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Article

The effect of fluconazole combined with amphotericin B on highly toxic miR-15b and TGF-β1 of *cronobacter* in neonates

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Abstract: Objective: To analyze the effects of fluconazole combined with amphotericin B on the levels of miR-15b and transforming growth factor-β1 in patients with *cronobacter* in neonates. **Methods:** Using the random number table method, twenty-eight patients who were admitted to our hospital between January 2018 and January 2021 with *cronobacter* pneumonia were chosen and split into two groups: the control group and the observation group. For 14 days, they received either fluconazole with amphotericin B or amphotericin B alone. The pulmonary function forced expiratory volume in one second (FEV1) and forced vital (FORCED vital) of the two groups were observed and recorded Capacity (FVC), forced expiratory volume/forced vital volume in one second/orced vital Capacity, FEV1/FVC), procalcitonin (PCT), soluble receptor expressed on myeloid (Triggering receptor expressed on myeloid) Cells-1, StreM-1), Mir-15b and TGF-β1, and the clinical efficacy was evaluated. **Results:** After treatment, the levels of FEV1, FVC and FEV1/FVC in patients were increased, and the levels of FEV1, FVC and FEV1/FVC in observation group were higher than those in control group ($P < 0.05$). After treatment, the levels of PCT and sTREM-1 were decreased, while the levels of miR-15b and TGF-β1 were increased. Compared with the control group, the levels of PCT and TREM-1 were lower in the observation group, while the levels of miR-15b and TGF-β1 were higher ($P < 0.05$). The total effective rate of observation group (92.86%) was significantly higher than that of control group (57.14%), the difference was statistically significant ($P < 0.05$). **Conclusion:** Fluconazole plus amphotericin B has demonstrated clinical efficacy in treating patients with *cronobacter* pneumonia in neonates. It can effectively improve the inflammatory state of the body, miR-15b, and TGF-β1, as well as aid in improving lung function with fewer side effects and high safety.

Keywords: fluconazole; amphotericin B; *cronobacter* in neonates pneumonia; microRNA-5b; transforming growth factor β1

1. Introduction

According to the Ministry of Health, *cronobacter* in neonates infection is the primary cause of *cronobacter* in neonates pneumonia, a common and frequent respiratory disease that is a subacute/chronic fungal infection [1]. Due to factors like the evolution of cryptococci themselves, climate change, and the growth of susceptible populations, the incidence of *cronobacter* pneumonia in neonates has been on the rise in recent years. The disease progresses quickly, endangering the health and quality of life of patients [2]. Antibacterial medications and glucocorticoids are currently the mainstays of clinical treatment for *cronobacter* in neonatal pneumonia; however, due to inadequate drug usage oversight and high drug resistance in patients with *cronobacter* in neonatal pneumonia, overall clinical

efficacy is low [3]. Amphotericin B, as a polyene antifungal agent, selectively binds to fungal cell membrane ergocalciferol, resulting in fungal death. However, clinical studies have pointed out that amphotericin B, as the antifungal drug with the broadest spectrum, has strong toxicity and is prone to adverse reactions and affects clinical efficacy, so it needs to be used in combination with other drugs to improve the efficacy [4,5]. Fluconazole, as a pyrrole antifungal drug, has excellent efficacy in *cronobacter* in neonates infections and inhibition of Pseudomonas albicans, but its narrow antibacterial spectrum makes it easy to affect the efficacy due to drug resistance. At present, there are few clinical reports on the efficacy and mechanism of fluconazole combined with amphotericin B in the treatment of *cronobacter* in neonates pneumonia [6,7]. Based on this, the combination of fluconazole and amphotericin B was given to patients with *cronobacter* in neonates pneumonia, and its efficacy and the effects of miR-15b and TGF-β1 were analyzed.

