World Journal of Psychiatry and Mental Health Research

Research Article
Published: 30 Nov, 2021

Comparison of the Clinical Efficacy of Penicillin and Ceftriaxone Sodium in the Treatment of Neurosyphilis with Psychiatric Symptoms

Shibin Wang[1], Wenming Gu[1], Yuping Cao[2], Hangxiao Zheng[1], Lei Zhang[1], Xiaoyun Guo[1], Wenzhong Chen[1]* and Xingguang Luo[3]*

[1]Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China

[2]Department of Psychiatry, Central South University, The China National Clinical Research Center for Mental Health Disorders, National Technology Institute of Psychiatry, Key Laboratory of Psychiatry and Mental Health of Hunan Province, China

[3]Department of Psychiatry, Yale University School of Medicine, USA

Abstract

Objective: To compare the clinical efficacy of penicillin and ceftriaxone sodium in the treatment of neurosyphilis with psychiatric symptoms.

Methods: Fifty neurosyphilis with mental symptoms patients were randomly divided into penicillin group (4 million units, Q4 h) and ceftriaxone sodium group (1 g, Q12 h). The total treatment time was 14 and 15 days respectively. The Activity of Daily Living Scale (ADL), Brief Psychiatric Rating Scale (BPRS) and Mini-Mental State Examination (MMSE) were scored as the measurement of efficiency in living ability, mental symptoms and cognitive function.

Result: There were no significant differences in ADL, MMSE and BPRS between the penicillin group and the ceftriaxone sodium treatment group (p>0.05). After treatment, the score of BPRS and ADL decreased from baseline, while MMSE scores increased from baseline, having a main time effect (F=31.098, F=26.342, F=79.916; p<0.05).

Conclusion: Penicillin or ceftriaxone sodium are both effective in the aspect of mental symptoms, cognitive function and life ability among neurosyphilis with psychiatric symptoms patients.

Keywords: Neurosyphilis; Psychiatric symptoms; Clinical efficacy; Penicillin; Ceftriaxone sodium

OPEN ACCESS

Correspondence:
Wenzhong Chen, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China, E-mail: cwz2002@msn.com
Wenming Gu, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China, E-mail: goondoit@126.com

Received Date: *25 Oct 2021*
Accepted Date: *10 Nov 2021*
Published Date: *01 Jan 2022*

Citation:
Wang S, Gu W, Cao Y, Zheng H, Zhang L, Guo X, et al. Comparison of the Clinical Efficacy of Penicillin and Ceftriaxone Sodium in the Treatment of Neurosyphilis with Psychiatric Symptoms. World J Psychiatry Ment Health Res. 2021; 5(1): 1030.

Introduction

Neurosyphilis is caused by the invasion of the central nervous system by *Treponema pallidum* infection and is a manifestation in late (tertiary) syphilis [1]. In recent years, there has been a resurgence of syphilis in both developed and developing countries [1]. Studies have shown that 33% to 86% of neurosyphilis patients experience concomitant psychiatric symptoms [2]. Therefore, due to the high complexity and diversity of symptoms in neurosyphilis patients with psychiatric symptoms, research efforts should be focused on the clinical treatment.

Cognitive impairment and psychotic disorders are currently regarded as the primary clinical presentations of neurosyphilis patients, with the former being manifested mainly as memory impairment, disorientation, attention deficiency, impaired conceptual reasoning, and articulation disorders [3-5], and the latter mainly as personality changes, hallucinations, delusions, mania and paranoia [2,6,7]. Generally, syphilis is treated using antibiotic therapy; however, specificity and poor treatment compliance have been observed in treating neurosyphilis patients with psychiatric symptoms. In the past, penicillin was regarded as the drug of choice for the treatment of neurosyphilis. However, its high frequency of use in anti-syphilis treatment imposes a great work burden on nursing care. Ceftriaxone sodium, a third-generation cephalosporin, has a longer half-life than penicillin and is currently regarded as having definite therapeutic effects in neurosyphilis treatment. The present study compared the clinical efficacies of penicillin and ceftriaxone sodium in treating patients with neurosyphilis with concomitant psychiatric symptoms to evaluate their treatment effects.

