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Original Research Article

Effect of treatment with benzathine penicillin combined with ceftriaxone in elderly patients with latent syphilis

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Abstract

Purpose: *To investigate the effect of the combination of benzathine penicillin and ceftriaxone in the treatment of latent syphilis in the elderly.*
Methods: *A total of 70 elderly patients with latent syphilis treated in the First People's Hospital of Yichang from March 2020 to March 2021 were enrolled in this study. Control group (CG) comprised thirty-two patients treated with benzathine penicillin, while 38 patients received the combination of benzathine penicillin and ceftriaxone were placed in the study group (SG). Therapeutic efficacy and adverse reactions in both groups were assessed. The difference in toludine red unheated serum test (TRUST) negative conversion rate at different periods of treatment (3, 6, and 12 months) after treatment was observed. Dermatological quality of life index (DLQI), self-rating anxiety scale (SAS) and self-rating depression scale (SDS) scores were also determined before and after treatment.*
Results: *Total efficacy in the study group was significantly higher than that in the control group after treatment ($p < 0.05$), but there was no significant difference in the total incidence of adverse reactions between both groups ($p > 0.05$). The TRUST negative conversion rate at 6 and 12 months in SG was higher than that in CG ($p < 0.05$), while DLQI, SAS and SDS scores in SG were significantly lower after treatment ($p < 0.05$).*
Conclusion: *Treatment of elderly patients with latent syphilis with the combination of benzathine penicillin and ceftriaxone effectively controls the disease and improves patients' negative emotions and quality of life with few adverse drug reactions. Further clinical trials are required prior to application in clinical practice.*

Keywords: *Benzathine penicillin, Ceftriaxone, Senile latent syphilis, Quality of life*

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INTRODUCTION

Syphilis is a chronic infectious disease caused by *Treponema pallidum*, and its main route of transmission is through the genitals. It may also be transmitted as neonatal congenital syphilis (mother-to-child transmission) [1,2]. Some patients with syphilis do not show positive signs or symptoms after infection, thereby resulting in these patients not being diagnosed early and causing great inconvenience in the prevention and control of syphilis [3]. As the population of

the elderly in society is increasing, elderly patients with syphilis are becoming more common [4]. Latent syphilis, because of its long latency period, is often expressed in old age. Older patients require more attention because of the decline of their immunity, and body functions, and the symptoms get more aggressive. Benzathine penicillin is a long-acting preparation of penicillin G, which may inhibit the synthesis of bacterial cell walls. It is active against *Treponema pallidum*, so it is a common drug for the treatment of syphilis [5,6]. However, some studies have shown that benzathine penicillin has a poor and slow therapeutic effect on some syphilis patients [7]. As a third-generation cephalosporin antibiotic, ceftriaxone can inhibit bacteria by interfering with the synthesis of bacterial cell walls [8]. Some studies have revealed that ceftriaxone is also effective in syphilis patients, even faster than penicillin [9].

Therefore, in this study, the effect of the combination of benzathine penicillin with ceftriaxone was determined in elderly patients with latent syphilis, and the efficacy and safety were determined to establish the basis for therapy.

METHODS

Patients' data

A total of 70 elderly patients with latent syphilis treated in the First People's Hospital of Yichang from March 2020 to March 2021 were enrolled in this research. Thirty-two patients treated with benzathine penicillin were regarded as the control group (CG) while 38 patients treated with benzathine penicillin combined with ceftriaxone were the study group.

Ethical issues

This study was conducted after obtaining permission from the Medical Ethics Committee of the First People's Hospital of Yichang (approval no. 20210203). All procedures comply with the ethical guidelines of the Declaration of Helsinki [18].

Inclusion and exclusion criteria

Inclusion criteria

All patients that were diagnosed with syphilis based on the diagnostic criteria according to the guidelines issued by the World Health Organization for the diagnosis of syphilis [10] as well as patients that had normal hydrocephalus, showed no significant clinical symptoms, above 60 years old with complete clinical profile were included in the study.

Exclusion criteria

Patients that were hypersensitivity to the therapeutic agents used in the treatment process, patients with cognitive impairment and who are unable to recognize the scale, and patients with co-morbidities with other infectious diseases were excluded from the study.

Treatments

Patients in the CG group were treated with benzathine penicillin (CSPC Zhongnuo Pharmaceutical (taizhou) Co. Ltd, SFDA approval no. H20033291), 2.4 million units per intramuscular injection, once a week. SG group was treated with ceftriaxone (Shanghai Roche Pharmaceutical Co. Ltd, SFDA approval no. H10983036) which was injected intramuscularly 1 g once daily. Ceftazidime was discontinued after 10 days of continuous administration, and benzathine penicillin was discontinued after 3 - 4 weeks of continuous administration [11].