2. Materials and methods

2.1. Clinical data

Study subjects: 28 patients with *cronobacter* in neonates pneumonia admitted to our hospital from January 2018 to January 2021 were selected and divided into 14 cases in the control group by random number table method, including 8 male and 6 female cases, age 22 to 72 years, mean age (47.00 ± 21.25) years, duration of illness 9 to 64 d, mean duration of illness (36.50 ± 23.38) d; 14 cases in the observation group, including 7 males and 7 females aged 24–72 years, mean age (48.00 ± 20.40) years, duration of illness 7–62 d, mean duration of illness (34.50 ± 23.38) d. The clinical data of all patients were compared without statistical differences ($P > 0.05$) and were comparable. The ethical selection principle was strictly followed with the approval of our ethics committee, and all signed the informed consent form.

The following criteria must be met for inclusion: fungal growth in sputum culture; confirmation of the diagnosis of *cronobacter* in neonates pneumonia by CT and other imaging tests; presence of signs of infection in the lungs on X-ray chest films; and fulfillment of the pertinent diagnostic criteria for *cronobacter* in neonates pneumonia in the Expert Consensus on the Diagnosis and Treatment of *cronobacter* in Neonates Infections [8].

Exclusion criteria: combination of organic dysfunction of the heart and kidneys; coagulation disorders; congenital heart disease; combination of acquired immunosuppression defects, respiratory diseases; immunodeficiency virus positive; combination of psychiatric disease or communication disorders; contraindications to the drugs in the study.

2.2. Methods

Group under control: Intravenous drip treatment was administered with amphotericin B (manufacturer: North China Pharmaceutical Co., Ltd., State Drug Administration: H13020284). The dosage of the medication was modified based on the patient's physical state, tolerance level, and extent of fungal infection, among other factors. A tiny dose of 0.5 mg/kg was used initially, and the next day the

amount was increased to 1 mg/kg. The drug dosage was then progressively increased to maintain a dose of 3–6 mL. If the adverse reaction is not considerable, the dosage can be increased more quickly. The drug was dissolved in 500 mL 5% glucose solution with sterile water for injection, and the infusion was completed within 6~8 h. Before each use, a small amount of the drug should be used for test injection to patients to observe whether there is any reaction related to the infusion, and if patients have acute reaction, the infusion speed should be slowed down immediately.

Observation group: Amphotericin B and fluconazole injection (manufacturer: Yangtze River Pharmaceutical Group Co., Ltd., State Drug quantification: H20030612, specification: 100mL: 0.2 g) were given as combined treatment, intravenous drip, 0.2 g/time, control drip rate lower than 10 mL/min, 2 times/d. Amphotericin B medication was kept the same as the control group. Both groups were treated continuously for 14 d.

To address the deficiencies related to clinical operations and adverse reaction management, we acknowledge the need for detailed prevention and treatment measures, particularly for highly toxic drugs like amphotericin B. Based on guideline recommendations, the following strategies could be incorporated:

(1) Electrolyte Imbalance Management: Amphotericin B is associated with significant risks of hypokalemia and hypomagnesemia. Routine monitoring of serum potassium and magnesium levels should be implemented, with supplementation protocols in place to correct imbalances promptly.

(2) Nephrotoxicity Prevention: Preemptive strategies, such as administering saline infusions before amphotericin B administration, can reduce the risk of nephrotoxicity. Lipid formulations of amphotericin B should also be considered to minimize renal damage.

(3) Infusion-Related Reactions: Gradual dose escalation and premedication with antipyretics, antihistamines, or corticosteroids can help mitigate infusion-related reactions such as fever, chills, or hypotension.

(4) Hepatotoxicity Monitoring: For fluconazole, regular liver function tests should be conducted to detect early signs of hepatotoxicity. Dose adjustments or alternative therapies should be considered for patients with pre-existing liver conditions.

(5) Comprehensive Patient Monitoring: Establishing protocols for regular monitoring of renal function, liver enzymes, and inflammatory markers (such as PCT and sTREM-1) ensures early detection and management of adverse effects during treatment.

