

Effect of nystatin prophylaxis on candidemia in patients with mechanical ventilation in the Intensive Care Unit

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Abstract

Background: The intensive care unit (ICU) is a treatment room exposed to nosocomial infections. Mechanical ventilation support is often required by 10%-20% of patients admitted to the ICU, where there is a risk of candidemia occurrence. Candidemia is a disease that occurs in any patient at a health care facility, where *Candida* species are found in blood culture specimens processed at laboratories. *Candida* species are some of the most common species causing bloodstream infections in nonneutropenic patients treated in the ICU and are responsible for 8%-12% of cases. Antifungal prophylaxis is often used in ICU for patients prone to candidemia using the *Candida* score, which includes parameters such as *Candida* colonization, history of surgery, severe sepsis, and total parenteral nutrition. Nystatin is considered a prophylactic antifungal in the ICU to reduce the incidence of candidemia and the morbidity and mortality of patients in the ICU.

Methods: This was a randomized clinical trial conducted using a double-blind method. After approval by the Faculty of Medicine Ethics Committee, Universitas Sumatera Utara, Medan, 40 research samples were collected, which were randomly divided into two groups af-

ter verifying the inclusion criteria. Groups A and B received 100,000 IU nystatin and 0.9% NaCl, respectively. The obtained research data were tested using a Statistical Package for the Social Sciences (SPSS).

Results: Positive blood culture results were fewer in the nystatin group than in the 0.9% NaCl group (3 vs. 4). Additionally, positive tracheal aspirate culture results were fewer in the nystatin group than in the 0.9% NaCl group (0 vs. 1). The largest distribution of *Candida* in blood culture was *Candida tropicalis*, whereas only one species of *Candida glabrata* was found in tracheal aspirate culture. The 7th-day mortality in the nystatin group was lower than that in the 0.9% NaCl group (11 vs. 14).

Conclusion: Nystatin effectively reduced the incidence of candidemia, which was lower in the nystatin group than in the 0.9% NaCl group. Moreover, tracheal aspirate culture results in the nystatin group were better than those in the 0.9% NaCl group. Furthermore, the 7th-day mortality rate in the nystatin group was lower than that of the 0.9% NaCl group. The most distributed *Candida* species in the blood culture was *Candida tropicalis*, whereas only one species, *Candida glabrata*, was found in the tracheal aspirate culture.

Key words: Intensive care unit, MV support, candidemia, *Candida*, nystatin, 0.9% NaCl.

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Introduction

The intensive care unit (ICU) is a treatment room susceptible to nosocomial infections, which are associated with high morbidity. Many patients have decreased immunity due to acute and severe illnesses, which are often caused by immunodeficiency or severe comorbidities, and most require invasive procedures. Mechanical ventilation (MV) support is often required by 10%-20% of patients treated in the ICU who require invasive procedures. MV support replaces ventilation function in patients with respiratory

problems or other critical illnesses. As a result, patients in the ICU with MV support are highly susceptible to infections, including candidemia. (1-3)

Candidemia is defined as a disease in any patient in a health care facility where *Candida* species are isolated from blood culture specimens processed at the laboratory. *Candida* can be endogenous or exogenous in origin. Recently, the incidence of candidemia caused by *Candida* species other than *Candida albicans* has increased. Several conditions are often predisposing factors to candidemia in patients in the ICU, including history of abdominal surgery, placement of an intravascular catheter, acute renal failure, administration of parenteral nutrition, use of broad-spectrum antibiotics, length of ICU stay, use of corticosteroids, and mucosal colonization with *Candida*. Reportedly, patients in the ICU with *Candida* colonization of the mucosa, especially multifocal, have a higher risk of developing invasive candidiasis. (4) Candidemia in the ICU is associated with a substantial increase in hospital costs and length of hospital stay. (4,5)

