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Fluconazole and selective digestive decontamination for prevention of Candida infection in high risk critically ill patients

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KEYWORDS

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Abstract *Objective:* Invasive fungal infections are common in critically ill patients specially those on prolonged mechanical ventilation. Fungal prophylaxis has been proven effective in certain high-risk patients such as bone marrow transplant and other immunocompromized patients. This study aimed to evaluate prophylactic use of fluconazole and selective digestive decontamination (SDD) in the prevention of invasive Candida infections in high risk critically ill patients.
Design: A prospective, randomized, placebo-controlled trial.
Setting: Critical care department, Main Alexandria University Hospital.
Patients: Seventy five critically ill patients with anticipated prolonged mechanical ventilation.
Methods: They were randomly assigned to three groups; control group, SDD group, and SDD + fluconazole according to the type of the drug they had received. Cultures were obtained after 5, 10, and 15 days. End point was 15 days from admission or the occurrence of Candida infection.
Results: In a time-to-event analysis, the SDD + fluconazole group showed an absolute risk reduction of 48% when compared to the control group, and 28% when compared to the SDD group. The number needed to treat was 2.08 in the SDD + Fluconazole group, while in the SDD group it was 5.

Abbreviations: SDD, Selective digestive decontamination; ICU, intensive care unit; PPMs, potentially pathogenic microbes; APACHE II, physiology and chronic health evaluation-II; SOFA, Sequential Organ Failure Assessment.

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Conclusion: SDD + fluconazole safely and effectively decreased the incidence of Candida infections in the high-risk, critically ill patients.

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1. Introduction

Candidiasis is caused by infection with species of the genus Candida, predominantly with *Candida albicans*. The growing problem of mucosal and systemic Candidiasis reflects the enormous increase in the number of patients at risk and the increased opportunity that exists for Candida species to invade tissues normally resistant to invasion. Candida species are true opportunistic pathogens that exploit recent technological advances to gain access to the circulation and deep tissues.[1]

Patients who are critically ill and in medical and surgical ICUs have been the prime targets for opportunistic nosocomial fungal infections, primarily due to Candida species. Studies suggest that the problem is not under control and, in fact, show it is worsening. Candidemia is associated with considerable prolongation in hospital stays (70 days versus 40 days in comparable patients without fungemia).[2]

Selective digestive decontamination (SDD) is used to prevent or to eradicate, if initially present, oro-pharyngeal and gastrointestinal carriage of potentially pathogenic microbes (PPMs), especially hospital PPMs, leaving the endogenous flora, which are thought to protect against overgrowth with resistant bacteria, largely undisturbed.[3]

Fluconazole is a triazole antifungal drug with excellent enteral bioavailability, low toxicity, and activity against many pathogenic Candida species.[4,5] Fluconazole has been shown to prevent both deep fungal infections in bone marrow transplant populations[5] and superficial fungal infections in patients with leukemia.[6] The role of the empiric use of fluconazole in intensive care unit (ICU) patients, however, remains controversial.[7,8]

Given the high incidence of Candida infection among critically ill patients, this study hypothesized that these infections could be prevented in high-risk patients by using prophylactic fluconazole[9] and SDD.

2. Patients and methods

This study was conducted on 75 adult patients admitted to Critical Care Medicine Department in the Main University Hospital of Alexandria University. The study period was 15 days from admission. Studied patients were included if they were mechanically ventilated for at least 48 h with an expectation to remain so for at least an additional 72 h, based on admitting diagnosis, magnitude of hemodynamic instability, respiratory failure, and baseline medical condition and severity of illness according to Acute Physiology And Chronic Health Evaluation-II (APACHE II) score.[10]

Patients were excluded for reasons such as: pregnancy, receipt of antifungal agents within 7 days before ICU admission, age younger than 18, an expectation that the patient would not survive more than 24 h, and patients who did not complete the 15 day period of the study either due to discharge from ICU or death.

According to whether receiving fluconazole as a part of SDD or receiving SDD alone, these patients were randomly categorized into three equal groups (25 patients each):

- Group I: (control group): patients who received neither fluconazole nor SDD.
- Group II: patients who received SDD alone without fluconazole.
- Group III: patients who received fluconazole as a part of their SDD.

Informed consent was taken from first degree relative of every patient included in the study. The research was approved from the Ethics Committee of Alexandria faculty of medicine. All selected patients fulfilling the inclusion criteria were subjected to the following on admission: full history, clinical examination, severity of illness (assessed by APACHE II score), and calculation of creatinine clearance.