(6) Patient Education and Support: Educating caregivers about potential adverse effects and ensuring access to supportive care can enhance the safety and effectiveness of the therapy.

Incorporating these strategies into clinical protocols would not only improve the safety profile of amphotericin B and fluconazole therapy but also enhance patient outcomes in the treatment of *cronobacter* pneumonia in neonates.

2.3. Index observation

2.3.1. Pulmonary function

The changes of pulmonary function in both groups were evaluated on the day the patients were seen and 14 d after treatment using a pulmonary function instrument (manufacturer: Jäger Kungfu Branch, Germany; model: Master Screenpaed), respectively, containing FEV1, FVC, FEV1/FVC, with repeated monitoring, taking the best values three times, taking their mean values, and comparing between groups.

2.3.2. PCT, sTREM-1, and TGF-β1 levels were measured

5 mL of fasting peripheral venous blood was collected on the day the patient was seen and 14 d after treatment, respectively, and left to stand at room temperature for 10 min, centrifuged at high speed (speed: 3000 r/min, radius: 12 cm) for 10 min, and the supernatant was separated and stored at −20 ℃ at low temperature for examination. Using double antibody sandwich ELISA method, set up the enzyme plate as blank wells, standard wells and sample wells to be tested, add 50 μL diluent in each well, add 50 μL each of sample diluent, standard wells and sample wells to be tested, shake evenly, laminate the enzyme plate and incubate at room temperature for 2 h. Discard the liquid in the wells, shake dry and wash the reaction plate repeatedly with washing solution. Add 100 μL of PCT, sTREM-1 and TGF-β1 detection solution to each well, re-laminate, incubate at room temperature for 1 h, discard the liquid in the wells, shake dry, wash the reaction plate, add 100 μL of substrate solution to each well, develop color at room temperature and avoid light for 30 min, add 50 μL of termination solution, flick the enzyme plate to terminate the reaction. After the reaction, the absorbance values of the standards and samples at 450 nm were detected using an enzyme marker (model iMark, Bio-RAD), and the sample content was calculated by plotting the standard curve, referring to the instructions of the kit and the operation of the instrument.

2.3.3. miR-15b level determination

Using real-time quantitative fluorescence polymerase chain reaction (PCR) method, total RNA of serum Let-7a cells was isolated using microRNA extraction and isolation kit, microRNA reverse transcription was performed using TaqMan microRNA reverse transcription kit, and quantitative PCR reaction was performed using SYBR Premix ExTaq II kit, setting reaction Conditions: pre-fire 95 ℃, pre-denaturation for 30 min, remove and cool down to 90 ℃, denaturation for 5 s, rapid cooling to 58 ℃, annealing for 20 s, temperature maintained at 60 ℃, extension for 45 s, 40 consecutive cycles, and repeat the experiment 3 times. The relative expression of miR-15b was calculated using the 2-ΔΔCt method with U6 as the internal reference. u6: upstream primer: 5'-ATGGAACGCTTCACGAAT-3'; downstream primer: 5'-TCGGCAGCACATATACTAA-3 ', miR-15b: upstream primer: 5'-AGCAGCACATCATGGTTTAC-3'; downstream primer: 5'-GTGCAGGGTCCGAGGT-3'.

2.4. Efficacy assessment

Following 14 days of treatment, the two groups' clinical efficacy was assessed based on the patients' physical symptoms, laboratory results, and pathological tests. The results were categorized as effective, efficient, and ineffective. Ineffective: clinical symptoms and signs did not significantly improve or even worsened after 72

hours of drug administration; effective: clinical symptoms and signs improved; ineffective: one of the laboratory and pathogenic tests had not disappeared or returned to normal. (Effective + Effective)/total number of instances times 100% is the total effective rate.

