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Original Article

Analysis of clinical efficacy and prognostic factors of vidarabine in combination with human immunoglobulin in the treatment of children with adenovirus pneumonia

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Abstract: Objective: To explore the clinical efficacy and prognostic factors of vidarabine in combination with human immunoglobulin in the treatment of children with adenovirus pneumonia. Methods: This is a perspective, randomized and double-blinded single-center study, which recruited 108 children with adenovirus pneumonia. They were divided into the control group and observation group, with 54 cases in each group. Children in the control group were treated with vidarabine, while others in the observation group were treated with vidarabine in combination with human immunoglobulin. After treatment, the improvement of clinical symptoms (disappearance time of fever, cough and moist rales; hospital stay) and changes of laboratory parameters [tumor necrosis factor-α (TNF-α), secreted phospholipase A2 (sPLA2), interleukin-1 (IL-1)] between the two groups were compared. The prognostic factors were analyzed by univariate analysis and multivariate logistic regression analysis. Results: After 15 days of treatment, the total effective rate in the observation group (92.59%) was significantly higher than that in the control group (77.78%) ($P<0.05$). The disappearance of fever, cough and moist rales as well as hospital stay [(2.65±1.02) d, (3.71±1.26) d, (7.12±1.38) d and (9.75±0.96) d, respectively] in the observation group was shorter than that [(3.16±1.14) d, (4.14±1.33) d, (7.67±1.46) d, and (10.21±1.03) d, respectively] in the control group (all $P<0.05$). The levels of TNF-α, sPLA2 and IL-1 in both groups decreased after treatment (all $P<0.05$). By multivariate logistic regression analysis, it was revealed that the unfavorable prognosis factors of pediatric adenovirus pneumonia included: hemoglobin <90 g/L, albumin <30 g/L, concurrent congenital airway dysplasia, concurrent acute respiratory distress syndrome, circulatory complications, with more than three complications. Conclusion: Vidarabine in combination with human immunoglobulin can improve the clinical symptoms of children with adenovirus pneumonia, reduce the inflammatory response, reduce sPLA2 levels and shorten the hospital stay. The unfavorable prognosis indicators of pediatric adenovirus pneumonia included anemia, hypoproteinemia, concurrent underlying pulmonary diseases, concurrent acute respiratory distress syndrome, circulatory complications, with multiple complications, which should be given special attention to in the clinic.

Keywords: Vidarabine, human immunoglobulin, children, adenovirus pneumonia, inflammatory factor, prognostic factor

Introduction

Pediatric adenovirus pneumonia is a disease caused by adenovirus infection, which has complex clinical symptoms and is prone to multiple system complications. About one-third of children with adenovirus pneumonia will develop into severe pneumonia and the mortality rate of the severe cases is as high as 10%. About 14% to 60% of survivors have pulmonary sequelae such as bronchiolitis obliterans and bronchiectasis, which have serious effects on the children's health and growth [1, 2]. Therefore, the early detection and treatment of adenovirus infection is of great clinical significance. The administration of antiviral drugs at the early stage of adenovirus pneumonia can significantly improve the children's clinical symptoms and shorten their hospital stay. Vidarabine is a nucleoside analogue with significant inhibitory activity against viral polymerase, and its antiviral effects are achieved by blocking the viral DNA replication.

Previous studies have shown that vidarabine has a good effect on the treatment of children

with respiratory adenovirus infection, viral pneumonia, bronchitis and Epstein-Barr (EB) virus infections [3-5]. However, studies have also shown that some children might develop drug resistance due to the long-term use of vidarabine. In addition, the clinical application of vidarabine can be limited due to the potential occurrence of adverse reactions, such as leukopenia, pulmonary and renal functional lesions and neurological impairment [6].