Candida species are one of the most common species causing bloodstream infection (BSI) in nonneutropenic patients treated in the ICU and are responsible for 8%-12% of the cases. Additionally, *Candida* species cause approximately 5% of cases of severe sepsis and septic shock. The Centers for Disease Control lists *C. albicans* as the seventh-most common nosocomial pathogen, and according to the National Nosocomial Infection Surveillance in the United States, *C. albicans* ranks fourth in causing BSI. The incidence of candidemia in the population is 1.7-10 episodes per 100,000 people. *Candida* is the most frequent cause of invasive fungal infections in critically ill patients, and the incidence of candidemia in the ICU is approximately 10-20 times higher than that in other rooms. An estimated 33%-55% of all episodes of candidemia occur in the ICU and are associated with 5%-71% mortality rates. Additionally, research conducted at Cipto Mangunkusumo Hospital in 2011-2014 identified 117 cases of sepsis and candidemia. (4,6-10)

Although many patients are at risk of developing candidemia, not all require prophylactic antifungals. Therefore, criteria for predicting the occurrence of candidemia are needed, including the colonization index, corrected colonization index, and *Candida* score (CS). CS was first proposed in 2006 and updated in 2009. The CS criteria include *Candida* colonization, history of surgery, severe sepsis, and total parenteral nutrition. $CS \geq 3$ has been used as a guideline in providing antifungal therapy to patients

at risk of candidemia. (11,12)

The incidence of candidemia is increasing worldwide and is associated with a drastic increase in morbidity and mortality rates. Additionally, the length of treatment is reportedly prolonged, thereby increasing the workload of health workers. (3) Moreover, it was found that patients with candidemia required the use of MV support for up to 10 days. Therefore, candidemia is associated with high morbidity, mortality, and resource use. (3,13,14)

Nystatin is considered a prophylactic antifungal in the ICU to reduce the incidence of candidemia. It is an antifungal that is widely used to treat candidemia and is a polyene antifungal agent produced by *Streptomyces noursei*, which has broad-spectrum fungicidal activity against pathogenic fungi. (3,15) Until now, limited research has assessed the effectiveness of nystatin in preventing candidemia in critical care patients in the ICU. We were interested in examining the effectiveness of using nystatin as a prophylactic antifungal in critical care patients in the ICU at Haji Adam Malik Hospital, Medan.

Methods

This was a randomized clinical trial conducted using a double-blind research method. The patients were divided into two groups receiving different treatments. This study was conducted from August 2023 to September 2023 in the ICU of Haji Adam Malik General Hospital, Medan. In total, 40 subjects, divided into two groups with 20 samples each, participated in the study, where Groups A and B received 100,000 IU nystatin and 0.9% NaCl, respectively. After the treatment, 2 subjects dropped out; thus, the remaining 38 subjects were obtained. Blood culture examination and tracheal aspirate culture were performed 48 hours after treatment, and the 7th-day mortality was assessed in both groups. Data were analyzed using the chi-square test, and effectiveness was assessed using absolute risk reduction (ARR), relative risk reduction (RRR), and number needed to treat (NNT) formulas.

Results

In this study, the characteristics of the samples are shown in **Table 1**, with no differences in age or weight between groups. The ARR and RRR from the use of nystatin in reducing the incidence of candidemia from blood culture were 5.3% and 25.12%, respectively (**Table 2**). The tracheal aspirate culture shown in **Table 3** shows the ARR and RRR were 5.3% and 100%, respectively. The distribution of *Candida* species obtained from blood

culture and tracheal aspiration is shown in **Table 4**. In the group receiving nystatin therapy, the ARR and RRR for mortality on the seventh day were 15.5% and 21.1%, respectively (**Table 5**).

Discussion

In this study, we obtained the demographic characteristics of the samples based on age ($p=0.597$), body mass index (BMI) ($p = 0.661$), CS ($p=0.324$), gender ($p=0.103$), and diagnosis ($p=0.732$). There were no significant differences in these factors between the two groups, indicating that the nystatin and 0.9% NaCl groups were homogeneous; therefore, they were suitable for comparison.

