

Original Article

Comparison of the curative efficacy of intrathecal and intravenous injection of ceftriaxone and vancomycin in the treatment of intracranial infection during the perioperative period

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Abstract: Objective: To compare the clinical efficacy of intrathecal and intravenous injection of ceftriaxone and vancomycin in the treatment of intracranial infection during the perioperative period of neurosurgery. Methods: Eighty patients with intracranial infection treated in our hospital from January 2014 to January 2017 were selected as subjects and randomized into four groups: intrathecal injection of ceftriaxone group (CT, n=20), intravenous injection of ceftriaxone group (CV, n=20), intrathecal injection of vancomycin group (VT, n=20) and intravenous injection of vancomycin group (VV, n=20). The clinical efficacy, hospital length of stay (LOS), and changes in indices 7 days after the treatment such as cerebrospinal fluid (CSF), intracranial pressure and body temperature were observed and compared. Results: In comparison to intravenous administration groups, efficacies in both CT (P=0.001) and VT (P=0.004) group appeared to be better, while efficacies in these two groups were similar (P=0.738). Besides, both CT and VT group experienced a greater reduction of CSF protein quantity (P=0.003, P=0.004), white blood cell (WBC) count (both P<0.01) and intracranial pressure (both P<0.05), and a more evident increase in the concentration of chloride and glucose in CSF (all P<0.01) than those in intravenous administration groups. No statistical difference in the aforementioned indices was observed between CT and VT group (all P>0.05). The body temperatures after treatment among the four groups were similar (P=0.321). The LOS in VV group was the longest (compared with other groups, all P<0.001), while the LOS in VT (P<0.001) and CT group (P<0.001) was shorter than that in CV group. Conclusion: Intrathecal injection of ceftriaxone and vancomycin can achieve better curative efficacy than intravenous injection in the treatment of intracranial infection, and can be more conducive to the rehabilitation of patients.

Keywords: Ceftriaxone, vancomycin, intracranial infection, efficacy

Introduction

The incidence rate of intracranial infection following neurosurgery operation is quite high, and the severe infection could lead to death of patients if not treated in a timely manner [1-3]. Using high-potency broad-spectrum antibiotics can greatly improve the curative efficacy in patients with severe infection [4-6], and the application of antibiotics has provided a new approach for the clinical treatment of intracranial infection during the perioperative period of neurosurgery [7, 8].

Ceftriaxone, a broad-spectrum antibiotic, belongs to the third-generation cephalosporin.

Between 2 and 24 h after the intravenous administration, its concentration in cerebrospinal fluid (CSF) can be several times higher than the minimum inhibitory concentration against common pathogens [9]. Besides, there have been studies revealing that the intrathecal injection can allow the ceftriaxone to enter directly into the CSF circulation to further increase its concentration in CSF and thereby makes it kill the bacteria more easily and thoroughly [10]. Clinically, vancomycin is usually administered intravenously to treat patients with intracranial infection. However, the influence of the blood brain barrier on the drug passing rate can greatly limit the bactericidal efficacy of vancomycin, which could prolong the

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course of treatment and aggravate the damage to liver and kidney function [11]. There have been studies in recent years demonstrating that in treating intracranial infection, the method of intrathecal injection of vancomycin can enhance the medication efficacy, reduce the damage to liver and kidney function, and achieve the goal of curing diseases [12]. Yet in these studies, the curative efficacies of ceftriaxone and vancomycin based on different modes of administration were not compared, neither were the changes of relevant indicators.

In this article, 80 cases of patients with intracranial infection treated in our hospital from January 2014 to January 2017 were selected for the comparison of the clinical efficacy of intrathecal and intravenous injection of ceftriaxone and vancomycin.

Materials and methods

Participants/subjects

The study was reviewed and approved by the Ethics Committee of the hospital and recognized by the patients and their families. A total of 80 patients with intracranial infection during the perioperative period of neurosurgery and treated in our hospital from January 2014 to January 2017 were selected. According to the random number table method, they were divided into 4 groups: intrathecal injection of ceftriaxone group (CT group), intravenous injection of ceftriaxone group (CV group), intrathecal injection of vancomycin group (VT group), and intravenous injection group of vancomycin (VV group), with 20 patients in each group.