2.5. Assessment of adverse reactions

The occurrence of adverse reactions such as hypokalemia, gastrointestinal reactions, and elevated transaminases during treatment was recorded in both groups and compared between groups.

2.6. Statistical processing

SPSS 20.0 software was used for analysis. The measurement data were described using mean ± standard deviation (), and independent sample *t*-test was performed for comparison between groups; the count data were expressed as %, and x^2 test was performed for comparison between groups, with $P < 0.05$ indicating that the differences were statistically significant.

3. Results

3.1. Comparison of lung function indexes between the two groups

As shown in **Table 1**, before treatment, there was no statistical difference between the levels of pulmonary function indexes in the two groups ($P > 0.05$); after treatment, the levels of FEV1, FVC, and FEV1/FVC of patients increased, and compared with the control group, the levels of FEV1, FVC, and FEV1/FVC in the observation group were higher, with statistical differences ($P < 0.05$).

Table 1. Comparison of lung function indexes between the two groups ($\bar{x} \pm s$).

Groups	Number of cases (*n*)	FEV1（%）		FVC（%）		FEV1/FVC	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	14	34.77 ± 5.89	47.01 ± 9.43	37.18 ± 7.25	56.44 ± 10.16	32.17 ± 6.15	53.17 ± 10.28
Observation group	14	33.67 ± 5.24	55.88 ± 8.63	37.29 ± 7.30	67.83 ± 7.21	32.71 ± 6.33	61.33 ± 9.10
t	-	0.522	2.596	0.041	3.421	0.229	2.224
P	-	0.606	0.015	0.968	0.002	0.820	0.035

3.2. Comparison of serum factor levels between the two groups

As shown in **Table 2**, before treatment, there was no statistical difference between the levels of PCT and sTREM-1 in the two groups ($P > 0.05$); after treatment, the levels of PCT and sTREM-1 decreased in patients, and compared with the control group, PCT and sTREM-1 were lower in the observation group, with statistical differences ($P < 0.05$).

Table 2. Comparison of serum factor levels between the two groups ($\bar{x} \pm s$).

Groups	Number of cases (n)	PCT (ng/L)		sTREM-1 (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	14	508.25 ± 43.11	472.54 ± 36.88	53.42 ± 4.20	43.16 ± 6.81
Observation group	14	508.95 ± 43.61	436.58 ± 31.26	53.77 ± 4.60	36.41 ± 3.44
t	-	0.043	2.783	0.210	3.311
P	-	0.966	0.010	0.835	0.003

3.3. Comparison of miR-15b and TGF-β1 levels between the two groups

As shown in **Table 3**, before treatment, there was no statistical difference in miR-15b and TGF-β1 levels between the two groups ($P > 0.05$); after treatment, miR-15b and TGF-β1 levels increased in patients, and compared with the control group, miR-15b and TGF-β1 levels were higher in the observation group, with statistical differences ($P < 0.05$).

Table 3. Comparison of miR-15b and TGF-β1 levels between the two groups ($\bar{x} \pm s$).

Groups	Number of cases (*n*)	miR-15		TGF-β1 (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	14	1.66 ± 0.34	3.11 ± 0.61	163.58 ± 15.81	188.41 ± 12.64
Observation group	14	1.58 ± 0.27	4.38 ± 0.52	164.33 ± 16.39	230.36 ± 15.61
T	-	0.689	5.928	0.123	7.815
P	-	0.497	0.001	0.903	0.001

3.4. Clinical efficacy assessment

As shown in **Table 4**, the total effective rate of treatment in the observation group was 92.86% significantly higher than that in the control group, 57.14%, with statistical differences ($P < 0.05$).

Table 4. Clinical efficacy assessment [n, %].