Children with severe adenovirus have strong inflammatory activation with decreased immune response and immune disorders. Active intervention during treatment is conducive to the control of disease [7]. Human immunoglobulin is an immunomodulator made from fresh healthy human plasma or frozen plasma within 2-years of storage. The purity of immunoglobulin is over 90%, which has a broad-spectrum antiviral effect and it is rich in other pathogenic immunoglobulin G (IgG) antibodies. In clinic, the passive immunization obtained by human immunoglobulin can strengthen immunity and improve disease resistance. Studies have found that the early application of intravenous immunoglobulin in children with severe hand-foot-mouth disease could significantly improve their clinical symptoms and shorten their hospital stay [8]. Studies also indicated that human immunoglobulin had good effects in the treatment of children with severe adenovirus pneumonia [9]. Therefore, we speculate that it may be conducive to disease control with active treatment of human immunoglobulin at the early stage of disease, and avoid the progression to severe pneumonia. Based on this, our study observed the clinical efficacy of vidarabine in combination with human immunoglobulin in the treatment of children with adenovirus pneumonia and analyzed the risk factors of prognosis for the disease; which provided a theoretical foundation for clinical intervention and improved efficacy in children with adenovirus pneumonia.

General information and methods

General information

There were 108 children with adenovirus pneumonia who underwent treatment in our hospital from January 2017 to January 2019 in this perspective, randomized and double blinded single-center study. According to a random number table, children were randomly divided into the control group and observation group, with 54 cases in each group. Inclusion criteria: patients met the diagnostic criteria for pneumonia in the Guidelines for the Management of Community-Acquired Pneumonia in Children (Revised in 2013) [10] and the result of direct immunofluorescence assay was positive for adenovirus antigen; patients were between 6 months to 6 years old; patients had no history of drug allergy; patients had no major surgery in the past 6 months; patient's family signed informed consent forms. Exclusion criteria: patients had combined cardiac, hepatic, pulmonary and kidney insufficiency; patients were complicated with mycoplasma and chlamydia infection; patients had systemic acute or chronic infections; patients had congenital immune deficiency; patients were in non-compliance with medical advice or didn't coordinate follow-up visits; patients with mental retardation or combined with mental disease; patients had severe malnutrition. This study was approved by our hospital's medical ethicals committee.

Methods [11]

Children in the control group were given vidarabine [Sinopharm Yixin Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval number H20067593, specification 0.1 g×5] at 5-10 mg/(kg·day) in 250 mL normal saline via intravenous drip. It was given once a day with continuous treatment for 7 days.

Children in the observation group were given vidarabine in combination with human immunoglobulin: the usage and dosage of vidarabine were the same as those in the control group, and they were treated continuously for 7 days. Children were also treated with human immunoglobulin (Hualan Bio-Engineering Chongqing Co., Ltd., SFDA approval number S10970033, specification 300 mg:3 mL) at 400 mg/kg via intravenous drip. This was given once a day with continuous treatment for 7 days.

Observation indexes

(1) Evaluation of clinical curative effects: recovery: the symptoms of fever and moist rales completely disappeared. Serum adenovirus antibody immunoglobulin M (IgM) was negative and the result of chest X-ray returned to normal. Improvement: the symptoms of fever and moist rales improved. Serum adenovirus anti-

Table 1. General information ($\bar{x}$ ± s, n)

Group	Observation group	Control group	χ^2/t	P
n	54	54		
Gender			0.178	0.673
M	37	39		
F	17	15		
Average age (year)	2.18±0.47	2.22±0.51	0.424	0.673
Duration of disease (d)	2.11±0.86	2.15±0.79	0.252	0.802
Body mass index (kg/m^2)	18.72±2.34	18.85±2.31	0.291	0.772

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Group	Observation group	Control group	χ^2	P
n	54	54		
Recovery	32 (59.26)	30 (55.56)		
Improvement	18 (33.33)	12 (22.22)		
Inefficiency	4 (7.41)	12 (22.22)		
Total effective rate	50 (92.59)	42 (77.78)	4.696	0.030

body IgM was negative and chest X-ray showed partial absorption of inflammation. Inefficiency: there was no significant improvement in clinical symptoms and signs, serum adenovirus antibody IgM was still positive or the child had died. Total effective rate = (Recovery + improvement)/54×100%. (2) Improvement time of clinical symptoms and hospital stay: the disappearance time of fever, cough and moist rales as well as hospital stay were compared between the two groups. (3) Laboratory tests: before treatment and 7 days after treatment, 5 mL venous blood was collected and centrifuged at 3000 r/min for 10 min. The serum was used, and TNF-α, sPLA2 and IL-1 were detected by enzyme-linked immunosorbent assay kit, which was purchased from R&D Inc., USA. (4) Children were divided into a favorable prognosis group (recovery + improvement) and an unfavorable prognosis group (inefficiency + death) according to their outcomes. Their gender, age, duration of fever, routine blood tests and complications were analyzed.

