Is this the time to introduce ketamine in acute respiratory distress syndrome? A pilot study

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Introduction
Acute respiratory distress syndrome is regarded to be an acute, diffuse inflammation of the lung that leads to an increase in the permeability of the pulmonary vascular tissue. The relations between ARDS classes and the permeability of the pulmonary microvasculature as well as the water content of the pulmonary extravasculature remains to be clarified. The anti-inflammatory and the antioxidant properties of ketamine were observed in acute lung injury; ketamine promotes the attenuation of the expression of mediators of inflammation.
The aim of the work
The aim of this study was to test whether ketamine treatment by the inhaled route or the infusion route could be an efficient method of treatment for ARDS.
Participants and methods
Mechanically ventilated critically ill adult trauma patients admitted to the ICU with developing ARDS were eligible to participate in this study. Group A was treated by ketamine inhalation, group B was treated with ketamine infusion, and group C was treated by pulse steroid therapy. The serum interleukin-6 level was analyzed.
Results
Concerning group A (ketamine inhalation) and group B (ketamine infusion), there were significant correlations in both the groups starting from day 2 till day 5 of treatment with regard to the tidal volume and positive end-expiratory pressure and from day 3 of treatment with regard to the blood pressure and FiO_2.

Keywords:
acute lung injury, anti-inflammatory, ARDS, ketamine

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Introduction

ARDS is considered as an acute, diffuse inflammation of the lung that leads to an increase in the permeability of the pulmonary vasculature, increased weight of the lung, and the loss of aerated tissue of the lung [1]. The definition covers mild, moderate, and severe ARDS depending on the degree of hypoxemia. Mortality is increased with progression from one class to another. The relations between ARDS classes and the permeability of the pulmonary microvasculature as well as the water content of the pulmonary extravascular tissue, which is considered as the hallmark of the pathophysiology of the lung, remains to be clarified [2]. Levels of severity according to the Berlin definition are as follows: mild [PaO_2/FiO_2 200 to ≤300 mmHg with positive end-expiratory pressure (PEEP)^{3}5 cmH_2O or continuous positive airway pressure^{3}5 cmH_2O], moderate (PaO_2/FiO_2 100 to ≤200 mmHg with PEEP^{3}5 cmH_2O), and severe (PaO_2/FiO_2≤100 mmHg with PEEP^{3}5 cmH_2O) [3]. ARDS could be established at any time during the first 4 days in the ICU. For diagnosis, we used a ratio of pulse oximetry saturation to the fraction of inspired oxygen (SpO_2/FiO_2); it was used as a validated substitute for PaO_2/FiO_2 between patients without measuring the arterial blood gas at the time of diagnosis: $SpO_2/FiO_2 = 64 + 0.84 \times (PaO_2/FiO_2)$ [4]. Ketamine is considered as a noncompetitive *N*-methyl-d-aspartate antagonist. Ketamine as an intravenous anesthetic agent was first used in 1965 in humans and is still used in a diversity of clinical situations today. The pharmacological properties of ketamine include analgesic, anesthetic, and sympathomimetic outcomes [5]. Recently, many studies have shown the protective role of ketamine against injury of the lung, through its anti-inflammatory properties. For example, neurogenic pulmonary edema is less noticed under ketamine anesthesia in a model of rat with spinal cord injury [6]. Ketamine has also been shown to diminish endotoxemic symptoms of sepsis in a rat model induced by lipopolysaccharide, through the reduction of NF-kB activation and tumor necrosis factor-α production [7], and by reducing the inducible nitric oxide synthase expression, which has been involved in injury of tissue

induced by endotoxin [8]. The administration of ketamine into the nasal cavity, the oral cavity, and the rectum has been recommended due to its effectiveness and feasibility [9]. The anti-inflammatory and the antioxidant properties of ketamine were observed in acute lung injury (ALI); ketamine promotes the attenuation of the expression of mediators of inflammation, while it maintains anti-inflammatory mediator expression. There is no certain pharmacological treatment for ALI. Ketamine may be successful in reducing markers of ALI and also attenuates the systemic response of inflammation, which leads to lipopolysaccharide/sepsis-induced ALI [10].

The aim of the study was to estimate and evaluate whether ketamine treatment by the inhaled route or the infusion route could prove as an efficient method for the treatment of post-traumatic ARDS.

