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Observation and analysis of the efficacy of dexamethasone in combination with anti-infectious treatment on the pediatric refractory purulent meningitis

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Abstract: To analyze the pathogenic bacteria, feature of drug resistance and the efficacy of dexamethasone as the auxiliary medication in pediatric refractory purulent meningitis (PM). The 190 refractory PM child patients were selected for the culture of pathogenic bacteria and analysis of drug resistance. In total, 190 pathogenic bacteria were detected, consisting of gram-positive bacteria (77.37%). Of the gram-positive bacteria, the resistance rate of patients with *staphylococcus epidermidis*, *streptococcus pneumoniae* or Staphylococcus haemolyticus to levofloxacin was 100%, while in gram-negative bacteria, the resistance rate of patients with *klebsiella pneumoniae* to gentamycin was 100%. In the observation group, patients had a higher effectiveness rate. Besides, patients in the observation group recovered rapidly from the fever and anomalies in cerebral spine fluid and peripheral white blood cells, and the inflammation was greatly improved. However, difference in the incidence rates of adverse reactions of patients between two groups showed no statistical significance. Pediatric refractory PM involves the pathogenic bacteria, mainly including *staphylococcus epidermidis* and *streptococcus pneumoniae*, showing a high resistance to levofloxacin, while the auxiliary medication of dexamethasone can improve the efficacy, and inhibit the inflammation.

Keywords: Child, refractory purulent meningitis, pathogenic bacteria, drug resistance, dexamethasone, clinical efficacy

INTRODUCTION

Purulent meningitis (PM) is mainly caused by the infection of various pathogenic bacteria, including *streptococcus pneumoniae* and *escherichia coli* (Zhu *et al.*, 2015), manifesting the fever, purulent changes in cerebral spine fluid and increase in intracerebral pressure, with acute onset. Any delay, or inappropriate treatment would result in the decline in intelligence or hearing loss, with a high morbidity rate and mortality rate (Bai *et al.,* 2016). Owing to the rapid progress and extensive application of antibiotic drugs, a significant decrease has been noted in the PM. However, the extensive application of these drugs has given rise to the widespread drug resistance, which, plus the decrease in the permeability of blood-brain barrier, deteriorates the efficacy or promotes the recurrence in child patients (He *et al*., 2014). Evidence derived from the clinical practice has shown the involvement of different types of pathogenic bacteria in different regions, resulting in the variance in therapeutic strategy and prognosis. Thus, it is quite significant to analyze the types of PM-associated pathogenic bacteria and drug resistance for stipulation of clinical medication. Dexamethasone, as one of the most common glucocorticoids, is featured by the potent anti-inflammatory effect, which is not applicable for all patients. Thus, in this study, we detected the pathogenic bacteria and their drug resistance in pediatric refractory PM, and performed the auxiliary medication of dexamethasone.

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MATERIALS AND METHODS

General data

With the 190 refractory PM child patients who were admitted to Hanchuan People's Hospital of Hubei Province for treatment between July 2013 and June 2018 as subjects, they were divided into two groups observation group and control group, with 95 patients in each group. Inclusion criteria: 1) Patients aged between 1 month and 12 years, regardless of genders; 2) Patients conforming to the diagnostic criteria of PM issued by *Zhu Futang Practice of Pediatrics* (Lucas *et al.*, 2015), with manifestations of vomiting, fever or consciousness changes, or the pathogens in cerebral spine; 3) Patients with no recovery, or mild changes in the culture of cerebral spine fluid, after 2 to 3 weeks of treatment via sensitive antibiotics or empirical antibacterial therapy; 4) Patients undergoing the culture of pathogenic bacteria and analysis of drug resistance; 5) Patients with intact clinical data. Exclusion criteria: 1) Patients with viral meningitis or tubercular meningitis; 2) Patients with infectious shock; 3) Patients complicated by other diseases in central nervous system; 4) Patients with the history of dexamethasone administration; 5) Patients with incomplete clinical data. This study had been approved by the Ethical Committee of Hanchuan People's Hospital of Hubei Province and the guardians of patients signed the written informed consents.

Culture of pathogenic bacteria and analysis of drug resistance

Following admission, cerebral spine fluid was collected for bacteria culture to identify the pathogenic bacteria using the VITEK32 Automatic Microorganism Analyzer (Pioneering Diagnostics, France). The resistance of pathogenic bacteria to the corresponding drugs was evaluated by measurement of the minimal inhibitory concentration (MIC) using the K-B agar diffusion method.

