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Investigating the effect of sodium chloride on the prevention of mucormycosis fungal infection in children with acute lymphocytic leukemia during treatment

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Abstract

Background: Given that no comprehensive study was conducted regarding the effect of sodium chloride on the prevention of mucormycosis fungal infection in acute leukemia patients during treatment, this study aimed the investigating the effect of sodium chloride on the prevention of mucormycosis fungal infection in acute lymphocytic leukemia patients during treatment.

Materials and Methods: This retrospective study was conducted on children with ALL who were undergoing chemotherapy in the induction phase and were susceptible to fungal and infectious diseases. Then 84 patients were randomly divided into the two groups. One group (n=46) received nasal drop containing sodium chloride (NORMONIX, 0.65%, three times a day) as the intervention group during treatment and another group did not receive sodium chloride (control group)(n=38). If the symptoms of mucormycosis was observed and detected (positive test), the injection of amphotrypsin B was started.

Results: In the current study, 84 patients entered the study. The mean age of patients in the control group and the intervention group was 7.84±3.45, and 6.45±3.4 years, respectively (P>0.05). Positive mucormycosis was seen in 24 (63.2%) patients in the control group and 16 (34.78%) patients in the intervention group (P=0.01).

Conclusion: According to the findings of this study, the frequency of patients with positive mucormycosis in the NaCl group was significantly lower than the control group. Therefore, it seems that NaCl drop can be effective regarding reducing the incidence of mucormycosis fungal infection and can decrease the need to amphotrypsin B, but further studies should be conducted in this regard.

Keywords: Mucormycosis fungal, Prevention**,** Sodium chloride

Introduction

Mucormycosis or zygomycosis is an invasive fungal infection caused by fungi and is belonged to the fungal order mucorales and the family mucoraceae. It is the third most common invasive fungal infection with high mortality and morbidity (1-5) due to inadequate empiric therapy and delayed diagnosis. It often affects immunocompromised persons and is rarely observed in apparently healthy persons.

The mucormycosis fungus is also an allergenic form of fungi with fast growth which is seen in thick patches. Recent studies have shown an increasing incidence of mucormycosis over the last two decades (5). Invasive fungal infections in children with hematologic and oncologic cancers with intensive protocols may lead to morbidity and mortality, but because of the rarity of the disease, the epidemiologic data in children are rare, especially children with cancer,

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and hematological disease (5). The mucormycosis can be divided into acute and chronic. This infection happens in about 50% of diabetic patients due to more accessibility of glucose to the pathogens that lead to mucormycosis, the increased expression of some host receptors that damage epithelial cells by black fungus or rhizopus, and the reduce of serum inhibitory activity against the Rhizopus (in lower pH). Moreover, it is seen in patients in the emergency department usually affecting immunocompromised individuals. The first-line therapy for mucormycosis is amphotericin B (6) which is used for invasive fungal infection therapy for more than 50 years. Its half time is from 24 hours to 15 days. Nowadays, newer lipid formulations of amphotericin B with less nephrotoxic than conventional amphotericin B are accessible (7). In addition, the lipid formulations of amphotericin B provide better delivery to organs, including liver, spleen, and lung, allow a higher daily dose, and have similar efficacy than conventional amphotericin B with less nephrotoxicity (7). The action of amphotericin B is that it binds to ergosterol in the cell membrane of most fungi. After binding, it causes to form the ion channels leading to loss of protons and monovalent cations, depolarization and concentration-dependent cell killing (7). Furthermore, amphotericin B as an antifungal drug produces reactive oxygen species and has multiple deleterious effects on fungal cell (8, 9). Asghari et al., reported that the use of amphotericin B may lead to adverse effects in mammals (10). Very few studies have been done regarding the effect of sodium chloride (NaCl) in prevention and treatment of mucormycosis fungal infection (11, 12). Given that no comprehensive study was conducted regarding the effect of sodium chloride on the prevention of mucormycosis fungal infection in acute leukemia patients during treatment, this study aimed the investigating the effect of sodium chloride on the prevention of mucormycosis fungal infection in acute lymphocytic leukemia patients during treatment.

Materials and Methods

Sample selection and therapy

This retrospective study was conducted on children with ALL who were undergoing chemotherapy in the induction phase and were susceptible to fungal and infectious diseases in 2020.. One group (n=46) received nasal drop containing sodium chloride (NORMONIX, 0.65% for three times a day) as the intervention group and another group (n=38) did not received sodium chloride. If the symptoms of mucormycosis was observed and detected (positive test), the injection of amphotrypsin B (injection at a dose of 1 mg/kg) for 3 days was started. The mucus from the patients' noses and throats was used for mucormycosis testing and culture in the laboratory. In addition, CT scan was used for diagnosis of mucormycosis.

Inclusion and exclusion criteria

The patients entered in the study after the first week of induction chemotherapy and the appearance of symptoms such as fever and nasal congestion in them. Moreover, patients were under 14 years old. Patients with incomplete medical records excluded from the study. In addition, patients who left the leukemia treatment for any reason during the period of induction chemotherapy and receiving liposomal amphotrypsin B drugs were excluded from the study.

Statistical analysis

Categorical variables were presented by frequency and percent and Chi-square test were used for comparison the frequencies between two groups. Odds ratio was used to show the effect of nasal drop containing sodium chloride on outcome of mucormycosis test. Age of patients was compared by student t-test. Data were analyzed by SPSS20 (IBM Corp. Released

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2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp)and Significance level for all of tests were considered as 0.05.

Ethical consideration

This study was approved by ethical committee of Shahid Sadoughi University of Medical sciences (IR.SSU.MEDICINE.REC.1396.222).

