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Original Research Article

KETOCONAZOLE EFFECT FOR THE PREVENTION OF THE ARDS IN HOSPITALIZED PATIENTS IN ICU

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Abstract

Objective: The acute respiratory distress syndrome (ARDS) is a common complication of a variety of illnesses and is associated with significant morbidity and mortality. It develops following a number of predisposing conditions. Ketoconazole can modulate inflammatory pathways known to be involved in ARDS. The aim of this study was to investigate, Ketoconazole effect for the prevention of the ARDS.

Material and Methods: In the Loghman Hakim's Hospital of Tehran, Iran (study hospital), we investigated ketoconazole effect in the prevention of the ARDS as clinical trial. Patients were placed into two groups receiving oral ketoconazole and placebo. Finally, statistical analysis was performed using SPSS (Version 11.5).

Results: There was no significant difference between two groups (receiving ketoconazole and placebo) in terms of sexual distribution. Also, there were no significant differences between them in terms of age groups mean and duration mean of ICU stay.

Conclusion: Data related to present study do not support the use of ketoconazole for the prevention of ARDS in Iran.

Keywords: ARDS, Ketoconazole, ICU

Introduction

The adult respiratory distress syndrome (ARDS) represents a complex constellation of signs and symptoms afflicting critically ill patients [1]. It, the most severe form of Acute Lung Injury (ALI), is an important clinical problem [2]. ARDS kills an estimated 70,000 people in the United States each year [2]. By many estimates, this unfortunate toll exceeds the deaths caused by breast cancer and AIDS combined [3-5]. ARDS develops following a number of predisposing conditions [5-8]. The most common are trauma and infection but the extensive list includes aspiration, hemorrhage, multiple transfusions, and pancreatitis [8]. Airway insults that lead to ARDS include pneumonia, aspiration, smoke or chemical inhalation [9]. Blood-borne insults include non-pulmonary infections leading to sepsis,

multiple fractures, and other organ insults including ischemia–reperfusion inciting abnormalities [10, 11].

Abundant research has led to improvements in supportive care, but mortality from ALI/ARDS remains substantial [11]. The mechanisms of ALI/ARDS offer an array of possible targets for prevention [11-14]. Epidemiologic studies suggest a protective role of early treatment of shock and infection, avoidance of tidal hyperventilation, and minimizing plasma transfusion from alloimmunized donors [15]. Early recognition of the patient at risk for or with ARDS and identification of the underlying cause allows more timely application of potentially life-saving therapies [16].

Ketoconazole is a synthetic antifungal imidazole that also has anti-inflammatory activities [16-18]. Ketoconazole inhibits thromboxane synthase, an enzyme in the synthetic pathway of thromboxane A2 (TXA2) that acts as a potent pulmonary vasoconstrictor and aggregator of platelets and neutrophils [17, 18]. Ketoconazole also inhibits 5-lipoxygenase, the enzyme necessary to generate leukotrienes, and decreases leukotriene B4 (LTB4) production, one of the primary neutrophil chemoattractants implicated in ARDS [17, 18]. Ketoconazole also inhibits endotoxin-stimulated alveolar macrophage production of procoagulant activity [17, 18]. Thus ketoconazole can modulate inflammatory pathways known to be involved in ALI and ARDS [18].

The purpose of this study was to investigate, Ketoconazole effect for the prevention of the ARDS in hospitalized patients in intensive care unit (ICU) of the hospital in Tehran, Iran.

Materials and Methods

This clinical trial study was conducted at Loghman Hakim's Hospital of Tehran, Iran. Patients were eligible for the study if they were in an ICU, aged above 16 years, had no symptoms of sepsis, required positive pressure ventilation via endotracheal or tracheostomy tube, and had acute onset of significantly impaired oxygenation with a PaO_2-to fraction of inspired oxygen (FIO_2) ratio less than or equal to 200 (adjusted for barometric pressure), bilateral infiltrates consistent with pulmonary edema on a frontal chest radiograph, and no clinical evidence of left atrial hypertension or, if a pulmonary artery catheter was in place, a pulmonary artery occlusion pressure less than or equal to 18 mmHg.