Inclusion criteria: 1) Patient met the diagnostic criteria for intracranial infection after neurosurgery, i.e. (A) patients had experienced headache or relatively severe headache, chills, fever, projectile vomiting, and clinical signs of meningeal irritation; (B) patients had infections detected by relevant tests, including a significant increase of white blood cell (WBC) count in blood routine test; (C) results of lumbar puncture showed that CSF WBC count $>0.01 \times 10^9/L$, protein quantity >450 mg/L, and sugar quantity <400 mg/L; (D) CSF culture was positive, and if this was met, the diagnosis of intracranial infection could be confirmed; otherwise, patients' clinical manifestations and associated examination results need to be reviewed,

along with more tests to be carried out for diagnosis [13]; 2) patients with clear consciousness; 3) patients or their families were willing to sign the informed consents; 4) patients were able to cooperate in completing relevant tests.

Exclusion criteria: 1) Patients with severe self-related diseases, such as uremia, coagulation abnormalities, heart diseases and so on; 2) patients with mental diseases; 3) patients had infections and were receiving antibiotic treatments; 4) patients who were not able to undergo lumbar puncture; 5) patients who could not take ceftriaxone and vancomycin; 6) patients with other fungal or viral infections; 7) patients with autoimmune disease; 8) patients with excessive sedation; 9) patients who were not willing to cooperate; 10) patients who were less than 18 years old or more than 80 years old.

Treatment methods

The gender, age, weight and intracranial infection severity score were recorded prior to the treatment [14]. Before administration of ceftriaxone and vancomycin, all patients were required to take routine examinations and associated allergic tests. Treatment could only be carried out if no allergic reaction occurred.

In CT group, patients were given the intrathecal injection of 0.1 g ceftriaxone dissolved in 10 ml of 0.9% sodium chloride (NaCl) solution once a day, with one week as a treatment course.

In CV group, patients received the intravenous injection of 2.0 g of ceftriaxone dissolved in 10 ml of 0.9% NaCl solution twice a day, with one week as a treatment course.

In VT group, patients received the intrathecal injection of vancomycin. Following the lumbar puncture, 20.0 mg vancomycin was diluted in 10 ml of 0.9% NaCl solution and injected intrathecally into the patients slowly within 0.5 h once a day, with one week as a treatment course.

In VV group, patients received intravenous injection of 1.0 g vancomycin diluted in 10 ml of 0.9% NaCl solution once a day, with one week as a treatment course.

Follow-up and outcome measures

Main outcome measures: Curative efficacy: During the course of treatment and hospitaliza-

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Table 1. Basic information of four groups

	No. of Case	Gender		Age (year)	Weight (kg)	IISS
		Male	Female			
CT group	20	11	9	56.3±11.0	63.3±22.2	15.6±5.1
CV group	20	10	10	57.1±13.3	62.9±19.0	14.9±6.3
VT group	20	12	8	55.4±9.8	60.7±24.1	15.4±4.8
VV group	20	13	7	57.6±12.1	63.1±20.3	14.6±7.2
χ^2/F		1.023		0.679	0.894	0.826
P value		0.796		0.943	0.812	0.851

Note: IISS, intracranial infection severity score.

Table 2. Comparison of curative efficacy among four groups

	Excellence	Improvement	Failure	Effective rate (%)
CT group (n=20)	10	9	1	95.00*.#
CV group (n=20)	4	4	12	40.00
VT group (n=20)	8	10	2	90.00*.#
VV group (n=20)	2	5	13	35.00
χ^2				40.211
P				0.008

Note: Compared with CV group, *P<0.01; compared with VV group, #P<0.01.

tion, patients were followed up closely once a day. After three days of treatment, changes in patients' symptoms were observed, and samples of patients' blood, CSF and so on were taken for clinical and bacteriological examination. If the results of laboratory tests and vital signs of patients turned to be normal three days after medication, it could be concluded that the drug had excellent effect. If patients' symptoms and related indices were positively controlled, it could be determined that the drug had effect of improvement; but if not controlled or even worsened, it could be determined that the drug was a failure in effect. Effective rate was the total rate of excellence and improvement.

Secondary outcome measures: The changes of clinical indicators such as those in blood and CSF, and the variations in body temperature and intracranial pressure were measured and compared 7 days after treatment; meanwhile the total length of stay (LOS) was compared among the four groups.