Laboratory test

Prior to the treatment and at 7 d after treatment, the peripheral venous blood was drawn to detect the levels of C-reactive protein (CRP), tumor necrotic factor -α(TNF-α) and procalcitonin (PCT) respectively by radical immunodiffusion, enzyme-linked immunosorbent assay (ELISA) and electrochemical luminescence(ECL). Besides, we also recorded and analyzed the recovery time of patients in two groups from the fever, anomaly of cerebral spine fluid and peripheral white blood cells, and the hospitalization time, as well as the incidence of the adverse reactions.

Treatment methods

All patients received the treatment, including decreasing the intracerebral pressure, nutrition support, protection of brain cells and anti-infectious therapy. Additionally, patients in the control group withdrew the ineffective antibiotics, and took the sensitive antibiotics through the drug sensitivity test. On the basis of treatment applied in the control group, patients in the observation group would take intravenous infusion of dexamethasoneat a dose of 10 mg/kg·d, 4 times/d for 7 to 10 days.

Evaluation of the efficacy

Excellence: Following treatment, patients manifested significant improvement in fever and other vital signs, with magnificent recovery of indicators in cerebral spine fluid and blood. Improvement: Following treatment, patients manifested improvement in fever and other vital signs, with the recovery of indicators in cerebral spine fluid and blood. Failure: Following treatment, patients manifested no improvement, or deterioration in fever, other vital signs or indicators in cerebral spine fluid and blood. Total effectiveness rate is the total of excellence rate and improvement rate.

STATISTICAL ANALYSIS

SPSS 20.0 software was applied to process the data. Enumeration data were presented with percentage (%), and compared by use of chi-square test. Measurement data were presented with mean ± standard deviation and compared by use of *t* test. $P<0.05$ suggested the statistical significance of difference.

RESULTS

Comparison of the clinical data between two groups

Of 190 patients, there were 127 males and 63 females, and comparison of the general data, sex ratio, age and temperature between two groups showed no significant differences ($P>0.05$; table 1).

Distribution of pathogenic bacteria in patients of two groups

In total, 190 pathogenic bacteria were detected, consisting of 147 cases of gram-positive bacteria (77.37%), mainly including 49 cases of *staphylococcus epidermidis* and 39 of *streptococcus pneumoniae*, and 43 cases of gram-negative bacteria, predominantly the *klebsiella pneumoniae* (19/43; table 2).

Resistance of bacteria to the antibiotics in patients of two groups

Of the gram-positive bacteria, the resistance rates of patients with *staphylococcus epidermidis*, *streptococcus pneumoniae* or *Staphylococcus haemolyticus* to levofloxacin were all 100%, while to cefazolin were 79.59%, 84.61% and 74.07%, and to vancomycin were all 0.00% (table 3). In gram-negative bacteria, the resistance rate of patients with *klebsiella pneumoniae* to levofloxacin was 95.24%, and to gentamycin was 100%, while to vancomycin or meropenem was all 0.00%.

Comparison of the efficacy between two groups

In the observation group, the total effectiveness rate of patients was 91.58%, significantly higher than 81.05% in the control group ($\chi^2=4.916$, $P=0.026$; table 4).

Comparison of the clinical indicators of patients in two groups

Besides, patients in the observation group recovered rapidly from the fever and anomalies in cerebral spine fluid and peripheral white blood cells when comparing to their counterparts in the control group, with a shorter hospitalization time ($P<0.05$; table 5).

Comparison of the levels of inflammatory cytokines before and after treatment between two groups

Before treatment, no significant difference was identified in comparison of the levels of CRP, TNF-α and PCT in serum between two groups ($P>0.05$), while the changes of these indicators in the observation group were more evident than those in the control group ($P<0.05$; table 6).

Adverse responses to the drugs in patients of two groups

During treatment, diarrhea was reported by 10 patients and mild increase of liver aminotransferase by 2 patients in the observation group, while in the control group, there were 6 patients reporting the diarrhea. However, difference in the incidence rates of adverse reactions of patients between two groups showed no statistical significance ($\chi^2= 1.992$, $P = 0.159$).