Participants and methods

This pilot prospective study was conducted in the ICUs of multiple centers and university hospitals between April 2013 and October 2014; 15 patients were enrolled and subdivided into three groups (each group included five patients) as shown in Fig. 1. The study procedure has been accepted by Fayoum university ethical committees. Mechanically ventilated critically ill adult trauma patients admitted to the ICU with developing ARDS were eligible for this study. Informed consents were obtained from patients' relatives. The patients were divided into three groups. Group 1(inhalational ketamine) was treated with 12.5 mg/ml ketamine aerosol for 30 min/day. Group 2 (intravenous ketamine) was treated with a ketamine infusion of 0.5 mg/kg/day. Group 3 (pulse steroid) was treated with methylprednisolone 1 g daily for 3 days. ARDS was defined and classified according to the Berlin definition [1]. In the new Berlin definition, the diagnostic criteria for ARDS rely on four categories:

(a) Timing: within 1 week of a known clinical insult or new or worsening respiratory symptoms;
(b) Radiography: bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodule;
(c) The origin of lung edema: respiratory failure not fully explained by cardiac failure or fluid overload; and
(d) Oxygenation impairment: subdivided into three categories according to the degree of hypoxemia severity (mild, moderate, and severe).

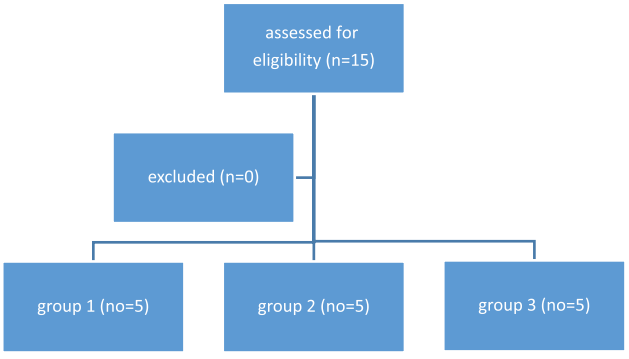
The Berlin definition eliminated the concept of ALI, which is now considered in the category of mild ARDS. The included patients were at least 18 years of age and diagnosed within 48 h with a PaO_2/FiO_2 ratio of below 200. Excluded patients included individuals with pre-existing severe disease of any major organs, pregnancy, and malignant disease.

A negative fluid balance was maintained by diuretics and fluid restriction. A low-tidal-volume protocol was adopted for standardized ventilator management, targeting a tidal volume of 6–8 ml/kg of the patient's ideal body weight and a plateau pressure less than 30 mmHg. All patients were ventilated by synchronized intermittent mandatory ventilation: the respiratory rate was 35/min and they were started on initial tidal volumes of 8 ml/kg predicted body weight in kg to deliver the expected minute ventilation requirement (generally, 7–9 l/min). Over a period of less than 4 h, the tidal volumes were reduced to 7 ml/kg, and then to 6 ml/kg [11]. The PEEP was set to at least 5 cmH_2O. FiO_2 and the PEEP was adjusted to maintain an arterial oxygen saturation (SaO_2) of 88–95% (PaO_2 55–80 mmHg). The patients were sedated to minimize ventilator-patient asynchrony.

Five milliliters of peripheral blood were collected from patients immediately before treatment (day 0), on day 3, and on day 5 after treatment. Serum samples were collected. The interleukin-6 (IL-6) level was determined by commercial enzyme-linked immunosorbent assays.

At the time of enrollment (day 0), patients were evaluated with regard to their clinical and radiological condition. The circulatory/respiratory status was also assessed, including the ventilator settings: PaO_2/FiO_2, the tidal volume (ml/kg), and PEEP. Other information collected included the age, the sex, and the number of organ dysfunctions.

Figure 1



A flow chart showing the study.

The following parameters were recorded periodically:

(1) Ventilator:
   (a) FiO_2 every 6 h.
   (b) Tidal volume every 6 h.
   (c) PEEP every 6 h.
(2) Radiological findings everyday.
(3) IL-6 at day 0, day 3, and day 5.
(4) Circulatory:
   (a) Mean arterial blood pressure every 2 h.
   (b) Central venous pressure every 2 h.

Statistical analysis

Data were analyzed by Microsoft Office 2003 (Excel, Seattle, WA, USA) and Statistical Package for Social Science (SPSS) version 22 (Armonk, IBM Corp., NY). Parametric data were expressed as mean ± SD, and nonparametric data were expressed as the number and percentage of the total. Comparison of the mean ± SD of the two groups was performed using paired and unpaired Student's *t*-test. *P* value less than 0.05 was considered significant.

Results

There were no significant differences between the three groups regarding their demographic data (age and sex) and organ dysfunction. The mean age in the ketamine inhalation group was 36.67 ± 9.69 years, the mean age in the ketamine infusion group was 35.53 ± 16.16, and the mean age in the pulse steroid group was 37.33 ± 11.20. The ketamine inhalation group was suffering from long-bone fracture, blunt brain injury, and deep venous thrombosis. The ketamine infusion group was suffering from long-bone fracture and acute renal failure. The pulse steroid group was suffering from penetrating fractures, deep venous thrombosis, and acute renal failure. ARDS development was secondary to either direct lung injury (pneumonia, pulmonary contusion) or indirect lung injury (severe sepsis, transfusion).