Patients in group I (control group) did not receive any prophylactic medications while those in group II and group III were given SDD starting at the first day of admission to ICU in the form of oral decontamination (by applying chlorhexidine to the mouth and gums every 6 h for the whole 15 day period of the study), GIT decontamination (by giving colistin (polymyxin-E antibiotic) 1,500,000 unit PO every 8 h for the whole 15 day period of the study), and respiratory tract decontamination (by giving cefotaxime (third generation cephalosporin antibiotic) 1 gram every 8 h for 4 days).

Patients in group III received antifungal fluconazole with a loading dose of 200 mg fluconazole PO on the first day, then half the loading dose (100 mg PO) every day. Patients who had creatinine clearance less than 50 ml per minute were given 50 mg fluconazole PO per day instead. Administration of the study drug was continued until initiation of systemic antifungal drug according to the cultures' results or ICU discharge. End point of the study was 2 weeks from admission or the institution of systemic antifungal drugs according to culture results.

- Patients were evaluated daily according to the Sequential Organ Failure Assessment score (SOFA score)[11] during the study till the patient was discharged or the development of established candida infection.
- Fungal cultures were obtained from oro-pharynx, urine, sputum (by mini-BAL technique), and rectal swab, 5 days after admission, then every 5 days till the end of the fifteenth day. These sites were named as non-serious as any positive Candida culture from these sites would denote colonization rather than true fungal infection.
- Fungal cultures were obtained from central venous catheter (CVC), blood, and ostomy/drainage tubes 5 days after admission, then every 5 days till the end of the fifteenth day. These sites were defined as serious as any positive Candida culture from these normally sterile sites would denote true fungal infection.

2.1. Statistical analysis of data

Group sample sizes of 23 patients achieved 82% power to detect a difference in the proportion of positive Candida cultures according to NCSS 2004 and PASS 2000 program. Data were analyzed using SPSS software package version 18.0 (SPSS, Chicago, IL, USA). Quantitative data were expressed using minimum, maximum, mean, standard deviation, median, and IQP while Qualitative data were expressed in frequency and percent. Qualitative data were analyzed using Fisher exact and Monte Carlo test to compare different groups. Not normally distributed quantitative data were analyzed using Mann Whitney test for comparing two groups while for more than two groups Kruskal Wallis test was applied. The level of significance was 5.0%.

2.2. Treatment effects

The study used some equations to describe the good effect of the studied drug. These equations used the term ''control event rate'' (CER) to express the number of events (in this study, the number of positive Candida culture) in the control group, and the term ''experimental event rate'' (EER) to express the number of events (the number of positive Candida culture) in the experimental group .The study used the following terms and calculations to describe these effects of treatment:

- ARR (absolute risk reduction), and calculated as: ARR = CER – EER
- RRR (relative risk reduction), and calculated as: RRR = (CER-EER)/CER
- NNT (number needed to treat), and calculated as 1/ARR

These tests were accompanied by a 95% confidence interval (CI).

3. Results

3.1. Demographic data and APACHE II score of the patients (Table 1)

The three studied groups were matched in age and sex without statistically significant difference in-between. The mean APACHE II score on admission in the three groups was more than 25 indicating severe disease without statistical significance between groups.

3.2. Effects on SOFA score (Table 2)

- There was a significant difference between group I and group II on the tenth and fifteenth days, also there was a significant difference between group I and group III, but there was no significant difference between groups II and III.
- It was noticed that there was an improvement in the outcome of SOFA score in group III in the 15 day follow up period in comparison with the control group as there was no significant difference between the control group and group III on the fifth day but on the tenth day there was a significant difference which increased on the fifteenth day.
- No patient deaths were recorded within the 15 day period in the three studied groups.

3.3. Effect on Candida culture from non-serious localizations (Table 3)

Fifth day cultures from the Oro-pharynx, urine, sputum, and rectal swab in the three groups yielded no fungal growth. Of notice was the significant decrease in positive cultures from almost all sites in group III compared to group I and more importantly group II on the fifteenth day.

3.4. Effect on Candida culture from normally sterile sites (Table 4)

Fifth day cultures from central venous catheter (CVC), blood, and ostomy/drainage tube in the three groups and tenth day cultures in these sites in groups II and III yielded no fungal growth. On the fifteenth day, there was a significant decrease in the number of positive cultures in group III when compared to both groups I and II, while there was no significant difference between the control group and group II.