Material and Methods

Participants

Patients with positive *Treponema pallidum* Particle Agglutination (TPPA) test and concomitant psychiatric symptoms hospitalized at Minhang Branch of Shanghai Mental Health Center between August 2015 and December 2016 were included as participants.

The inclusion criteria were:

- Fulfilment of the diagnostic criteria for neurosyphilis in the International Classification of Diseases, 10th revision (ICD-10), and positive results obtained in the blood and cerebrospinal fluid tests for syphilis, including the Rapid Plasma Reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests
- Age ≥ 18 years with no restrictions on patient gender
- Concomitant psychiatric symptoms such as hallucinations, delusions, and cognitive decline
- Patients who had not previously received anti-syphilis treatment.

The exclusion criteria were:

- HIV infection, autoimmune diseases, pregnancy, intravenous drug use;
- Previous history of psychiatric conditions;
- Other organic brain disorders;
- Other psychiatric disorders, including schizophrenia, mood disorders, schizoaffective disorders, delusional disorders, acute and transient psychotic disorders, substance dependence, and mental retardation. The guardians of all the participants provided written informed consent for participation in the study. This study was approved by the ethical committee of Shanghai Mental Health Center.

Research methods

A randomized controlled trial design was adopted. Before treatment initiation, patients were screened by trained physicians according to the inclusion and exclusion criteria. The patients were then allocated randomly to the penicillin treatment group and the ceftriaxone sodium treatment group, using the random numbers generated from a random number table (randomization ratio: 1:1). The dose levels and routes of administration of the two groups were determined according to the criteria stated in the Guidelines for the Diagnosis and Treatment of Sexually Transmitted Diseases [8] : **(1)** Penicillin group (SFDA Approval No.: H31020930): 4 million units of penicillin sodium added to 100 ml of isotonic sodium chloride solution was administered intravenously Q4 h for 14 days; **(2)** Ceftriaxone sodium group (SFDA Approval No.: H10983036): 1 g of ceftriaxone sodium added to 250 ml of isotonic sodium chloride solution was administered intravenously Q12 h for 15 days. Antipsychotics were not used during the treatment period.

Evaluation tools and methods

All the evaluators received training to enable consistency in the use of the rating scales. The evaluations were performed before treatment, one week after treatment initiation, and after treatment completion. Any adverse events experienced by the participants during the study period were recorded. The psychiatric symptoms were evaluated using the Brief Psychiatric Rating Scale (BPRS) [9]; cognitive function using the Mini-Mental State Examination (MMSE) [10]; and the ability to perform activities of daily living using the Activities of Daily Living (ADL) Scale [11]. During the treatment period, drug safety was evaluated, and the adverse events were recorded.

Primary outcome measure

The primary outcome was measured using the BPRS score.

Seconary outcome measures

The secondary outcomes were measured using the MMSE and ADL scores.

Statistical analysis

The data analysis was performed using SPSS 18.0 (IBM®). Normally distributed data of the two groups were compared using the independent samples t-test, while data that did not follow a normal distribution were compared using the rank-sum test. Enumeration data were compared using the chi-squared test, and data before and after treatment were compared using a two-way repeated-measures Analysis of Variance (ANOVA). The differences were considered to be statistically significant when $P<0.05$.

Results

Demographic data of participants

A total of 50 participants were included in this study and followed up for 15 days. None of the participants dropped out from the treatment or the follow-ups. The participants consisted of 49 men (98%) and one woman, of whom 50% were retired, had a mean age of 55.88 ± 8.84 years, and a mean total disease duration of 9.97 ± 9.25 months. Before treatment, the highest and lowest RPR titers were 1:256 and 1:1, respectively, and the highest and lowest cerebrospinal fluid VDRL titers were 1:64 and 1:1, respectively. The baseline BPRS, MMSE, and ADL scores were 48.00 ± 11.26 points, 14.46 ± 8.67 points, and 29.34 ± 10.51 points, respectively. The differences in the data mentioned earlier between the penicillin and ceftriaxone sodium groups were not statistically significant (all $P>0.05$) (Table 1).