There were no significant differences among the three groups on day 1 in relation to the mean arterial blood pressure, the central venous pressure, FiO_2, the tidal volume, and PEEP.

On day 2, the mean arterial pressure showed a significant difference between the ketamine inhalation group and the pulse steroid group and also between the ketamine infusion group and the pulse steroid group. The central venous pressure showed a significant difference between the ketamine inhalation group and the pulse steroid group and between the ketamine infusion group and the pulse steroid group. FiO_2 showed a significant difference between the ketamine inhalation group and the pulse steroid group and between the ketamine infusion group and the pulse steroid group. The tidal volume showed a significant difference between the ketamine inhalation group and the ketamine infusion group and between the ketamine inhalation group and the pulse steroid group. The PEEP showed a significant difference between the ketamine inhalation group and the ketamine infusion group and between the ketamine inhalation group and the pulse steroid group, as shown in Table 1.

On day 3, the mean arterial pressure, FiO_2, and the tidal volume showed significant differences between the three groups. The central venous pressure showed significant differences between the ketamine inhalation group and the pulse steroid group and between the ketamine infusion group and the pulse steroid group. The PEEP showed a significant difference between the ketamine inhalation group and the ketamine infusion group and between the ketamine inhalation group and the pulse steroid group, as shown in Table 2.

On days 4 and 5, the mean arterial pressure, FiO_2, the tidal volume, and the PEEP showed significant differences between the three groups. The central venous pressure showed significant differences between the ketamine inhalation group and the pulse steroid group and between the ketamine infusion group and the pulse steroid group as shown in Tables 3 and 4.

Table 5 shows the IL-6 level on days 0, 3, and 5 of treatment. There were significant differences between the ketamine inhalation group and the ketamine infusion group and between the ketamine inhalation

Table 1 Ventilator and circulatory parameters on day 2

Parameters	MAP (d2)	CVP (d2)	FiO_2 (d2)	TV (d2)	PEEP (d2)
Group ketamine inhalation	67.27	7.47	92.67	4.33	9.33
Group ketamine infusion	70.13	7.73	95.33	5.47	12.67
Group pulse steroid	60.07	12.33	99.00	5.87	12.93
Group ketamine inhalation vs. group ketamine infusion	0.015	0.540	0.040	0.000	0.000
Group ketamine inhalation vs. group pulse steroid	0.000	0.000	0.000	0.000	0.000
Group ketamine infusion vs. group pulse steroid	0.000	0.000	0.005	0.020	0.075

CVP, central venous pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PEEP, pressure end expiratory pressure; TV, tidal volume.

Table 2 Ventilator and circulatory parameters on day 3

Parameters	MAP (d3)	CVP (d3)	FiO_2 (d3)	TV (d3)	PEEP (d3)
Group ketamine inhalation	66.33	7.73	79.33	3.60	8.60
Group ketamine infusion	71.07	7.07	92.33	5.13	12.27
Group pulse steroid	59.00	12.27	99.33	5.93	12.87
Group ketamine inhalation vs. group ketamine infusion	0.001	0.148	0.000	0.000	0.000
Group ketamine inhalation vs. group pulse steroid	0.000	0.000	0.000	0.000	0.000
Group ketamine infusion vs. group pulse steroid	0.000	0.000	0.000	0.001	0.015

CVP, central venous pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PEEP, pressure end expiratory pressure; TV, tidal volume.

Table 3 Ventilator and circulatory parameters on day 4

Parameters	MAP (d4)	CVP (d4)	FiO_2 (d4)	TV (d4)	PEEP (d4)
Group ketamine inhalation	66.53	7.73	71.33	2.80	7.87
Group ketamine infusion	71.67	7.40	88.67	4.87	11.60
Group pulse steroid	60.67	12.60	99.67	5.80	12.80
Group ketamine inhalation vs. group ketamine infusion	0.000	0.512	0.000	0.000	0.000
Group ketamine inhalation vs. group pulse steroid	0.000	0.000	0.000	0.000	0.000
Group ketamine infusion vs. group pulse steroid	0.000	0.000	0.000	0.000	0.001

CVP, central venous pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PEEP, pressure end expiratory pressure; TV, tidal volume.

Table 4 Ventilator and circulatory parameters on day 5

Parameters	MAP (d5)	CVP (d5)	FiO_2 (d5)	TV (d5)	PEEP (d5)
Group ketamine inhalation	66.93	7.13	61.67	2.33	7.33
Group ketamine infusion	73.13	7.73	82.67	4.27	10.60
Group pulse steroid	60.33	12.33	99.00	5.73	12.53
Group ketamine inhalation vs. group ketamine infusion	0.000	0.224	0.000	0.000	0.000
Group ketamine inhalation vs. group pulse steroid	0.000	0.000	0.000	0.000	0.000
Group ketamine infusion vs. group pulse steroid	0.000	0.000	0.000	0.000	0.000

CVP, central venous pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PEEP, positive end expiratory pressure; TV, tidal volume.