3.5. Effect of studied drugs on the overall incidence of Candida infection (Table 5)

In the control group, 13 patients acquired Candida infection out of 25 patients (52%). In group II, 8 patients acquired

Table 1 Comparison between the different studied groups according to demographic data and APACHE II score on admission.

	Group I (Control)		Group II (SDD)		Group III (SDD + Fluconazole)		Test of sig.
	No.	%	No.	%	No.	%	
Sex:							
Male	15	60.0	12	48.0	13	52.0	$\chi^2 = 0.750$ $p = 0.770$
Female	10	40.0	13	52.0	12	48.0	
Age:							
Mean ± SD	50.92 ± 21.62		51.92 ± 20.31		48.48 ± 21.27		$^{\#}\chi^2 = 0.469$ $p = 0.791$
APACHE II:	26.44 ± 7.14		26.32 + 4.45		27.0 ± 4.75		F (p): 0.513 (0.601)

χ^2: Chi square test.
$^{\#}\chi^2$: Chi square for Kruskal Wallis test.
F: F test (ANOVA).
* Statistically significant at $p \leqslant 0.05$.

Table 2 Comparison between the different studied groups according to SOFA score.

	Group I (Control)	Group II (SDD)	Group III (SDD + Fluconazole)	χ^2 (p)
SOFA score 5th day	7.48 ± 1.98	6.24 ± 2.05	6.87 ± 1.28	4.999 (0.082)
10th day	7.56 ± 2.48	6.08 ± 1.87	5.95 ± 1.14	7.177* (0.028)
$Z_1(p)$		0.026*	0.011*	
$Z_2(p)$		0.107		
15th day	7.92 ± 2.97	5.48 ± 1.83	5.12 ± 1.76	16.955*(0.001)
$Z_1(p)$		0.016*	0.008*	
$Z_2(p)$			0.36	

χ^2: Kruskal Wallis test.
Z1: Z for Mann Whitney test between control and other groups.
Z2: for Mann Whitney test between SDD and SDD + Fluconazole groups.
* Statistically significant at $p \leqslant 0.05$.

Table 3 Comparison between the different studied groups according to positive Candida culture from non-serious sources.

	Group I (Control)		Group II (SDD)		Group III (SDD + Fluconazole)		MCp
	No.	%	No.	%	No.	%	
oro-pharynx:							
10th day	2	8.0	0	0.0	0	0.0	0.331
15th day	14	56.0	1	4.0	0	0.0	0.001*
FEp_1			0.001*		0.001*		
FEp_2					0.236		
Urine:							
10th day	3	12.0	0	0.0	0	0.0	0.09
15th day	9	36.0	11	44.0	3	12.0	0.024*
FEp_1			0.332		0.015*		
FEp_2					0.021*		
Sputum:							
10th day	1	4.0	1	4.0	0	0.0	0.62
15th day	5	20.0	3	12.0	0	0.0	0.011*
FEp_1			0.076		0.0113*		
FEp_2					0.042*		
Rectal swab:							
10th day	2	8.0	1	4.0	0	0.0	0.465
15th day	6	24.0	8	32.0	1	4.0	0.003*
FEp_1			0.107		0.002*		
FEp_2					0.001*		

MCp: p for Monte Carlo test.
FEp1: p value for Fisher Exact test between control and other groups.
FEp2: p value for Fisher Exact test between SDD and SDD + Fluconazole.
* Statistically significant at $p \leqslant 0.05$.

Candida infection out of 25 patients (32%). In group III, only 1 patient acquired Candida infection out of 25 patients (4%). The absolute risk reduction (ARR) was 48% in group III when compared to the control group and 28% when compared to group II, while it was 20% in group II when compared to the control group.

The relative risk reduction (RRR) was 92.3% in group III when compared to the control group and 87.5% when compared to group II, while it was 38.4% in group II when compared to the control group. The number needed to treat (NNT) was 2.08 in group III versus 5 in group II. (See Tables 1–5)

4. Discussion

The study has shown that prophylactic fluconazole prevents invasive Candida infections in critically ill patients, independent of other risk factors for fungal infection. Even though it was used with selective digestive decontamination, prophylactic fluconazole proved that it can prevent Candida infection as the group who received selective digestive decontamination alone had almost the same incidence of Candida infection. Enteral rather than intravenous fluconazole was chosen because it costs less than the intravenous preparation and appears to have adequate enteral bioavailability.[12–14]

It was noticed that in the SDD group, the only significant effect was decrease in the number of positive Candida cultures in the Oro-pharynx which means that SDD was only effective in the prevention of oro-pharyngeal colonization.