There were more positive blood culture results in the 0.9% NaCl group than in the nystatin group (3 vs 4), which showed that the incidence of candidemia was lower in the nystatin group than in the 0.9% NaCl group. Chen et al. (2013) conducted a study in the ICU of Jiangxi Provincial People's Hospital on 124 patients where the incidence of candidemia was slightly lower in the nystatin group than in the placebo via nasogastric tube (NGT) group (5% [3/60] vs 7.8% [5/64], $p>0.05$). Despite the non-significant decrease in candidemia incidence between groups, the corrected colonization index (CCI) in the nystatin group was significantly lower compared to the control group ($p<0.05$). (15) Giuliano et al. conducted a study on patients treated at the Policlinico Umberto I Hospital in Rome, Italy, where they found that nystatin prophylaxis and optimal central venous catheter treatment could prevent candidemia ($p=0.008$). (16)

Similar results were also found in Russo et al.'s research on 672 patients undergoing heart surgery at the Policlinico Umberto I Hospital in Rome, Italy. They reported that nystatin prophylaxis effectively prevented the incidence of candidemia in the ICU, with seven incidences of candidemia in the group that did not receive nystatin. (17)

In this study, the control event rate (CER) was 21.1%, indicating that the incidence rate of candidemia in the 0.9% NaCl group was 21.1%, while the experimental event rate (EER) was 15.8%, indicating that the incidence rate of candidemia in the nystatin group was 15.8%. Herein, the ARR value was 5.3%, which meant that the difference in actual failure between the nystatin and 0.9% NaCl groups was 5.3%; the RRR value was 25.12%, which implied that nystatin could reduce failure by 25.12% compared with 0.9% NaCl. Finally, the NNT value obtained in this study was 18.87, which means that 18 people were required to be adminis-

tered nystatin for 1 year to prevent them from experiencing candidemia.

Tracheal aspirate culture results were also found to be better in the nystatin group than in the 0.9% NaCl group (0 vs 1), which shows that nystatin was effective in preventing *Candida* growth in tracheal aspirates, although it was not statistically significant. Normand et al. conducted a study on 98 patients and found that nystatin prophylaxis was effective in preventing the occurrence of candidemia in patients in the ICU through multiple-site culture examination, namely culture of tracheal aspirates, stomach contents, rectal swabs, urine, and blood. (18)

In this study, the CER was 5.3%, which meant that the *Candida* incidence rate from the tracheal aspirate culture in the 0.9% NaCl group was 5.3%, while the EER was 0%, which implied the incidence rate of *Candida* from the tracheal aspirate culture in the nystatin group was 0%. Moreover, the ARR value was 5.3%, which indicated that the difference in actual failure between the nystatin and 0.9% NaCl groups was 5.3%. In contrast, the RRR value was 100%, indicating that nystatin could reduce failure by 100% compared with 0.9% NaCl. Finally, the NNT value obtained in this study was 18.87, which revealed that 18 people were required to administer nystatin for 1 year to prevent 1 person from experiencing *Candida* infection from tracheal aspirate culture.

Furthermore, the 7th-day mortality rate was lower in the nystatin group than in the 0.9% NaCl group (11 vs 14). This finding was similar to the research conducted in the ICU of Jiangxi Provincial People's Hospital on 124 patients, where the mortality rate was lower in the nystatin group than in the placebo (18.3% vs 34.4%, $p<0.05$). Even though the 7th-day mortality results were less in the nystatin group than in the 0.9% NaCl group, this still cannot be a reference that nystatin can reduce 7th-day mortality in patients because the causes of mortality in critical care patients in the ICU are multifactorial.

The CER was 73.4%, which meant that the 7th-day mortality in the 0.9% NaCl group was 73.4%, and the EER was 57.9%, which revealed that the 7th-day mortality in the nystatin group was 57.9%. The ARR value was 15.5% in this study, which meant that the difference in actual failure between the nystatin and 0.9% NaCl groups was 15.5%. In contrast, the RRR value was 21.1%, which meant that nystatin could reduce failure by 21.1% compared with 0.9% NaCl. Finally, the NNT value in this study was 6.45, indicating that it should take 6 people to administer nystatin for 1 year to prevent 1 person from having the 7th-day mortality.

In this study, *C. tropicalis* has the largest colony. Suhartono et al. (19) at Zainoel Abidin Hospital, Banda Aceh, Indonesia, conducted *Candida* culture examinations on blood and found that *C. tropicalis* and *C. albicans* were the most common causes of candidemia. This finding seemed different from what we know to date, where *C. albicans* is the most common cause of candidemia in the ICU and was found only in one sample in the 0.9% NaCl group. This showed that nystatin was effective in killing *Candida*, especially *C. albicans*. Additionally, in this study, only one positive result was found in the tracheal aspirate culture in both groups: *C. glabrata* was found in the 0.9% NaCl group.