Comparison of the efficacies of penicillin and ceftriaxone sodium in treating neurosyphilis

The efficacies of penicillin and ceftriaxone sodium in treating neurosyphilis were compared using a two-way repeated-measures ANOVA (Table 2).

Psychotic symptoms: The Multivariate ANOVA (MANOVA) results were used as the data and did not satisfy the sphericity assumption ($P=0.000$). With regard to the interaction term group × time, the variance-covariance matrices of the dependent variables were equivalent across the groups ($P>0.05$), indicating that the interaction effect did not influence the MMSE score significantly ($P>0.05$). The main effect of the group factor on the MMSE score was not statistically significant ($P>0.05$), whereas the main effect of the time factor on the MMSE score was statistically significant ($P<0.01$). Pairwise comparisons revealed that MMSE scores at one week after the start of the treatment and after treatment completion were significantly different compared with the pretreatment MMSE scores, with the differences being 2.280 (95% confidence interval: 1.255 to 3.305) and 3.380 (95% confidence interval: 1.992 to 4.768), respectively. The differences in the MMSE scores between the two treatment groups were not statistically significant ($P>0.05$). The MMSE scores were influenced by the treatment time, with the scores after the completion of anti-syphilis treatment being significantly lower than the pretreatment scores in both groups ($P<0.05$) (Table 2).

Table 1: Demographic data of the participants.

		Penicillin group (n=25)	Ceftriaxone sodium group (n=25)	*P*
Age		57.96 ± 8.45	53.80 ± 8.90	0.097
Sex (% of men)		96.00%	100%	0.5
Employment status	Employed	16.00%	20.00%	0.972
	Unemployed	32.00%	32.00%	
	Retired	52.00%	48.00%	
Marital status	Single	0.00%	4.00%	0.553
	Married	68.00%	60.00%	
	Divorced/widowed	32.00%	36.00%	
Total disease duration (months)		9.37 ± 12.12	9.79 ± 9.25	0.891
Percentage of participants living alone (%)		0.16	0.12	0.833
ADL		28.52 ± 10.76	30.16 ± 10.41	0.586
BPRS		55.48 ± 13.81	57.52 ± 11.79	0.577
MMSE		15.36 ± 9.11	13.56 ± 8.30	0.469

Table 2: Comparison of the efficacies of penicillin and ceftriaxone sodium in the treatment of neurosyphilis. **P <0.01

	Penicillin group			Ceftriaxone sodium group			*F*	
	Before treatment	**1 w**	**After treatment**	**Before treatment**	**1 w**	**After treatment**	**Group effect**	**Time effect**	**Interaction effect**
ADL	28.52 ± 10.76	27.80 ± 11.33	26.40 ± 10.50	30.16 ± 10.41	28.44 ± 10.82	26.44 ± 10.59	0.066	26.342**	2
BPRS	55.48 ± 13.81	48.00 ± 15.4	43.44 ± 14.14	57.52 ± 11.79	48.00 ± 14.66	43.75 ± 12.78	0.03	79.916**	0.367
MMSE	15.36 ± 9.11	17.60 ± 9.87	18.52 ± 9.70	13.56 ± 8.30	15.88 ± 9.70	17.16 ± 9.30	0.393	31.098**	0.144

Activities of daily living: Mauchly's test of sphericity indicated that the data satisfied the sphericity assumption (P=0.167). With regard to the interaction term group × time, the variance-covariance matrices of the dependent variables were equivalent across the groups (P>0.05), indicating that the interaction effect did not influence the ADL scores significantly (P>0.05). The main effect of the group factor on the ADL scores was not statistically significant (P>0.05), whereas the main effect of the time factor on the ADL scores was statistically significant (P<0.01). Pairwise comparisons revealed that the ADL scores at one week after the start of treatment and after treatment completion were significantly different compared with the pretreatment ADL scores, with the differences being 1.220 (95% confidence interval: 0.217 to 2.223) and 2.920 (95% confidence interval: 1.806 to 4.034), respectively. The difference in the ADL scores between the two treatment groups was not statistically significant (P>0.05). The ADL scores were influenced by the treatment time, with the scores after the completion of the anti-syphilis treatment being significantly lower than the pretreatment score in both groups (P<0.05).