Statistical analysis

The data were analyzed by SPSS 25.0 statistical analysis software. The measurement data were presented as mean ± standard deviation ($\bar{x}$ ± sd) and independent sample t-test was applied. Paired t-test was used for the intra-group comparison before treatment. The count data was expressed as cases number/percentage (n/%) and Chi-square (χ^2) test was applied. Hemoglobin <90 g/L, albumin <30 g/L, concurrent congenital airway dysplasia, concurrent acte respiratory distress syndrome, circulatory complications, with no less than three complications were considered as independent variables, and the unfavorable prognosis was considered as the dependent variable. All data were involved in the multiple logistic regression analysis. P<0.05 was considered statistically significant.

Results

Comparison of general information

There were no significant differences between the two groups in general information including gender, average age, duration of disease and body mass index before treatment (P>0.05). The two groups were comparable. See **Table 1**.

Comparison of clinical efficacy between the two groups

The total effective rate in the observation group (92.59%) was higher than that in the in the control group (77.78%), which showed statistical significance (P<0.05). See **Table 2**.

Comparison of improvement time of clinical symptoms and hospital stay between the two groups

The disappearance time of fever and moist rales as well as hospital stay in the observation group was shorter than that in the control group, which was statistically significant (P< 0.05). The disappearance time of cough in the observation group was slightly shorter than that in the control group, but this didn't show statistical significance (P>0.05). See **Table 3** and **Figure 1**.

Comparison of serum indexes between two groups before and after treatment

Before treatment, there were no statistical differences in serum indexes between the two

Table 3. Comparison of improvement time of clinical symptoms and hospital stay between the two groups ($\bar{x} \pm s$, d)

Group	Observation group	Control group	*t*	P
n	54	54		
Disappearance time of fever	2.65±1.02	3.16±1.14	2.456	0.016
Disappearance time of cough	3.71±1.26	4.14±1.33	1.725	0.087
Disappearance time of moist rales	7.12±1.38	7.67±1.46	2.012	0.047
Hospital stay	9.75±0.96	10.21±1.03	2.401	0.018

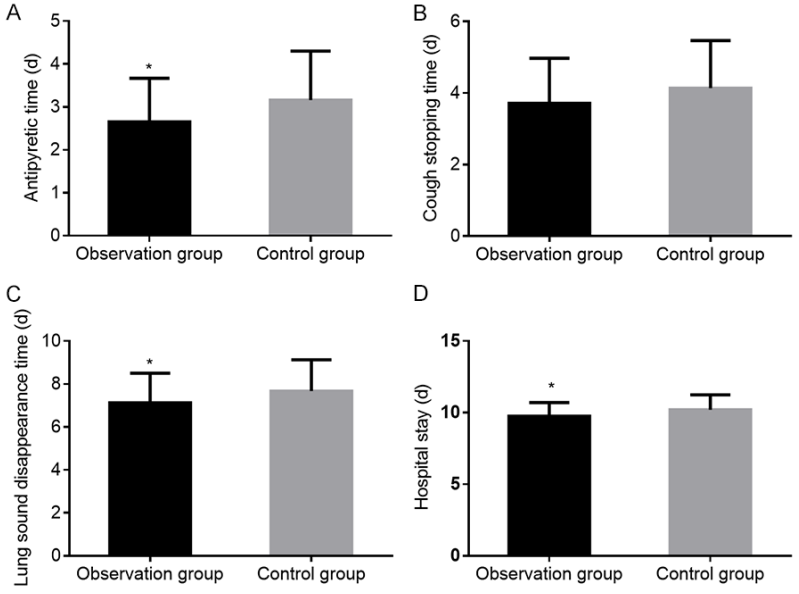

Figure 1. Comparison of improvement time of clinical symptoms and hospital stay between the two groups. Note: (A) for disappearance time of fever; (B) for disappearance time of cough; (C) for disappearance time of moist rales; (D) for hospital stay. Compared with control group, *P<0.05.