Groups	Number of cases (n)	Effective	Proven effectiveness	Ineffective	Total effective rate (%)
Control group	14	3	5	6	8(57.14)
Observation group	14	6	7	1	13(92.86)
x^2	-	-	-	-	4.762
P	-	-	-	-	0.029

3.5. Assessment of adverse reactions

As shown in **Table 5**, the overall incidence of hypokalemia, gastrointestinal reactions, and transaminase elevation adverse reactions was observed to be slightly higher compared to the control group, but the difference was not statistically significant due to the poor sample size ($P > 0.05$).

Table 5. Adverse reaction assessment [*n*, %].

Groups	Number of cases (*n*)	Hypokalemia	Gastrointestinal reactions	Elevated transaminases	Total effective rate (%)
Control group	14	1	1	1	3(21.43)
Observation group	14	1	1	2	4(28.57)
x^2	-	-	-	-	0.190
P	-	-	-	-	0.663

4. Discussion

Amphotericin B, a polyene broad-spectrum antifungal agent, is effective against fungi such as Aspergillus, Trichoderma, Bacillus, and Cryptococcus, with low resistance rates and notable efficacy in invasive and severe pulmonary fungal infections [9–11]. Administered primarily via intravenous infusion, it is excreted in active form by the kidneys and, despite high liver detoxification capacity, has minimal impact on hepatic metabolism [12,13]. However, its significant adverse effects warrant caution in clinical use. Fluconazole, a triazole antifungal with low toxicity, good water solubility, and long half-life, has fewer adverse effects but a narrower spectrum, limiting its efficacy against infections like Pseudomonas gramine arum and Aspergillus. Studies highlight the synergistic antifungal effect of combining amphotericin B with fluconazole [14,15]. In treating neonatal pneumonia caused by *cronobacter*, this combination significantly improved lung function, demonstrating its clinical feasibility and superior efficacy compared to amphotericin B alone [16].

This study demonstrated that combining fluconazole with amphotericin B reduced serum PCT and sTREM-1 levels in neonates with *cronobacter* pneumonia, highlighting a correlation between the inflammatory response and disease progression [17,18]. PCT, normally stable and absent from circulation, is highly expressed in the peripheral blood of affected patients, correlating with pneumonia severity and suggesting its involvement in lung disease development [19,20]. Similarly, sTREM-1, a soluble form of TREM-1, showed elevated levels in fungal infections like Aspergillus and Pseudomonas aeruginosa, emphasizing its role in fungal disease progression. The combination therapy effectively lowered PCT and sTREM-1 levels, demonstrating superior anti-inflammatory efficacy [21,22].

Furthermore, Cryptococcus infections activate the immune system, challenging host immune regulation. MicroRNAs, such as miR-15b, regulate immune responses, with miR-15b specifically upregulating regulatory T cells [23,24]. While its role in *cronobacter* pneumonia remains underexplored, TGF-β1, known for promoting extracellular matrix synthesis in pneumonia, showed increased levels post-treatment, indicating its role in disease development and recovery. This study revealed that the combination therapy elevated miR-15b and TGF-β1 levels, effectively enhancing immune regulation and promoting recovery, confirming the feasibility of this therapeutic approach [25].

As mentioned above, fluconazole combined with amphotericin B in the treatment of patients with *cronobacter* in neonates pneumonia effectively improves clinical symptoms and signs, reduces the inflammatory response of the organism,

and helps to promote the recovery of lung function in patients. Although the study concluded that the combination of fluconazole and amphotericin B given to patients with *cronobacter* in neonates pneumonia was effective, the study sample included in this paper was small and no prognostic follow-up was performed, resulting in some limitations of the study, and the result data may be biased, which needs to be confirmed by further multi-center studies with increased sample size.

Author contributions: Conceptualization, YX and HL; methodology, YX; software, YX; validation, YX and HL; formal analysis, HL; investigation, YX; resources, YX; data curation, YX; writing—original draft preparation, YX; writing—review and editing, YX; visualization, YX; supervision, HL; project administration, YX; funding acquisition, HL. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest: The authors declare no conflict of interest.

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