Cognitive function: The results of the MANOVA did not satisfy the sphericity assumption (p=0.000). With regard to the interaction term group × time, the variance-covariance matrices of the dependent variables were equivalent across the groups (P>0.05), indicating that the interaction effect did not significantly influence the MMSE scores (P>0.05). The main effect of the group factor on the MMSE scores was not statistically significant (P>0.05), whereas the main effect of the time factor on the MMSE scores was statistically significant (P<0.01). Pairwise comparisons revealed that the MMSE scores at one week after the start of treatment and after treatment completion were significantly different compared with the pretreatment scores, with the differences being 2.280 (95% confidence interval: 1.255 to 3.305) and 3.380 (95% confidence interval: 1.992 to 4.768), respectively. The differences in the MMSE scores between the two treatment groups were not statistically significant (P>0.05). The MMSE scores were influenced by the treatment time, with the MMSE scores after the completion of anti-syphilis treatment being significantly higher than the pretreatment scores in both groups (P<0.05) (Table 2).

Adverse events

A total of five adverse events (10%) occurred in the present study, which consisted of two cases of insomnia and one case of pyrexia in the penicillin group, and one case each of dizziness and pyrexia in the ceftriaxone sodium group. The insomnia was alleviated after symptomatic treatment with benzodiazepines; the pyrexia was alleviated spontaneously after physical cooling was implemented, and the reduced appetite and dizziness were alleviated spontaneously without specific treatment. Compared with the corresponding pretreatment results, the routine blood test, hepatic function test, renal function test, and electrocardiogram results of the participants during the follow-ups did not exhibit significantly abnormal changes.

Discussion

Since the clinical effectiveness of different anti-syphilis therapeutic regimens remains unclear, difficulties exist in the clinical treatment of neurosyphilis with concomitant psychiatric symptoms. In the present study, a randomized controlled trial design was adopted to compare the clinical efficacies of penicillin and ceftriaxone sodium in treating neurosyphilis patients with concomitant psychiatric symptoms.

The patients included in this study were middle-aged and older adults with various degrees of cognitive impairment prior to treatment, which was related to the invasion of the central nervous system and damage of cerebral cortical neurons in corresponding brain regions by *T. pallidum*. After one cycle of treatment, both groups of participants showed a decrease in the ADL and BPRS scores and an increase in the MMSE scores. This indicated that both types

of treatment led to improvements in the ability to perform activities of daily living, psychiatric symptoms, and cognitive function. Our results also showed that the differences in improvement between the two groups were statistically insignificant, suggesting that the efficacy of ceftriaxone sodium was comparable to that of penicillin. Existing guidelines have recommended using penicillin as the first-line drug for treating early and late latent syphilis and using ceftriaxone sodium as a substitute for patients allergic to penicillin [12]. Ceftriaxone sodium, a third-generation cephalosporin, has a longer half-life than penicillin and a higher effective plasma concentration. It has potent bactericidal activity on extracellular *T. pallidum* and is also effective against *T. pallidum* in the central nervous system because it can cross the blood-brain barrier [13]. Previous research studies have reported that ceftriaxone sodium provides definitive therapeutic effects in treating syphilis [14,15]. Moreover, a recent meta-analysis has also indicated the lack of evidence of differences in the effectiveness of ceftriaxone sodium and penicillin in treating neurosyphilis [16].

Our results indicated that antibiotic treatment of syphilis leads to improved cognitive function, which is similar to the results reported in previous studies in China and other countries [17,18]. However, another study has indicated the lack of significant changes in the MMSE and BPRS scores after penicillin therapy [5]. This may be attributed to differences in the follow-up durations and sample sizes, as the study involved the follow-up of 19 neurosyphilis patients for 12 months. The clinical diagnosis and treatment of neurosyphilis patients with concomitant psychiatric symptoms require careful consideration due to the high diversity and low specificity of symptoms. Some researchers have recommended the use of low-dose antipsychotics to alleviate psychiatric symptoms, but close attention should be paid to adverse drug reactions [18,19].

