg was compared with doxycycline 100mg for the inflammatory acne lesions, the study concluded similar efficacy with MR-DC and doxycycline. However, superior safety was observed with doxycycline 100 mg [14]. Similarly azithromycin in combination with other drugs showed superior efficacy in treating the acne vulgaris. Patients treated with a combination of low-dose isotretinoin and pulsed oral azithromycin 500mg/day over three consecutive days in each week for one month is effective in moderate to severe acne [28]. Further, azithromycin and levamisole combination is more effective than azithromycin alone in decreasing of inflammatory lesions [17].

4. CONCLUSION

Our study shows that both azithromycin and doxycycline are efficient in reducing acne. However towards the end of the study, presence of less grade III and grade IV patients treated with doxycycline compared to the azithromycin clearly indicates that doxycycline is more efficient in reducing the severity of the acne compared to azithromycin. Percentage of good and excellent responses are also higher with doxycycline. Hence for the treatment of acne vulgaris, doxycycline 100 mg daily for 2 months is better than azithromycin pulse therapy - 500 mg daily for three consecutive days in a week for 2 month in terms of efficacy.

CONSENT AND ETHICAL APPROVAL

The study protocol was reviewed and approved by the Institutional Ethics Committee and all trial participants have been informed about the study procedures and written informed consent was obtained.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