Table 4. Comparison of serum indexes between two groups before and after treatment ($\bar{x} \pm s$)

Group	Observation group	Control group	*t*	P
n	54	54		
TNF-α (ng/L)				
Before treatment	85.57±18.70	86.45±16.82	0.257	0.798
After treatment	46.31±12.86###	48.45±14.63###	0.807	0.421
sPLA2 (U/L)				
Before treatment	149.95±25.64	151.37±26.61	0.282	0.778
After treatment	102.43±18.87###	105.91±20.25###	0.924	0.358
IL-1 (ng/L)				
Before treatment	7.59±2.11	7.63±2.05	0.100	0.921
After treatment	4.29±0.65###	4.57±1.13###	1.7458	0.084

Note: compared with before treatment, ###P<0.001.

groups (P>0.05), including TNF-α, sPLA2 and IL-1. After treatment, the serum indexes in both groups were lower than those before treatment (P<0.05). The serum indexes in the observation group were slightly lower compared with those in the control group, but there were no statistical differences between the two groups (P>0.05). See **Table 4** and **Figure 2**.

Univariate analysis of prognosis in children with adenovirus pneumonia

It was revealed that the prognostic factors of pediatric adenovirus pneumonia included: hemoglobin <90 g/L, albumin <30 g/L, concurrent congenital airway dysplasia, concurrent acute respiratory distress syndrome, circulatory complications, with no less than three complications by univariate analysis (P<0.05). See **Table 5**.

Multiple logistic regression analysis of prognosis in children with adenovirus pneumonia

Hemoglobin <90 g/L, albumin <30 g/L, concurrent congenital airway dysplasia, concurrent acute respiratory distress syndrome, circulatory complications, with no less than three complications were considered as independent variables, and the unfavorable prognosis in children with adenovirus pneumonia was considered as the dependent variable. All were involved in the multiple logistic regression analysis. The results showed that the independent risk factors of unfavorable prognosis in children with adenovirus pneumonia included hemoglobin <90 g/L, albumin <30 g/L, concurrent with congenital airway dysplasia, concurrent acute respiratory

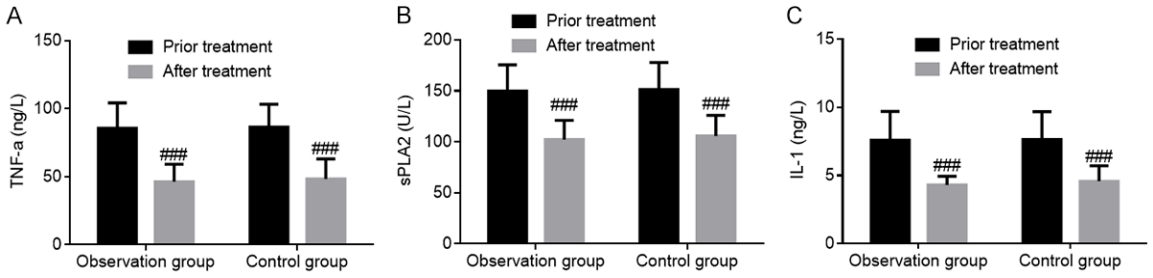

Figure 2. Comparison of serum indexes between two groups before and after treatment. Note: Compared with before treatment, ###P<0.001. (A) for TNF-α; (B) for sPLA2; (C) for IL-1. TNF-α for tumor necrosis factor-α; sPLA2 for secreted phospholipase A2; IL-1 for interleukin-1.

