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Study Of Efficacy Of Doxycycline In The Management Of Primary Syphilis

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Abstract:
Introduction: *Syphilis is caused by Treponema pallidum and is one of the oldest venereal diseases known to the mankind. Primary syphilis is the earliest and the commonest presentation of syphilis and benzathine penicillin is the treatment of choice. But benzathine penicillin has the obvious disadvantages that it should be given intramuscularly, very painful and has a risk of transmitting blood borne infections. In penicillin sensitive patients, doxycycline or erythromycin are given orally for the treatment of syphilis.*
Objectives: *In this context, a study was undertaken in the department of DermatoVenereology to assess the efficiency of doxycycline in the treatment of primary syphilis.*
Methodology: *All the patients with the clinical signs of primary syphilis were included in the study after taking their consent. Serological testing for syphilis by Venereal Diseases Research Laboratory test (VDRL) was done quantitatively. The patients were then given doxycycline orally as per the protocol and assessed for clinical resolution and serological resolution periodically. The results were analysed.*
Results: *All the patients showed clinical resolution by 4 weeks, decreasing VDRL dilutions by 16 weeks and serological resolution in the form of negative VDRL test by 24 weeks.*
Conclusion: *Doxycycline is very effective in the management of primary syphilis and it also has the advantage in that it can be given orally and thus it may be considered as the first line of management of syphilis.*
Key words: *Primary syphilis, Doxycycline.*

I. Introduction

Syphilis is a chronic systemic disease characterized by periods of active clinical disease that are interrupted by periods of latency[1] . Syphilis ravaged the mankind for almost 350 years after it's spread in Europe in the 16th century. It was referred to as Great Pox compared to Small Pox because of it's devastating nature[2] . Syphilis is caused by Treponema pallidum, a Spirochaete. It can be broadly classified in to Congenital and Acquired Syphilis. Acquired Syphilis can be further classified in to Early Infectious Phase (first two years of acquiring the infection) and Late Non infectious Phase. Early infectious phase is further classified into Primary stage, Secondary stage, Recurrent stage and Early latent stage. Late non infectious phase is classified further into Late latent stage and Teritiary stage. Cardiovascular syphilis and Neurosyphilis are considered by some as teritiary syphilis while by others as quarternary syphilis. Syphilis which was thought to be on the verge of extinction is once again on a rise due to the Human Immunodeficiecy Virus [HIV] pandemic[3].

Although the commonly quoted range of incubation period is 3-90 days, usually the variation is much less and in most cases it varies between 3-4 weeks[4]. The initial macular lesion turns papular which breaks down in to an ulcer. The ulcer is mostly solitary with regular out line and is non tender. The floor is pale and the base is indurated. Regional lymph nodes which will enlarge in 7-10 days are mostly bilateral, non tender, discrete, firm with rubbery consistency and they do not suppurate[5].

Diagnosis is made by a combination of clinical and laboratory examinations but never on clinical evidence alone[6]. Diagnosis of primary syphilis is mainly by history, clinical examination, dark ground microscopic examination and serological tests for syphilis. Serological tests may be non specific tests like Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) test or Specific treponemal tests like Treponemal Pallidum Haem Agglutination (TPHA) test. Quantitative non specific tests such as VDRL / RPR remain the method of choice for follow up testing, the object being to demonstrate a decline in titre[7]. To monitor the efficacy of treatment, quantitative non treponemal tests should be performed on the patient's serum samples drawn at 3 month intervals.. Following adequate therapy for primary syphilis, there should be atleast 4 fold decline in titre by 3rd to 4th month. Non treponemal screening tests have a sensitivity of 70-90% in primary syphilis with a high negative predictive value[8].

Penicillin still remains the therapeutic agent of choice in all forms of syphilis on grounds of effectiveness, low cost and safety[9]. Recommended regimen for treatment of primary syphilis is Benzathine

penicillin G 2.4 million units intramuscular single dose. Alternate regimens in penicillin sensitive patients are Doxycycline 100 mg orally twice daily for 2 weeks or Erythromycin 500 mg orally four times daily for 2 weeks[10].

Tetracyclines act by binding to 30s ribosomes and interfering with the protein synthesis of the susceptible bacteria. Doxycycline is a long acting semi synthetic tetracycline. Doxycycline has many advantages over other tetracyclines like better gastro intestinal absorption, longer half life, higher lipid solubility, elimination independent of renal function and less propensity to cause diarrhea[11].

There is no ideal test of cure for syphilis available that can be carved out with in days after treatment to determine whether the disease has been cured. When the quantitative serological test becomes negative, the patient is considered to be cured[12].