In the present study, three cases of adverse reactions occurred in the penicillin group, which included two cases of insomnia. Two cases of adverse reactions also occurred in the ceftriaxone sodium group, which included one case of dizziness. Further studies with larger sample sizes are required to confirm the adverse reactions and tolerance related to the use of penicillin and ceftriaxone sodium for the treatment of neurosyphilis.

This Study had Certain Limitations

- The efficacies and safety of penicillin and ceftriaxone sodium in neurosyphilis treatment were evaluated only during the hyperacute phase (14 to 15 days). Currently, the participants are still being followed up, and the long-term efficacies of penicillin and ceftriaxone sodium will be reported.

- The neurobiological mechanisms by which cognitive impairment and psychotic symptoms occur in neurosyphilis patients remain unclear. Future research efforts should be devoted to evaluating the efficacies of penicillin and ceftriaxone sodium at the molecular level based on the measurement of serological and cerebrospinal fluid markers.

References

1. The L. Syphilis: An ancient disease in a modern era. Lancet. 2017;389(10078):1492.
2. Costiniuk CT, MacPherson PA. Neurocognitive and psychiatric changes as the initial presentation of neurosyphilis. CMAJ. 2013;185(6):499-503.
3. Wang J, Guo Q, Zhou P, Zhang J, Zhao Q, Hong Z. Cognitive impairment in mild general paresis of the insane: AD-like pattern. Dement Geriatr Cogn Disord. 2011;31(4):284-90.
4. Stefani A, Riello M, Rossini F, Mariotto S, Fenzi F, Gambina G, et al. Neurosyphilis manifesting with rapidly progressive dementia: Report of three cases. Neurol Sci. 2013;34(11):2027-30.
5. Roberts MC, Emsley RA. Cognitive change after treatment for neurosyphilis. Correlation with CSF laboratory measures. Gen Hosp Psychiatry. 1995;17(4):305-9.
6. Hutto B, Adimora AA. Syphilis in psychiatric inpatients: Prevalence, treatment and implications. Gen Hosp Psychiatry. 2000;22(4):291-3.
7. Lin LR, Zhang HL, Huang SJ, Zeng YL, Xi Y, Guo XJ, et al. Psychiatric manifestations as primary symptom of neurosyphilis among HIV-negative patients. J Neuropsychiatry Clin Neurosci. Summer 2014;26(3):233-40.
8. Wang QQ, Zhang GC. Clinical diagnosis and treatment guidelines for sexually transmitted diseases. Shanghai: Shanghai Science and Technology Press; 2007.
9. Gottlieb GL, Gur RE, Gur RC. Reliability of psychiatric scales in patients with dementia of the Alzheimer type. Am J Psychiatry. 1988;145(7):857-60.
10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.
11. Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's disease cooperative study. Alzheimer Dis Assoc Disord. 1997;11(Suppl 2):S33-9.
12. Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potočnik M, et al. 2014 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2014;28(12):1581-93.
13. Rosen T, Vandergriff T, Harting M. Antibiotic use in sexually transmissible diseases. Dermatol Clin. 2009;27(1):49-61.
14. Psomas KC, Brun M, Causse A, Atoui N, Reynes J, Le Moing V. Efficacy of ceftriaxone and doxycycline in the treatment of early syphilis. Med Mal Infect. 2012;42(1):15-9.
15. Hook EW 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. J Infect Dis. 1988;158(4):881-4.
16. Buitrago-Garcia D, Marti-Carvajal AJ, Jimenez A, Conterno LO, Pardo R. Antibiotic therapy for adults with neurosyphilis. Cochrane Database Syst Rev. 2019;5(5):CD011399.
17. Marra CM, Boutin P, McArthur JC, Hurwitz S, Simpson PA, Haslett JA, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. Clin Infect Dis. 2000;30(3):540-4.
18. Sanchez FM, Zisselman MH. Treatment of psychiatric symptoms associated with neurosyphilis. Psychosomatics. 2007;48(5):440-5.
19. Taycan O, Ugur M, Ozmen M. Quetiapine *vs.* risperidone in treating psychosis in neurosyphilis: A case report. General Hospital Psychiatry. 2006;28(4):359-61.