Several candidemia incidents were found in both groups. On the basis of the guidelines, azole (fluconazole) and echinocandins (micafungin) antifungals can treat candidemia in patients with

stable hemodynamics and those with unstable hemodynamics, respectively. (20)

Conclusion

Nystatin is effective in reducing the incidence of candidemia. Moreover, the incidence of candidemia was lower in the nystatin group than in the 0.9% NaCl group. Tracheal aspirate culture results in the nystatin group were better than those in the 0.9% NaCl groups. Additionally, the 7th-day mortality in the nystatin group was less than that in the 0.9% NaCl group. The most distributed *Candida* species in the blood culture was *C. tropicalis*, whereas only one species of *Candida* was found (*C. glabrata*) in the tracheal aspirate culture.

Conflict of interest

The authors declare no conflicts of interest.

Table 1. Sample characteristics

Characteristic	Group		p-value
	Nystatin (Group A)	0.9% NaCl (Group B)	
Age (years), mean±SD	48.10±14.64	46.00±13.09	0.597**
BMI (kg/m ²), mean±SD	24.02±3.91	22.85±2.03	0.661**
Candida score, mean±SD	3.21±0.53	3.10±0.45	0.324**
Gender, n (%)			
- Male	8 (42.1)	13 (68.4)	0.103*
- Female	11 (57.9)	6 (31.6)	
Diagnosis, n (%)			
- Surgical	6 (31.6)	7 (36.8)	0.732*
- Nonsurgical	13 (68.4)	12 (63.2)	

Legend: SD=standard deviation; BMI=body mass index.

*Chi-square; **Mann-Whitney.

Table 2. Comparison of the incidence of candidemia from blood culture results in the nystatin and 0.9% NaCl groups in the ICU

Group	Blood culture		Total, n (%)	ARR (%)	RRR (%)
	Positive, n (%)	Negative, n (%)			
Nystatin (Group A)	3 (15.8)	16 (84.2)	19 (100)	5.3	25.12
0.9% NaCl (Group B)	4 (21.1)	15 (78.9)	19 (100)		

Legend: ICU=intensive care unit; ARR=absolute risk reduction; RRR=relative risk reduction.

Table 3. Comparison of the incidence of candidemia from tracheal aspirate culture results in the nystatin and 0.9% NaCl groups in the ICU

Group	Tracheal aspirate culture		Total, n (%)	ARR (%)	RRR (%)
	Positive, n (%)	Negative, n (%)			
Nystatin (Group A)	0 (0)	19 (100)	19 (100)	5.3	100
0.9% NaCl (Group B)	1 (5.3)	18 (94.7)	19 (100)		

Legend: ICU=intensive care unit; ARR=absolute risk reduction; RRR=relative risk reduction.

Table 4. Distribution of *Candida* species from blood and tracheal aspirate culture results in the nystatin and 0.9% NaCl groups

	Nystatin (Group A) (n)		0.9% NaCl (Group B) (n)	
	Blood	Tracheal aspirate	Blood	Tracheal aspirate
<i>Candida albicans</i>	0	0	1	0
<i>Candida glabrata</i>	0	0	0	1
<i>Candida tropicalis</i>	1	0	3	0
<i>Candida parapsilosis</i>	2	0	0	0
<i>Candida krusei</i>	0	0	0	0
Total	3	0	4	1

Table 5. Comparison of the 7th-day mortality in the nystatin and 0.9% NaCl groups in the ICU

Group	7th-day mortality, n (%)		Total, n (%)	ARR (%)	RRR (%)
	Positive	Negative			
Nystatin (A)	11 (57.9)	8 (42.1)	19 (100)	15.5	21.1
0.9% NaCl (B)	14 (73.7)	5 (26.3)	19 (100)		

Legend: ICU=intensive care unit; ARR=absolute risk reduction; RRR=relative risk reduction.

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