II. Objectives

Though penicillin is the treatment of choice for syphilis, as it is unavailable in our hospital, we are treating the syphilis patients with doxycycline orally. So this study is conducted to assess the clinical and serological response to doxycycline in patients presenting with primary syphilis.

III. Materials And Methodology

The study period is from 01-01-2014 to 31-10-2015. All the patients who attended the STD clinic of department of DVL with genital ulcers during this study period were clinically examined for syphilis. They were then investigated for syphilis by the non specific serological VDRL test quantitatively.

Inclusion criteria: Genital ulcer patients with clinical primary syphilis with a positive VDRL test with dilutions of 1:8 and above.

Exclusion criteria: 1. Clinical signs suggestive of primary syphilis but with a negative VDRL test or with dilutions less than 1:8.

2. Positive VDRL test without any genital ulcers.
3. Patients who were already under treatment elsewhere for the genital ulcers and referred to our department.
4. Patients on treatment with penicillin or tetracycline group of drugs for any other ailment.
5. Pregnant women.

All the patients who met the above criteria were enrolled in the study after taking their consent. These patients were put on doxycycline 100 mg capsules twice daily orally as per National AIDS Control Organisation(NACO) guidelines.

These patients were asked to return for follow up after completion of the treatment. They were examined clinically for resolution of the ulcers after 2 weeks and 4 weeks. They were also tested by quantitative VDRL testing for decreasing dilutions after 4, 8, 16 and 24 weeks. The results were recorded , analysed and statistical significance was measured using chi square test with Yate's correction.

IV. Results

Though a total of 25 patients met the criteria (14 male and 11 female patients), 1 male patient refused to participate in the study. So the study group included 24 patients only and these 24 patients were analysed.

1.20 patients of the total 24 patients presented with total clinical resolution after 20 weeks and the rest 4 patients showed total clinical resolution by 4 weeks.(table no.1).

2 .Out of the total 24 patients, 14 patients presented decreasing VDRL dilutions after 8 weeks and all the 24 patients by 24 weeks.(table no.2).

3. Among the 24 patients, 11 patients presented with negative VDRL test after 16 weeks and all the 24 patients presented with negative VDRL test by 24th week.(table no.3).

Table1:- Clinical resolution.

Total study population	Patients with Clinical resolution			
24	After 2 weeks		After 4 weeks	
	Number	Percentage	Number	Percentage
	20	83.33%	24	100%

Table 2:- Decreasing VDRL Dilutions.

Total study population	***Patients with decreasing dilutions***			
24	***After 8 weeks***		***After 16 weeks***	
	Number	***Percentage***	***Number***	***Percentage***
	14	***58.3%***	***24***	***100%***

Table3 :- Negative VDRL test after Treatment.

Total study population	Patients with negative VDRL test			
24	After 16 weeks		After 24 weeks	
	Number	Percentage	Number	Percentage
	11	45.83%	24	100%

V. Discussion

All the 24 patients who were enrolled in the study returned for the follow up.20 of them showed clinical resolution during the first follow up ie., after 2 weeks[83.33%] and all the 24 patients showed clinical resolution by the time of second follow up ie., after 4 weeks[100%] [table 1].There is also no statistical significance in the clinical resolution between 2 and 4 weeks as the p-value using chi square test with Yate's correction is 0.9023 which is statistically not significant.

When we analysed the serological response after the treatment in the form of decreasing VDRL dilutions,14 out of the 24 patients showed decreasing dilutions {more than 4 dilutions] after 8 weeks [58.3%] and all the 24 patients showed decreasing dilutions after 16 weeks [100%] [table 2]. Though the comparision between the percentages after 8 and 16 weeks appears significant, the p-value using chi square test with Yate's correction is 0.3165 which is statistically not significant. Thus not only the clinical resolution is obvious by the

second week but the serological response is also obvious by the end of eighth week in our study in the form of decreasing VDRL dilutions.

VDRL test which is positive before the initiation of treatment turned out negative after the completion of treatment by 16 weeks in 11 patients [45.83%] and by 24 weeks in all the patients [100%] leading us to stop VDRL testing in the study group after 24 weeks [table 3]. Again, though there appears to be a significant difference in VDRL test after 16 and 24 weeks, p-value according to chi square test with Yate's correction equals 0.1424 which is statistically not significant showing that there is not much statistically significant difference in the results between the two time periods.