Table 1: Comparison of the clinical data between two groups

Clinical data		Observation group (n=95)	Control group (n=95)	Statistics	*P*
Sex	Male	65	62	0.357	0.549
	Female	30	33		
Age (yr)		3.74±0.46	3.80±0.53	0.876	0.382
Temperature (°C)		38.82±0.51	38.84±0.47	0.295	0.768

Table 2: Distribution of pathogenic bacteria infection in refractory PM patients

Pathogenic bacteria	N (n=190)	Ratio (%)
Gram-positive bacteria:	147	77.37
Streptococcus pneumoniae	39	20.53
Staphylococcus epidermidis	49	25.79
Staphylococcus aureus	10	5.26
Staphylococcus haemolyticus	27	14.21
Others	22	11.58
Gram-negative bacteria	43	22.63
Klebsiella pneumoniae	19	10.00
Escherichia coli	8	4.21
Others	16	8.42

Table 3: Resistance of the major gram-positive bacteria to the antibiotics in patients of two groups

Antibiotics	*Staphylococcus epidermidis* (n＝49)		*Streptococcus pneumoniae* (n＝39)		*Staphylococcus haemolyticus* (n＝27)	
	N	Resistance rate (%)	N	Resistance rate (%)	N	Resistance rate (%)
Levofloxacin	49	100.00	39	100.00	27	100.00
Ceftriaxone	20	40.82	0	0.00	0	0.00
Cefazolin	39	79.59	33	84.61	20	74.07
Cefuroxime	19	38.78	16	41.03	13	48.15
Penicillin G	19	38.78	19	48.72	17	62.96
Gentamycin	5	10.20	13	33.33	14	51.85
Clindamycin	5	10.20	13	33.33	13	48.15
Vancomycin	0	0.00	0	0.00	0	0.00
Piperacillin	39	79.59	35	89.74	20	74.07
Meropenem	4	8.16	13	33.33	12	44.44

Table 4: Comparison of the efficacy between two groups

Efficacy	Observation group (n=95)		Control group (n=95)		χ^2	*P*
	N	%	N	%		
Total effectiveness	87	91.58	77	81.05	4.916	0.026
Excellence	55	57.89	36	37.89	8.411	0.004
Improvement	32	33.69	41	43.16	2.016	0.157
Failure	8	8.42	18	18.95	4.836	0.031

Table 5: Comparison of the clinical indicators of patients in two groups (mean ± standard, d)

Group	N	Time of fever abatement	Recovery time of WBC	Recovery time of CSF	Hospitalization time
Observation group	95	2.35±0.58	5.83±1.67	9.13±1.79	11.23±1.36
Control group	95	3.64±0.76	8.64±2.15	12.36±1.58	16.78±2.52
t		3.312	3.213	3.432	5.536
P		<0.05	<0.05	<0.05	<0.05

Table 6: Comparison of the levels of CRP, TNF-α and PCT in serum of patients before and after treatment (mean ± standard deviation)

Indicators	Observation group (n=95)				Control group (n=95)				$P^{\#}$	
	Before treatment[a]	After treatment	P^*	Difference[c]	Before treatment[b]	After treatment	P^*	Difference[d]	a vs. b	c vs. d
CRP (mg/L)	75.17±14.73	27.50±8.18	<0.001	47.66±12.15	73.96±16.49	39.63±11.27	<0.001	34.31±10.70	0.574	<0.001
TNF-α (pg/mL)	140.27±42.79	55.28±14.55	<0.001	84.71±23.66	138.70±39.14	68.83±18.48	<0.001	69.86±21.49	0.781	<0.001
PCT (pg/mL)	532.25±80.36	185.7±42.64	<0.001	346.50±51.09	520.97±87.35	242.39±66.44	<0.001	278.61±70.13	0.33	<0.001

Note: *, pairwise *t* test; #, independent *t* test.

DISCUSSION

As the rapid development in diagnosis and drug research, the mortality rate of pediatric PM has been continuously decreasing, but the efficacy of antibiotics is still affected owing to the emergence of drug-resistant bacteria in some regions or hospitals, resulting in the occurrence of refractory PM and increasing the difficulty of clinical treatment. Relevant research (Malheiro *et al.*, 2015) has shown that the generation of drug-resistant bacteria may associate with the abuse of antibiotics, especially the inappropriate, overdose or prolonged use of antibiotics. Thus, analysis of the distribution pattern and drug resistance of pathogenic bacteria in pediatric PM is significant for guiding the medication of pediatric refractory PM and screening the sensitive antibiotics (Li *et al*., 2016; Yang *et al.*, 2017).