Results

In the current study, 84 patients entered the study. The mean age of patients in the control group and the intervention group was 7.84±3.45, and 6.45±3.4 years, respectively (P>0.05).

The frequency of the two groups in terms of gender was demonstrated in Table I. The comparison of the results of diagnosis of mucormycosis was shown in Table II. Positive mucormycosis was seen in 63.2% of patients who did not received the nasal drop containing sodium chloride and 34.78 % of patients who received the nasal drop containing sodium chloride (P=0.01). Receiving nasal drop containing sodium chloride decreased the chance of the positive outcome 69% (OR= 0.31(0.13-0.76).

Table I: The frequency of the two groups in terms of gender

Gender	**Not received** nasal drop group **(%)**	**Received** nasal drop **group Number (%)**	
Boy	23 (60.5)	18 (39.14)	0.05
Girl	15 (39.5)	28 (60.86)	
Total	38 (100)	46 (100)	

Table II: The comparison of the results diagnosis of mucormycosis in two groups

Mucormycosis test	**Not received** nasal drop **group Number (%)**	**Received** nasal drop **group Number (%)**	**P-value**
Positive	24 (63.2)	16 (34.78)	0.01
Negative	14 (36.8)	30 (65.22)	
Total	38 (100)	46 (100)	

Discussion

Mucormycosis is a fungal infection in various diseases, including severe COVID-19 infection, diabetes, cancer, and trauma and in critically ill disease (13). Moreover, invasive mucormycosis is observed in acute leukaemia, lymphoma and allogeneic stem cell transplantation after chemotherapy (5). The characterization of mucormycosis is extensive angioinvasion leading to vessel thrombosis and tissue necrosis (14). It is an aggressive fatal fungal infection. After inhalation of fungal spores, infection was happen, leading to respiratory tract disease presenting with sinusitis and pneumonia (13).

Prosperous management of mucormycosis disease is based on a multimodal approach, such as discontinuation, or reversal of underlying predisposing factors, early prescription of active antifungal agents with the optimal dosage, the use of various treatments, and complete removal of all infected tissues (14).

One of the most often used medications in treatment of mucormycosis is

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amphotericin B except for some Cunninghamella and Apophysomyces isolates (15-18). Lanternier et al., evaluated the high dose liposomal amphotericin B (10 mg/kg/day) for mucormycosis therapy and observed that the combination of high dose of liposomal amphotericin with surgery was associated with overall response rate of 36%, and 45% at 4 and 12 weeks in 71% of cases (19).

Fisher et al., evaluated a case with advanced mucormycosis and treated by combination therapy, including liposomal amphotericin B., supportive therapy, and surgery. The advantage of liposomal delivery is that the drug is more effective and less toxic (20). Saedi et al., treated rhinocerebral mucormycosis with intravenous and topical amphotericin B, in this regard, the combination of amphotericin B with endoscopic surgical debridement, followed by intravenous amphotericin B treatment may lead to less morbidity compared to conventional treatments. Therefore, according to these studies, amphotericin B with other combinations can be more effective (21).

Handzel et al., assessed iposomal amphotericin B in the treatment of rhinocerebral mucormycosis and treated a case at a rate of 3 mg/kg/d and a total dose of 5.6 gram for 29 days and evaluated the answer to therapy via physical examination, pathological and radiological studies, and microbiological cultures. They reported that the complex of amphotericin B with lipid structures avoids the negative side effects. In addition, there is no consensus regarding the appropriate duration, and the total dose of treatment. Additionally, they reported that due to the high cost of liposomal Amphotericin B and other lipid formulations, it is necessary to find the appropriate treatment regime for rhinocerebral and other mucormycosis infections (22).

Very few studies have been conducted regarding the effect of sodium chloride on the prevention of mucormycosis fungal infection. The findings of the current study demonstrated that the frequency of patients with negative mucormycosis in the intervention group (NaCl group) was significantly higher than the control group. Moreover, the frequency of patients with positive mucormycosis in the intervention group (NaCl group) was significantly lower than the control group. Perhaps the type of assessment of mucormycosis fungal infection affects the results.

Trenser et al., evaluated the effect of NaCl on species of terrestrial fungi. The most resistant species were aspergilla and penicillia; because the majority of these species have ability to grow in 20% or more NaCl. Moreover, the least tolerance was related to Basidiomycetes and more than half of the species can not tolerate more than 2% NaCl(23). Kane et al., assessed the effect of NaCl on Phaeoannellomyces werneckii and 17 species of human dematiaceous fungi. According to the findings of this study, the inhibition of the most dematiaceous pathogens were seen at ≤ 7% NaCl, however, the distinction of phaeoannellomyces werneckii from others was done by its tolerance (≥ 15% NaCl)(12). Mona et al., evaluated the effect of NaCl on morphological changes in some halotolerant fungi and reported low growth of Penicillium canescens, Syncephalastrum racemosum, Mucor racemosus, Emericill anidulans, and Aspergillus parasiticusa at 15% NaCl, while all fungal isolates couldn't grow at 20% NaCl (11). A 47-year old man with COVID pneumonia was diagnosed with rhino-orbito-cerebral mucormycosis. Therapy in this patient was started with Inj phenytoin, amphotericin B, 3% Nacl, and planned for emergency surgery (24). Therefore, according to these studies, different strategies and therapies were applied in the treatment of mucormycosis fungal infection.

Conclusion

According to the findings of this study, the frequency of patients with positive

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mucormycosis in the NaCl group was significantly lower than the control group. Therefore, it seems that NaCl drop can be effective regarding reducing the incidence of mucormycosis fungal infection, and can decrease the need to injection of amphotrypsin B, but further studies should be conducted in this regard.

Conflict of interest

The authors declare no conflict of interest.

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