Robert et al.[15] performed a double-blind placebo-controlled trial of fluconazole (400 mg daily PO) to prevent Candida infections in critically ill surgical patients ($n = 260$), in this trial the risk of Candida infection in patients receiving fluconazole was significantly less than the risk in patients

Table 4 Comparison between the different studied groups according to positive Candida culture from normally sterile sites.

	Group I (Control)		Group II (SDD)		Group III (SDD + Fluconazole)		MCp
	No.	%	No.	No.	%	No.	
CVC:							
10th day	1	4.0	0	0.0	0	0.0	0.028*
FEp_1		0.042*	0.042*				
FEp_2		0.0					
15th day	5	20.0	6	24.0	1	4.0	0.013*
FEp_1		0.552	0.045*				
FEp_2		0.033*					
Blood:							
10th day	4	16.0	0	0.0	0	0.0	0.68
15th day	8	32.0	6	24.0	0	0.0	0.02*
FEp_1		0.285	0.013*				
FEp_2		0.022*					
Ostomy/drainage tube:							
10th day	1	4.0	0	0.0	0	0.0	0.28
15th day	4	16.0	3	12.0	0	0.0	0.03*
FEp_1			0.336	0.036*			
FEp_2			0.041*				

MCp: *p* for Monte Carlo test.
FEp1: *p* value for Fisher Exact test between control and other groups.
FEp2: *p* value for Fisher Exact test between SDD and SDD + Fluconazole.
* Statistically significant at $p \leqslant 0.05$.

Table 5 Comparison between the different studied groups according to the overall incidence of Candida infection, the ARR, and the RRR.

	Group I (Control)		Group II (SDD)		Group III (SDD + Fluconazole)		MCp
	No.	%	No.	%	No.	%	
Positive culture	13	52.0	8	32.0	1	4.0	0.013*
ARR			20.0%#		48.0%#		
RRR			38.4%#		92.3%#		
NNT			5		2.083		

MCp: *p* for Monte Carlo test.
ARR: Absolute risk reduction.
RRR: Relative risk reduction.
NNT: Number needed to treat.
Compared with control group.

receiving placebo. The risk of fungal infection was reduced by 55% in the fluconazole group, but this study did not use SDD and did not include medical ICU patients.

Garbino et al.[16] conducted a study on adult patients mechanically ventilated for at least 48 h with an expectation to remain so for at least an additional 72 h, and receiving selective decontamination of the digestive tract, patients were randomly assigned fluconazole 100 mg daily ($n = 103$) or placebo ($n = 101$). In this study, Candida infections occurred less frequently in the fluconazole group (5.8%) than in the placebo group (16%; rate ratio 0.35, relative risk reduction was 63.75%), some 90% of Candidemia episodes occurred in the placebo group in this study.

As regards the SDD, many prospective, randomized studies in which SDD is compared with controls[17–19] have been published in the past years. They showed that SDD resulted in a significant reduction in the number of ventilator-associated pneumonia, but this reduction in the incidence of ventilator-associated pneumonia in individual studies was not associated with improved patient survival, reduction of duration of ventilation or ICU stay, or reduction in antibiotic use.[20]

A significant improvement in the outcome was noticed in the SDD + Fluconazole group and also in the SDD group as there was a significant decrease in the average SOFA score from the fifth day till the fifteenth day, and as there was no significant decrease in the incidence of Candida infection in the SDD group, the effect of SDD on the outcome may be due to its effect in the prevention of other types of infection like nosocomial bacterial infection. This was not shown in any previous studies as regards the effect on SOFA score.

To sum up, fungal infections are an increasingly common and serious problem in the critically ill patients. In this study, it showed that the use of prophylactic enteral fluconazole in critically ill patients with an expected prolonged mechanical

ventilation results in fewer fungal infections. Additional long-term epidemiologic data must be obtained to determine the effect on fungal resistance patterns.

5. Conclusion

As mentioned previously we can conclude that Candida infection is common in critically ill patients. SDD did not significantly decrease Candida infection while adding fluconazole to SDD decreased significantly the incidence of fungal infection. Fluconazole is an effective agent in the prevention of Candida infection in such patients. SDD was only effective in the prevention of Oro-pharyngeal Candidiasis. Fluconazole has an effect in the improvement of the SOFA score in high risk critically ill patients while SDD has an effect on the SOFA score probably due to its effect in the prevention of other types of infection like other bacterial infections.

Conflict of interest

None declared.

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