Table 5. Univariate analysis of prognosis in children with adenovirus pneumonia [$\bar{x}$ ± s, n (%)]

Characteristics	Favorable prognosis group (n=92)	Unfavorable prognosis group (n=16)	t/χ^2	P
Gender (M/F)	65/27	11/5	0.024	0.878
Age (year)	2.24±0.48	1.96±0.53	1.742	0.084
Duration of fever (d)	6.46±1.85	7.25±2.03	1.554	0.123
Hemoglobin <90 g/L	23 (25.00)	11 (68.75)	12.094	0.001
Albumin <30 g/L	20 (21.74)	10 (62.50)	9.347	0.001
Concurrent bacterial infection	11 (16.30)	4 (25.00)	1.002	0.164
Concurrent congenital airway dysplasia	3 (3.26)	4 (25.00)	7.343	0.000
Digestive complications	48 (52.17)	9 (56.25)	0.091	0.763
Concurrent acute respiratory distress syndrome	4 (4.35)	5 (31.25)	9.631	0.000
Circulatory complications	12 (13.04)	9 (56.25)	13.603	0.000
Neurological complications	26 (28.26)	5 (31.25)	0.003	0.807
No less than three complications	32 (34.78)	13 (81.25)	12.108	0.001

Table 6. Multiple logistic regression analysis of prognosis in children with adenovirus pneumonia [$\bar{x}$ ± s, n (%)]

Variable	β	Wald	OR	P	95% CI	
					Upper limit	Lower limit
Hemoglobin <90 g/L	1.985	8.636	0.885	0.000	1.253	1.684
Albumin <30 g/L	1.355	7.363	1.332	0.003	1.151	2.025
Concurrent congenital airway dysplasia	1.146	5.425	1.893	0.006	1.204	2.787
Concurrent acute respiratory distress syndrome	1.372	7.437	1.497	0.003	1.086	2.164
Circulatory complications	2.297	9.231	0.526	0.000	1.108	1.492
No less than three complications	2.036	8.931	0.824	0.000	2.038	2.459

Note: OR for odds ratio; CI for confidence interval.

distress syndrome, circulatory complications, with no less than three complications (P<0.05). See **Table 6**.

Discussion

Pediatric adenovirus pneumonia is difficult to treat, and no effective antiviral drugs have been found useful in clinic. It has been reported that the prognosis of children with adenovirus pneumonia can be affected by concurrent severe bacterial infection, hepatic insufficiency and multiple complications, etc., which can lead to the unfavorable prognosis of prolonged disease course, and even death [12, 13]. At present, researchers are still looking for effective treatment therapies for pediatric adenovirus pneumonia, exploring the risk factors of

prognosis, and aiming to find a better way to improve disease prognosis.

The inflammatory response plays an important role in the occurrence and development of pediatric adenovirus pneumonia, and a variety of inflammatory cytokines are involved in this process [14, 15]. The inflammatory cytokine TNF-α is mainly derived from mononuclear macrophages, while IL-1 is mainly derived from activated mononuclear macrophages. When the inflammatory response occurs, TNF-α and IL-1 are abnormally increased and involved in the inflammatory and immune response [16, 17].

Phospholipase A2 (PLA2) is mainly produced by alveolar. The cytokines TNF-α and IL-1 act as PLA2 inducers, which can stimulate the release of PLA2. PLA2 hydrolyzes arachidonic acid to produce leukotrienes, thromboxane and prostacyclin, which cause a vicious circle of a series of inflammatory responses [18, 19]. Relevant studies have found that serum TNF-α, sPLA2 and IL-1 in children with adenovirus pneumonia were up-regulated compared with healthy controls, suggesting that TNF-α, sPLA2 and IL-1 were involved in the pathogenesis of pediatric adenovirus pneumonia [20, 21]. Our study indicated that serum TNF-α, sPLA2 and IL-1 in both groups decreased after treatment. Wu found that levels of sPLA2 in severe adenovirus pneumonia group was at 138.00 IU/mL (135.00-141.00), which was significantly higher than the normal control group of 97.30 IU/mL (96.20-98.30). Meanwhile, the result of TNF-α also showed a similar trend change. Both changes suggested that TNF-α and sPLA2 are involved in the pathogenesis of adenovirus pneumonia [22], which is consistent with our study. The reason for these changes may be that vidarabine can inhibit the proliferation of the virus. Human immunoglobulin can strengthen the clearance effect on the virus by immuno-enhancement, reduce the inflammatory infiltration of the lungs, decrease the release of inflammatory factors, lower TNF-α, sPLA2 and IL-1 levels and prevent the inflammatory cascade [23]. These may be important mechanism for the use of vidarabine in combination with human immunoglobulin, which can promote the disappearance of symptoms, accelerate the recovery of children, and shorten hospital stay. However, the results of our study showed that after treatment in combination with human immunoglobulin, serum TNF-α, sPLA2 and IL-1 in the observation group were slightly lower than those in the control group, with no statistical significance between the two groups. This suggested that human immunoglobulin could shorten the disappearance time of fever and moist rales, as well as hospital stay, but didn't have significant effect on decreasing inflammatory factors. This results might be related to milder and limited participants selected in this study; whose inflammatory responses were not very intense. This can be further explored with larger samples in the next study.