According to a comparative study by Wong, et al, doxycycline/tetracycline has a similar high serological treatment rate when compared with penicillin in the treatment of primary syphilis[13]. Though our study is not a comparitive study, it has similar serological response rate. It also correlates with another study by Tsai JC, et al[14] in HIV infected patients though we did not take the HIV status of the patients into consideration in our study though they were screened for the HIV status. But the total clinical cure and the total serological cure in all the patients in our study irrespective of their HIV serostatus shows that doxycycline is equally effective in both HIV reactive and HIV non reactive patients. According to Ghanem KG, et al, serological failure rate with doxycycline is 0% [15]. Our study has totally similar results with 0% clinical failure rate and 0% serological failure rate.

VI. Conclusion

Penicillin is the drug of choice for the management of syphilis and doxycycline is used only when there is penicillin sensitivity. Like other studies, our study has also shown that doxycycline is very effective in the management of primary syphilis. Our study has shown that clinical resolution and serological resolution in primary syphilis is 100% on administration of doxycycline orally. In our study the patient compliance is also good and no side effects were reported. But our study has limitations in that it is not a comparative study between penicillin and doxycycline and the study group is small. Doxycline has an advantage over penicillin in that it can be given orally thus needing no technical skills which are needed for parenteral administration of penicillin. Likewise there is no risk of transmitting blood borne infections. Hence larger studies on the efficacy of doxycycline in the management of syphilis is the need of the hour so that if those studies also prove that doxycycline is very effective in the management of syphilis, then doxycycline can replace penicillin as the drug of choice for the management of syphilis for the obvious advantages mentioned above.

Figure 1 :Typical presentation with solitary ulcer :

Figure 2: Atypical presentation with multiple ulcers :