Patients were placed into two groups receiving oral ketoconazole and placebo based on table of random numbers. They were 240 patients. Both groups received their main treatment based on type of toxicity. Ketoconazole group received 400 mg/d of oral ketoconazole to hospitalization time in ICU and placebo group received 10 mg/d normal saline solution.

In this study, patients that during the research affected by nosocomial pneumonia, acute renal failure and disseminated intravascular coagulation (DIC) were excluded from study. Then, patients were evaluated in the case of ARDS. Diagnostic criteria of ARDS in the patients were including: respiratory distress, chest radiograph indicating ARDS and arterial blood gas as $Po_2 / Fio_2 \leq 200$.

Statistical Methods

Statistical analysis was performed using Statistical Package for the Social Sciences 11.5 (SPSS Inc., Chicago, IL, USA), Fisher's exact test and Student's t test. $P < 0.05$ was accepted as significant. The research protocol of the study was approved by the Ethics Committee of Shahid Beheshty University of Medical Sciences.

Results: In total, 240 consecutive patients (120 (receiving oral ketoconazole) and 120 (placebo)) met the eligibility criteria. This selection was performed randomly. There

was no significant difference between two groups in terms of sexual distribution (Fisher's exact test). Also, there were no significant differences between them in terms of age groups mean and duration mean of ICU stay (Table 1).

Table 1: The comparison between two groups based on Sex, Age and Duration of ICU stay (No Significant Difference Between two groups)

Characteristics		Receiving oral ketoconazole Group	Placebo Group
Sex	**Male N (%)**	68 (56.6)	73 (60.8)
	Female N (%)	52 (43.4)	47 (39.2)
Age (mean ± SD, years)		29.3 ± 11.3	30.6 ± 15.2
Duration mean of ICU stay (days)		5.5 ± 1.4	5 ± 3.7

Types of toxicity related to group of receiving oral ketoconazole were including: 16 cases TCA (Tricyclic Antidepressant) poisoning, 6 cases with Anticonvulsants, 10 cases Opium poisoning and 88 cases poisoning with mixing drugs. These types of toxicity about placebo group (TCA, Anticonvulsants, Opium and mixing drugs) were 17, 5, 22, and 76, respectively. There was no significant difference between two groups in terms of type of toxicity (Student's t test).

In the group of receiving oral ketoconazole was not observed nothing related to ARDS but, in the placebo group was 3 patients. There was no significant difference between two groups as being infected to ARDS (Fisher's exact test).

11 people died in the group of receiving oral ketoconazole and 8 cases in the placebo group that in this respect also had not significant difference (Fisher's exact test).

Discussion

ARDS is an increased permeability pulmonary edema that occurs most often as a complication of bacterial sepsis, aspiration of gastric contents, or massive trauma [18, 19]. Clinically, the syndrome is recognized as acute respiratory failure with bilateral infiltrates on chest radiograph, a marked oxygenation defect, and normal or nearly normal cardiac function [18, 19]. This study investigated Ketoconazole effect for the prevention of the ARDS in hospitalized patients in ICU.

A study evaluated a practice guideline using ketoconazole for the prevention of ARDS in critically ill patients. Patients at risk of ARDS were similar in hospitals. It was observed a significantly lower rate of ARDS in the guideline hospital but no difference in mortality, duration of ventilation, or duration of ICU stay [19]. In present study, similar to the mentioned study there was no significant difference between two groups in mortality and duration mean of ICU stay.

In another study was investigated the efficacy of ketoconazole in reducing mortality and morbidity in patients with ALI or ARDS. In-hospital mortality was 34.1% (4.3%) for the placebo group and 35.2% (4.3%) for the ketoconazole group (*P*=.85). The median number of ventilator-free days within 28 days of randomization was 9 in the placebo group and 10 in the ketoconazole group (*P*=.89). There were no statistically significant differences in the number of organ failure–free days, pulmonary physiology, or adverse events between treatment groups [20]. Results of present study were similar to mentioned study because, there was no significant difference between two groups.

Conclusion

This study proved that there was no significant difference between two groups

(receiving ketoconazole and placebo) in terms of type of toxicity, being infected to ARDS and mortality.

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