Statistical analysis

The related statistics tool, SPSS software version 17.0, was used to sort and analyze all data acquired in the study. The measurement data was expressed as mean \pm sd, and the four

groups were compared by one-factor analysis of variance and Bonferroni post hoc test; comparison of pre- and post-treatment within the group was conducted by paired t test. The count data was expressed as rate, and the differences among the four groups and between two independent samples were examined by χ^2 test and segmentation probability method (test level $0.05/6 = 0.0083$). P<0.05 was considered statistically significant.

Results

Patients' characteristics

A total of 80 patients suffering from perioperative infection after neurosurgery were included with 20 cases in CT, CV, VT and VV group respectively. There was no significant difference among the four groups in regard to patients' characteristics (all P>0.05, **Table 1**).

Curative efficacy

The differences in the curative efficacy among the four groups displayed statistical significance (P=0.008). Compared with CV and VV group, the curative efficacies in CT (vs. CV, P=0.001; vs. VV, P<0.001) and VT group (vs. CV, P=0.004; vs. VV, P=0.001) were evidently better (**Table 2**). The efficacies between CT and VT group were similar, with no statistically significant difference (P=0.738).

Secondary outcome measures

Prior to the treatment, the WBC count (P=0.674), protein quantity (P=0.553), glucose level (P=0.614), and chloride level (P=0.703) in CSF were similar among the four groups with no statistically significant difference (**Table 3**). From the comparison between pre- and post-treatment within each group, it can be seen that all groups experienced improvements in these CSF indices after treatment (all P<0.01).

Compared with CV and VV group, the reduction of CSF protein quantity and the WBC count in CT and VT group appeared to be greater (all P<0.01), and the increase of CSF chloride and

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Table 3. Comparison of changes in CSF indices among four groups before and after treatment

	CT group (n=20)	CV group (n=20)	VT group (n=20)	VV group (n=20)
WBC (*10 ⁶ /L)				
BT	182.32±44.21	178.99±36.28	187.56±32.78	181.92±42.85
AT	45.67±23.45 ^{*,#,&}	87.83±19.89 ^{&}	43.11±24.01 ^{*,#,&}	79.92±26.43 ^{&}
Protein quantity (g/L)				
BT	0.99±0.35	0.96±0.21	0.97±0.12	0.98±0.28
AT	0.40±0.12 ^{*,#,&}	0.68±0.11 ^{&}	0.42±0.19 ^{*,#,&}	0.66±0.09 ^{&}
Glucose (mmol/L)				
BT	1.56±0.12	1.49±0.15	1.54±0.17	1.55±0.21
AT	3.35±0.21 ^{*,#,&}	2.35±0.14 ^{&}	3.44±0.19 ^{*,#,&}	2.31±0.23 ^{&}
Chloride (mmol/L)				
BT	80.45±9.32	81.21±9.25	79.89±9.01	80.65±7.68
AT	120.21±6.58 ^{*,#,&}	100.12±6.39 ^{&}	123.28±9.23 ^{*,#,&}	101.69±8.65 ^{&}

Note: BT, before treatment; AT, after treatment. Vs. CV group (after treatment), *P<0.01; vs. VV group (after treatment), #P<0.01; vs. before treatment, &P<0.01.

Table 4. Comparison of changes in body temperature among four groups before and after treatment

Temperature (°C)	CT group (n=20)	CV group (n=20)	VT group (n=20)	VV group (n=20)
BT	39.28±0.36	39.65±0.55	39.87±0.61	39.52±0.32
AT	36.35±0.23	37.21±0.15	36.22±0.19	37.45±0.21
P	0.024	0.031	0.021	0.036

Note: BT, before treatment; AT, after treatment.

glucose concentration was also more significant (all P<0.01). No statistical difference was found between CT and VT group (all P>0.05, **Table 3**).

The basal body temperatures of patients among the four groups were similar before treatment, with no statistically significant difference (P=0.722). After the treatment, patients' body temperature in each group all improved (P=0.024, P=0.031, P=0.021, P=0.036), with no intergroup difference (P=0.321, **Table 4**).

The intracranial pressure of the patients among the four groups were similar before the treatment (P=0.631) and all lowered after the treatment (all P<0.001). Compared with CV and VV group, the intracranial pressure in CT (vs. CV P=0.021; vs. VV P=0.019) and VT (vs. CV P=0.025; vs. VV P=0.017) group decreased much more. There was no statistical difference in the intracranial pressure between CT and VT group after treatment (P=0.356, **Table 5**).