Parameters evaluated

The treatment efficacy of both groups of patients was counted with the following criteria: ***Significantly effective:*** titer of decrease in serum RPR ≥ 4 after treatment; ***Effective:*** decreasing titers of serum RPR < 4 and ≥ 2; ***Ineffective:*** failed to achieve the above efficacy. Total efficacy (TE) was computed as shown in Eq 1.

$$TE = SE + E \quad \ldots\ldots\ldots (1)$$

Where SE = significantly effective, and E = effective

The incidence of treatment-related adverse reactions in the two groups was compared. A total of 3 mL Peripheral venous blood was collected at 3, 6, and 12 months after treatment. The titer was detected and the negative conversion rate was calculated by toludine red unheated serum test (TRUST). The quality of life of patients before and after treatment was evaluated by dermatology quality of life index (DLQI). The total score was 30, the higher the score, the worse the quality of life of patients. The negative emotions of patients before and after treatment were evaluated through self-rating anxiety scale (SAS) and self-rating Depression scale (SDS). The total scores of SAS and SDS were 80, the higher the score, the more

serious the degree of anxiety and depression [12].

Statistical analysis

Statistical analysis was performed using SPSS version 20.0. The collected data were plotted using GraphPad Prism 7 (GraphPad Software Corporation, San Diego, USA). Qualitative data were compared by chi-square test, and results represented as χ^2. Quantitative data were expressed as mean ± standard deviation (SD). The independent samples *t*-test was conducted for two groups, while paired samples *t*-test was used for comparison between groups. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data

The clinical baseline data of both groups showed that there was no significant difference in age, BMI, gender, serum TRUST titer, place of residence, marital status and education level ($p > 0.05$, Table 1).

Therapeutic efficacy

The analysis of the therapeutic effect of both groups revealed that there was no significant difference in the effectiveness rate ($p > 0.05$), but the total effective rate of the SG was higher than that of the CG ($p < 0.05$) (Table 2).

Incidence of adverse reactions

The adverse reactions occurred in the treatment process of patients were counted, such as nausea, local pain, rash, and vomiting. Comparing the incidence of adverse reactions between both groups, it was observed that there was no significant difference in the total adverse reaction rate ($p > 0.05$) (Table 3).

Table 1: Baseline data sheet

Parameter	Item	Control group (n=32)	Study group (n=38)	t/χ^2	*P*-value
Age (years)		70.6±5.7	71.0±5.2	0.307	0.760
BMI (kg/m^2)		22.41±2.10	21.86±2.17	1.072	0.288
Gender					
	Male	25 (78.13)	25 (65.79)	1.295	0.255
	Female	7 (21.88)	13 (34.21)		
Serum TRUST titer					
	≤ 1:4	16 (50.00)	20 (52.63)		
	1:8-1:16	12 (37.50)	15 (39.47)		
	≥ 1:32	4 (12.50)	3 (7.90)	0.401	0.815
Place of residence					
	Cities and towns	20 (62.50)	19 (50.00)	1.100	0.294
	Countryside	12 (37.50)	19 (50.00)		
Marital status					
	Married	27 (84.38)	31 (81.58)		
	Unmarried	3 (9.37)	5 (13.16)	0.264	0.877
	Divorced or widowed	2 (6.25)	2 (5.26)		
Educational level					
	Junior high school and below	19 (59.37)	25 (65.79)		
	High school	9 (28.13)	8 (21.05)		
	University and above	4 (12.50)	5 (13.16)	0.477	0.788

Table 2: Therapeutic efficacy (n (%))

Parameter	Control group (n=32)	Study group (n=38)	χ^2	*P*-value
Significantly effective	7 (21.88)	15 (39.47)	2.496	0.114
Effective	15 (46.88)	19 (50.00)	0.794	0.068
Ineffective	10 (31.25)	4 (10.53)		
Total efficiency	22 (68.75)	34 (89.47)	4.663	0.031

Table 3: List of adverse reactions (n (%))

Parameter	Control group (n=32)	Study group (n=38)	χ^2	*P*-value
Nausea	2 (6.25)	1 (2.63)		
Local pain	1 (3.13)	2 (5.26)		
Rash	1 (3.13)	1 (2.63)		
Vomiting	0 (0.00)	2 (5.26)		
Total adverse reactions	4 (12.50)	6 (15.79)	0.154	0.685

Results of TRUST negative conversion

There was no statistical difference in the rate of TRUST conversion at 3 months between the two groups ($p > 0.05$), but the rate of conversion at 6 and 12 months in the study group was higher than that in the control group, with statistically significant differences ($p < 0.05$) (Table 4).