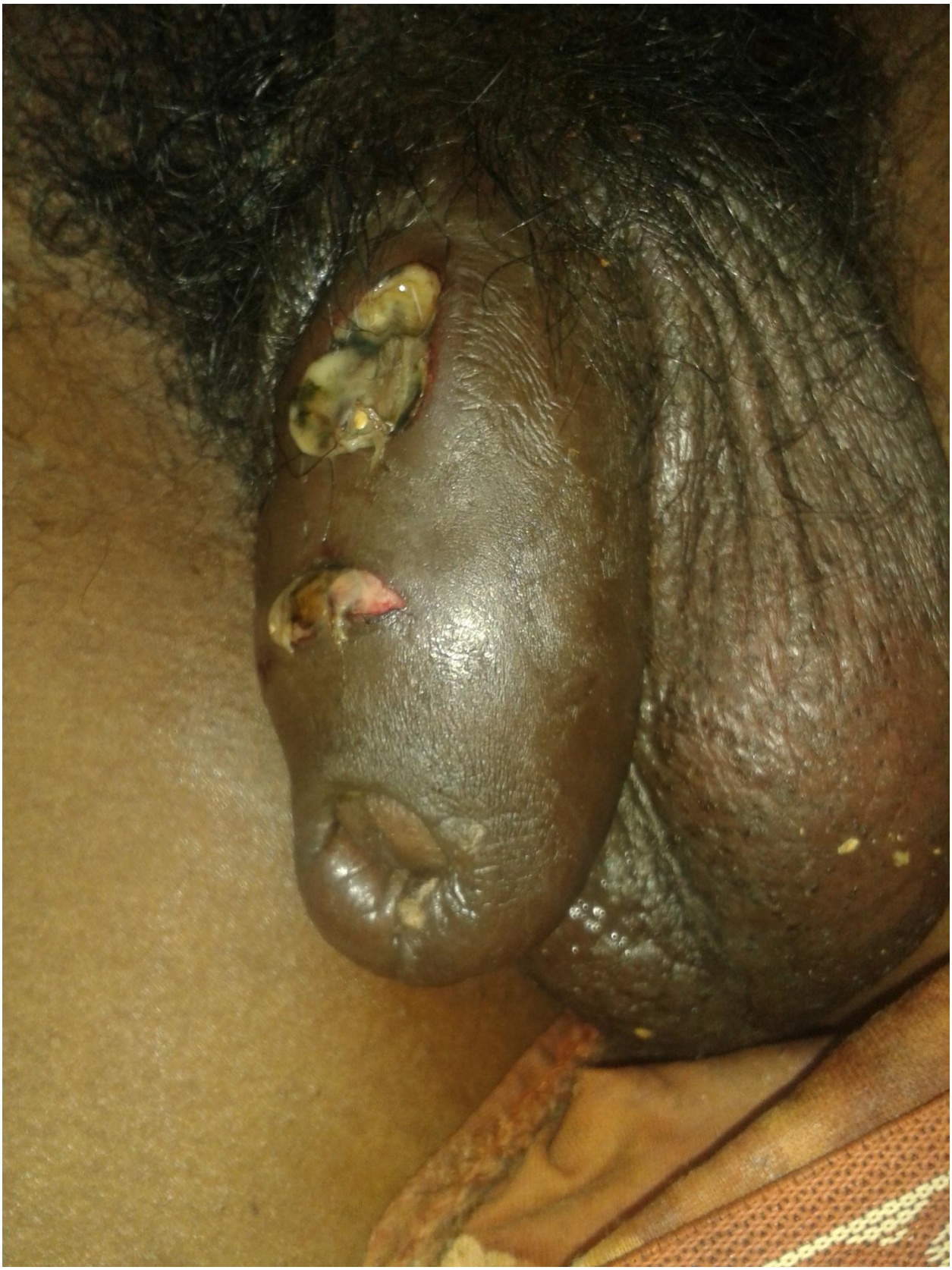
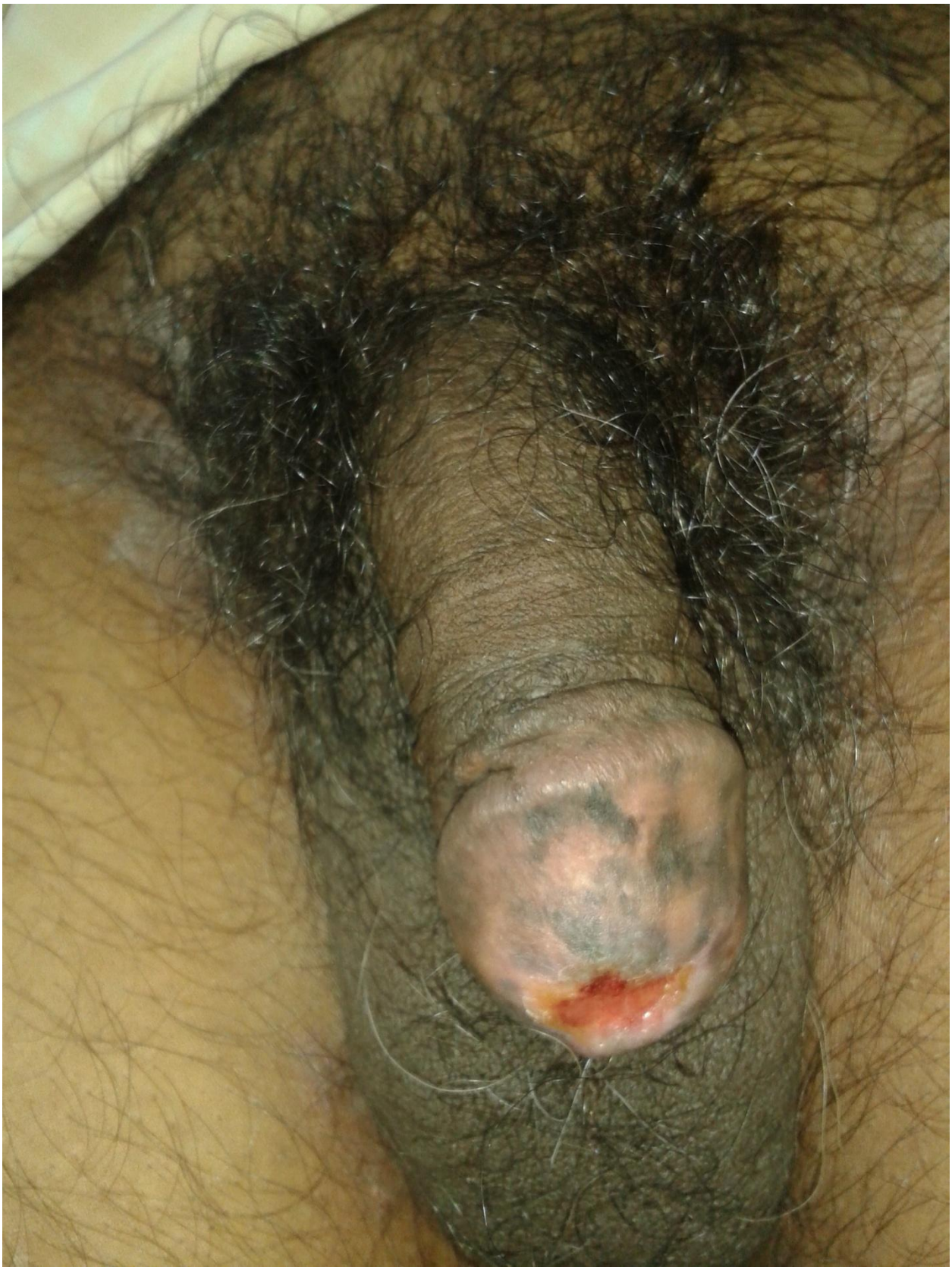


Figure 3: At the external urinary meatus :



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