Previous studies have found that there are a variety of factors affecting the prognosis of pediatric adenovirus pneumonia [24]. In our study, it was indicated by univariate analysis that the unfavorable prognosis factors of pediatric adenovirus pneumonia included hemoglobin <90 g/L, albumin <30 g/L, concurrent congenital airway dysplasia, concurrent acute respiratory distress syndrome, circulatory complications, with no less than three complications. It was revealed by further multiple logistic regression analysis that independent risk factors for unfavorable prognosis of pediatric adenovirus pneumonia included hemoglobin <90 g/L, albumin <30 g/L, concurrent congenital airway dysplasia, concurrent acute respiratory distress syndrome, circulatory complications and no less than three complications, which were basically consistent with previous studies [21, 22]. The results proved that unfavorable prognosis factors of pediatric adenovirus pneumonia included anemia, hypoproteinemia, concurrent underlying pulmonary diseases, concurrent acute respiratory distress syndrome, circulatory complications and multiple complications. The reasons were summarized as below: (1) Anemia and hypoproteinemia: children with anemia and hypoproteinemia suffer from malnutrition, low immune function and poor disease resistance. The disease severity can easily develop, which is not conducive to their recovery [25]. (2) Concurrent underlying pulmonary diseases and acute respiratory distress syndrome: children combined with congenital airway dysplasia and acute respiratory distress syndrome have poor pulmonary function. Their pulmonary function will further decline due to the occurrence of pediatric adenovirus pneumonia, which is not conducive to their rehabilitation and prognosis [26]. (3) Circulatory complications: extrapulmonary compli-

cations are common complications in children with adenovirus pneumonia. The circulatory complications include myocarditis, myocardial damage, heart failure, etc., which can cause circulatory dysfunction and are not conducive to the children's recovery [27]. (4) Concurrent multiple complications: children with multiple complications often have severe conditions and are less likely to recover compared with milder conditions. Therefore, during the treatment of children with adenovirus pneumonia, medical staff should pay attention to children with high risk factors, monitor children's albumin and hemoglobin actively, learn about their medical histories and handle complications with symptomatic treatment positively. They should try best to eliminate risk factors for an unfavorable prognosis to promote the recovery of children.

This study still has the following shortcomings: (1) The sample size is small, which need to be expanded. (2) This study used intravenous drugs, the efficacy of which may be affected by lower local blood concentration. The combined nebulization inhalation therapy needs to be explored. (3) The efficacy of different types of adenovirus infection needs to be classified and observed. (4) Inclusion factors may be incomprehensive in the factor analysis.

In conclusion, the therapeutic effect of vidarabine in combination with human immunoglobulin in the treatment of children with adenovirus pneumonia is beneficial. It can improve the clinical symptoms of children, reduce the inflammatory response, reduce sPLA2 levels and shorten the hospital stay. The unfavorable prognosis factors of pediatric adenovirus pneumonia include anemia, hypoproteinemia, concurrent underlying pulmonary diseases, concurrent acute respiratory distress syndrome, circulatory complications and multiple complications, which should be paid special attention to in clinic.

Disclosure of conflict of interest

None.

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