Table 4: Comparison of TRUST negative conversion rates in patients (n (%))

Group	3 months	6 months	12 months
Control group (n=32)	4 (12.50)	10 (31.25)	23 (71.88)
Study (n=38)	11 (28.95)	20 (55.26)	35 (92.11)
χ^2	2.791	4.060	5.005
P-value	0.095	0.044	0.025

Improvement of patients' quality of life

There was no statistical difference between the DLQI scores of the two groups before treatment ($p > 0.05$), and the DLQI scores of the study group were lower than those of the control group after treatment ($p < 0.05$) (Figure 1).

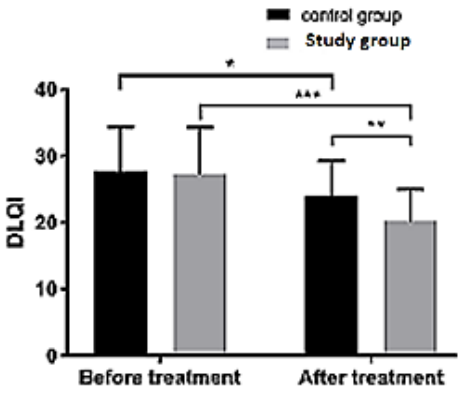

Figure 1: Comparison of improvement of patients' quality of life. **Note:** **P* < 0.05; ***p* < 0.01; ****p* < 0.001

Improvement of negative emotions

The SAS and SDS scores of both groups before treatment were not significantly different, but the scores decreased after treatment. However, the SAS and SDS scores of the SG were significantly lower than those of the CG after treatment ($p < 0.05$) (Figure 2).

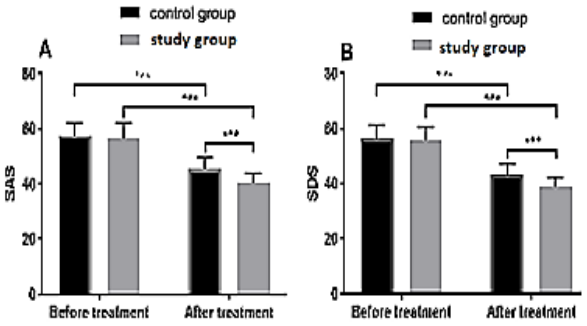

Figure 2: Comparison of improvement of negative emotions between both groups. (A) SAS score between both groups. The score in SG is lower than that in the CG after treatment (****p* < 0.001). (B) SDS score between both groups. The score in the SG is lower than that in the CG after treatment (****p* < 0.001)

DISCUSSION

Latent syphilis fuels the spread of syphilis because of its characteristic lack of significant symptoms and causes more patients to delay treatment because of delayed diagnosis [13]. Early syphilis can also increase the risk of HIV infection by two to five folds, so that the incidence of AIDS in syphilis patients is very high [14]. Some studies have shown that among the inpatients, the proportion of latent syphilis in patients over 50 years old is relatively high, which may be because the elderly are more likely to be hospitalized than young people because of their reduced immunity. But the number of elderly syphilis patients is also increasing [15].

Benzathine penicillin is a first-line drug recommended by World Health Organization's guidelines for the treatment of syphilis, but previous studies have found that there are some limitations in the use of benzathine penicillin. It is mentioned in the World Health Assembly report that benzathine penicillin has been in short supply in recent years, so it is necessary to explore other effective treatments [16]. The total effective rate of treatment efficacy of benzathine penicillin alone was lower than that of benzathine penicillin combined with ceftriaxone. The

conversion rates at month 6 and month 12 of the combined treatment were significantly better than those of benzathine penicillin alone, indicating that benzathine penicillin combined with ceftriaxone has a faster onset of action. This study also showed that the combination of ceftriaxone did not increase the incidence of adverse reactions in patients, so the treatment regimen had a good safety profile.

As a sexually transmitted disease, syphilis causes many patients to suffer from social prejudice and discrimination, which makes syphilis patients more prone to negative moods in the long run, while long-term treatment and repeated infections also reduce the quality of life of patients and are detrimental to their treatment [17]. After comparing patients' dysphoria and quality of life, it was further observed that the quality of life was better in the study group than in the control group after treatment. The reason should be that benzathine penicillin combined with ceftriaxone relieves patients' symptoms and improves the treatment efficacy, thus improving the quality of life, and reducing patients' depression and anxiety adverse emotions, improves their feeling of illness, daily activities, and daily work and socialization.

Limitations of this study

This study was conducted mainly in the elderly population, but it is not clear how well benzathine penicillin combined with ceftriaxone works in other populations, such as young adults and pregnant women. So, it is hoped that a wider range of subjects will be included in subsequent studies.

CONCLUSION

The treatment of latent syphilis in elderly patients with the combination of benzathine penicillin and ceftriaxone results in better therapeutic effect, effective disease control, improve patients' negative emotions, and quality of life, with fewer adverse drug reactions. Hence, further large-scale and multi-center investigation is worthwhile before clinical promotion.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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