Yang *et al.* (2015) reported that in pediatric PM, gram-positive bacteria dominates, including *staphylococcus epidermidis*. The investigation of Hu *et al*. (2017) showed that from 2010 to 2014, *streptococcus pneumoniae* and *escherichiacoli*pediatric dominate in PM in Jinan, Shandong and the resistant rate of gram-positive bacteria to azithromycin has attained over 90%. Kamoun F *et al*. (2015) revealed that between 2007 and 2014, S*treptococcus pneumoniae*, *Escherichia coli*, coagulase negative staphylococcus and enterococcus faecium are the major bacteria in the culture of child CSF. Thus, the distribution pattern of child PM-specific pathogenic bacteria may vary in different regions or different periods. In this study, we investigated the pediatric refractory PM cases between 2013 and 2018 and found that gram-positive bacteria dominated in the culture of CSF, taking up 77.37%, similar to the results of Wang *et al*. (2017) However, infection of *staphylococcus epidermidis* was reported in the majority of cases, followed by *streptococcus pneumoniae*, which was totally different from the result of Wang *et al*. (2017). This may attribute to the differences in age distribution and disease severity patients. Nichols *et al*. (2015) found that in patients aged between one month and 11 years, the proportion of *staphylococcus epidermidis* infection takes up 21.84%, while in those between 1 year and 6 years, they are more prone to the infection of *staphylococcus epidermidis*. In this study, among the identified gram-positive bacteria, we found that *Staphylococcus epidermidis* and *Streptococcus pneumoniae* dominated, corresponding to the previous report (Ma *et al*., 2015). As for the drug resistance, most of the gram-positive bacteria and gram-negative bacteria were resistant to levofloxacin, and generally, gram-negative bacteria had higher resistant rates to the cefazolin, piperacillin, gentamycin and cefotaxime. Moreover, we found that these bacteria were sensitive to vancomycin and meropenem. As such, we suggested that selection of antibiotics should be dependent on the drug-sensitivity test to improve the rationality of medication.

In the observation group, the total effectiveness rate of patients was 91.58%, significantly higher than 81.05% in the control group (χ^2=4.916, *P*=0.026). Besides, patients in the observation group recovered rapidly from the fever and anomalies in cerebral spine fluid and peripheral white blood cells when comparing to their counterparts in the control group, with a shorter hospitalization time (*P* <0.05). Furthermore, changes of the levels in C-reactive protein (CRP), tumor necrotic factor α(TNF-α) and procalcitonin (PCT) in serum of patients in the observation group were more evident than those in the control group (t = 8.456, 4.762 and 8.018; *P*<0.01). However, difference in the incidence rates of adverse reactions of patients between two groups showed no statistical significance (*P* >0.05).

Owing to the influence of antibiotics abuse and emergence of drug-resistant bacteria, we should also consider the auxiliary antibiotic therapy from the aspects of Traditional Chinese Medicine and glucocorticoid in addition to the individualized antibiotic therapy. Dexamethasone, as a kind of glucocorticoid, has the anti-inflammatory effect and immunosuppression, which expands its application in prophylaxis and treatment of infection of pathogenic bacteria. Previous evidence of animal experiments showed that after onset of PM, the secondary brain injury or even death associates closely with the subarachnoid inflammatory response. For meningitis patients, bacterial membrane and wall activate the macrophage and epithelial cells, giving rise to the acute release of cytokines and relevant substances, causing the inflammatory responses and damage to the blood-brain barrier, leading to the leakage of capillaries, brain edema and increase of intracerebral pressure. Furthermore, this condition may be deteriorated by the administration of antibiotics that could resolve the cell membrane to induce the burst of cytokines and relevant substances. However, dexamethasone, via inhibiting the macrophage and epithelial cells, can antagonize the inflammation for treatment of PM. Currently, no unified conclusion has been yet developed regarding to the dose of dexamethasone in treatment of PM. Animal experiment (Uppal *et al*., 2017) has shown that dexamethasone can decrease the CSF pressure to abate the edema, while some researchers put forward that dexamethasone fails to decrease the mortality rate of PM (Macagno *et al*., 2016). Chang *et al.* (2017) showed that dexamethasone, as an auxiliary method, promotes the recovery of patients from PM, with fewer adverse responses. Divergences above may derive from the differences in region, bacteria and age of patients. In this study, we found that dexamethasone as an auxiliary method can improve the efficacy on pediatric refractory PM. PM attack activates the inflammatory cells in CSF to facilitate the secretion of pro-inflammatory factors, which, plus the damage of antibiotics to the bacterial structure, may induce the cascade responses of inflammatory cytokines. In PM, the most common inflammatory cytokines include CRP, TNF-α and PCT. CRP, as an acute time-phase factor, is increased in serum after infection; TNF-α serves as not only the initiator of the inflammatory reaction, but also the key factor inducing the inflammatory cascade reactions; acute increase of PCT is frequently in severe infection of bacteria.

CONCLUSION

Pediatric refractory PM involves the pathogenic bacteria, mainly including *Staphylococcus epidermidis* and *Streptococcus pneumoniae* showing a high resistance to levofloxacin. The auxiliary medication of dexamethasone can improve the efficacy, shorten the hospitalization time and inhibit the inflammation, worthy of being promoted in clinical practice.

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