The difference in the LOS among the four groups was significant (P<0.001). Compared

with CV and VV group, the LOS in CT and VT group appeared to be much shorter (all P<0.001). The LOS in CT and VT group were similar (P=0.551, **Table 6**).

Discussion

Intracranial infection is one of the common complications in neurosurgery. Some studies have documented that the probability of intracranial infection in patients following the craniotomy can be as high as 18% and the mortality rate of intracranial infection can even reach 40% [15-17]. Therefore, if patients had intracranial infection during perioperative period of neurosurgery, it is crucial for them to receive treatment as early as possible. At present, the main method to prevent and treat intracranial infection is intravenous administration of antibiotics. The third-generation cephalosporin was often chosen for its relatively good function of killing bacteria [18]. While vancomycin is a glycopeptide antibiotic with a narrow antibacterial spectrum, it is quite active against gram-positive coccus, the main pathogen for intracranial infection after neurosurgery [19, 20]. However, vancomycin has a rather strong toxicity to the kidney, and as a result, the clinical medication time of vancomycin and its dosage should be controlled strictly [21]. In recent years, intrathecal injection of antibiotics has been widely applied in the clinical treatment of intracranial infection, for the antibiotics can directly enter into the subarachnoid space, thereby elevates the drug

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Table 5. Comparison of changes in intracranial pressure among four groups before and after treatment

		CT group (n=20)	CV group (n=20)	VT group (n=20)	VV group (n=20)
ICP (mmH ₂ O)	BT	192.32±23.54	189.56±21.96	195.36±25.32	191.23±19.89
	AT	130.23±19.39 ^{*,#,&}	153.01±16.32 ^{&}	129.84±16.36 ^{*,#,&}	152.88±21.02 ^{&}

Note: ICP, intracranial pressure; BT, before treatment; AT, after treatment. Vs. CV group, ^{*}P<0.05; vs. VV group, [#]P<0.05; vs. before treatment, [&]P<0.001.

Table 6. Comparison of patients' LOS among four groups

	CT group	CV group	VT group	VV group
Case	20	20	20	20
LOS (d)	5±1.12 ^{*,#}	11±3.41	6±2.14 ^{*,#}	12±4.01

Note: vs. CV group, ^{*}P<0.001; vs. VV group, [#]P<0.001.

concentration in CSF and achieve a relatively good curative efficacy. Meanwhile, this method can also effectively prevent the risks caused by the intravenous injection of antibiotics [22, 23].

The results in this study showed that both intrathecal and intravenous injection could improve the clinical symptoms of patients to some extent, but relatively speaking, the intrathecal injection method could deliver better clinical test results and curative efficacy, as well as more improvement in patients' vital signs and clinical symptoms than the intravenous injection method. Some studies reported that the therapeutic effect of intrathecal injection in treating intracranial infection was indeed better than that of intravenous injection [24], however, the LOS of patients was not observed. The result of this study confirmed that the intrathecal injection can reduce the LOS of patients and speed up the rehabilitation.

There have already been studies demonstrating that both intrathecal injection of vancomycin and ceftriaxone can bring about therapeutic effect on intracranial infection [25, 26], but the comparisons between the two were not conducted in those studies. Hence, we carried out this study and found that there was no difference between the intrathecal injection of these two drugs in terms of the improvement of various indices and their curative efficacy. The study revealed that both antibiotics can achieve quite good clinical efficacy in treating intracranial infection, and also demonstrated that the intrathecal injection of ceftriaxone was curatively effective. The result aligned with the findings from Sokolov et al. on the efficacy of intra-

thecal injection of ceftriaxone in treating neurological infections [27]. Concerning the severe nephrotoxicity of vancomycin, intrathecal injection of ceftriaxone might become a more ideal treatment method for the perioperative intracranial infection.

At the same time, since the total sample size of this study was relatively small, and the follow-up may be relatively inadequate, there might be some slight variations in the results. Prospective trial will be conducted in the future with a bigger sample size and longer follow-up time for verification, in order to support extensive clinical application of the intrathecal injection of antibiotics in treating intracranial infection during perioperative period of neurosurgery.

In conclusion, using ceftriaxone and vancomycin to treat intracranial infection can obtain good therapeutic effects. But in terms of the way of administration, the intrathecal injection method can achieve better efficacy and be more conducive to patients' rehabilitation than intravenous injection method. As a result, the intrathecal injection method can be further promoted and applied clinically.

Disclosure of conflict of interest

None.

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