Table 5 Interleukin-6 levels during treatment

Interleukin-6	IL-6 (0)	IL-6 (3)	IL-6 (5)
Group ketamine inhalation	64.87	47.07	25.87
Group ketamine infusion	66.33	55.13	34.13
Group pulse steroid	66.47	56.07	45.87
Group ketamine inhalation vs. group ketamine infusion	0.546	0.004	0.000
Group ketamine inhalation vs. group pulse steroid	0.575	0.003	0.000
Group ketamine infusion vs. group pulse steroid	0.965	0.690	0.000

IL-6, interleukin-6.

group and the pulse steroid group on days 3 and 5, but there was a significant difference between the ketamine infusion group and the pulse steroid group on day 5 only.

Discussion

Ketamine is being used in clinical application for different forms of anesthesia, especially in cases with hypovolemic shock and sepsis, due to its stimulating effects on the cardiovascular system [12]. Recently, it was found that ketamine inhibits proinflammatory cytokine production, including tumor necrosis factor-α, IL-1, and IL-6 [13,14]. Ketamine also has anti-inflammatory, antioxidant, and immunosuppressive actions [15].

It has been outlined that ARDS pathogenesis involves mechanisms of procoagulation and inflammation as well as compartmental damage of the epithelium and the endothelium. Inflammatory biomarkers (IL-6 and IL-8) have been associated with increased severity of the disease and poor clinical outcomes in ARDS patients [16], but still information on the mechanism of the suppression of ketamine on the production of cytokines is little.

In this study, we explored the potential therapeutic outcomes of ketamine inhalation and infusion in comparison with pulse steroid in ARDS, as after 5 days, the steroid response may be apparent. We found that ketamine treatment provided anti-inflammatory effects, as evidenced by the improvement of ventilator

and circulatory parameters and lowering of the IL-6 level during 5 days of treatment. Furthermore, on comparison of the effects of ketamine with pulse steroid therapy on the anti-inflammatory process in the lung, we can propose that ketamine treatment by both the inhaled and the injected routes could be used early as a line of treatment.

Inhaled ketamine occludes the cascade of inflammation response effectively in an in-vivo model of allergic asthma. Ketamine in the nebulized form at different concentrations was found to inhibit allergen-induced airway hyper-responsiveness (AHR) and to reduce markers of inflammation as confirmed by lung histological examination, total and differential cell counts in the broncho-alveolar lavage fluid, and Th2 cytokine levels in broncho-alveolar lavage fluid [17].

A significant correlation was present with ventilator and circulatory parameters including the blood pressure, the central venous pressure, FiO_2, the tidal volume, and PEEP between the ketamine inhalation group and the steroid therapy group on day 2 of treatment till day 5 of treatment.

On comparing the ketamine infusion group and the steroid therapy group regarding the blood pressure, the central venous pressure and FiO_2 showed a significant correlation starting from day 2 till day 5. The tidal volume showed a significant correlation only from day 3 till day 5.

When the ketamine inhalation group and the ketamine infusion group were compared, there were significant correlations between both groups starting from day 2 till day 5 of treatment with regard to the tidal volume and PEEP and from day 3 of treatment with regard to the blood pressure and FiO_2.

Levels of the proinflammatory cytokine IL-6 were decreased significantly, starting from day 3 of treatment till day 5 between the ketamine inhalation group and the ketamine infusion group and between the ketamine inhalation group and the pulse steroid group. On day 5 only, there was a significant difference between the ketamine injection group and the pulse steroid group.

Conclusion

Ketamine inhalation and infusion decreased the level IL-6 and improved ventilator and circulatory parameters. ARDS is an important complication of many diseases, which needs to be recognized and treated early. Ketamine, either by inhalation or by infusion or by both, could improve survival in developing countries where its outcome is poor. There is no specific pharmacological therapy for ARDS. Ketamine may be effective in decreasing markers of ALI and ARDS and attenuating the systemic inflammatory response which leads to serious complication. Additional large studies with a long follow-up period are necessary to confirm the safety and efficacy profile of ketamine in ARDS and to establish the best strategy for their administration.

Limitation

This study is considered a pilot study for humans as investigation the role of katamine as anti-inflammatory in ALI. Our pilot study is limited primarily by the small sample size. The current sample size limits the statistical power of our findings and, thus, our conclusions regarding safety and efficacy. Another limitation is that the follow-up period was only 5 days.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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