and mucus.[1] Ketamine is a phencyclidine derivative intravenous anesthetic. It produces dose- related unconsciousness and analgesia, termed dissociative anesthesia.[2] Ketamine was synthesized in 1962, by Stevens and was first used in humans by Crossen and Dommino, in 1965.[3] It was released for clinical use in 1970 and is still used in a variety of clinical settings.[2] Ketamine is a bronchial smooth muscle relaxant. When it is administered to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved.[4,5] The mechanism by which ketamine produces airway relaxation is still unclear although several mechanisms have been suggested, including increased catecholamine concentrations, inhibition of catecholamine uptake, voltage-sensitive Ca^{2+} channel block and inhibition of postsynaptic nicotinic or muscarinic receptors.[6] Owing to its bronchodilatory effect, ketamine has been used to treat status asthmaticus unresponsive to conventional therapy (e.g. b2-agonists, corticosteroids, theophyllines).[7] In some case reports, bolus administration and or continuous infusion of ketamine has been used for treatment of intraoperative status asthmaticus.[8] On the other hand, in several other studies, ketamine has been used successfully in the management of status asthmaticus resistant to conventional therapy.[9,10,11] In another study the potentialization of bronchodilatory effect of isofluran (an inhalatoinal anesthetic), by intravenous administration of ketamine in status asthmaticus was observed.[12] However, no clinical trial has been carried out to support this empirical use of ketamine. For this reason, we designed a clinical trial to study the effects of ketamine in patients with status asthmatitus, as an adjuvant therapy with standard treatment, in intensive care unit.

MATERIALS AND METHODS

After an approval by the legal and ethical committee, in four years period, eleven, 15-40 years old patients (7 males/4 females) with status asthmaticus, whose respiratory failures had not responded to conventional therapy (as mentioned above) and mechanical ventilation (after 24h), were enrolled in this study. Although, we had only 11 patients that could enroll in this study during a 4 year peroid, fortunately, the sample size of our study was very close to the study of Petrillo TM.[13] Patients with hypertension, ischemic heart disease, psychiatric disease (e.g. schizophrenia or a history of adverse reaction to ketamine), central nervous system problems (increased intracranial pressure, intracranial mass lesions), and patients with other contraindications (vascular aneurysms, open eye injury or other ophthalmologic disorders, in which a ketamine induced increase in intraocular pressure would be detrimental) to ketamine, were excluded. The patients that entered in the study and were under standard treatment of asthma and mechanical ventilation and after 24h, received ketamine at a loading dose of 1mg/kg IV, followed by a continuous infusion of 1mg/kg/h for 2h. Ketamine has various doses for several clinical end points,[2] but we administered ketamine in a dose that was almost equal to that used by Petrillo TM.[13] With the aim of decreasing airway secretions, atropine 0.02mg/kg IV, and for prevention of psychologic emergence reactions (as side effects of ketamine), midazolam 0.03 mg/kg IV were administered. With these doses, there is not any significant drug interaction between atropine and midazolam. Although, in this study we did not use any control group, we analized the patient's respiratory variables at times prior to and after administration of ketamine.

Peak airway pressure values were obtained from the panel of ventilator (Drager, Evita 2 dura) and PaO2 and PaCO2 were measured by using ABG analyzer (PHOX nova biocamera), at three times setting, prior to ketamine administration, 15min after ketamine administration and 2h after infusion (upon termination of infusion). In all patients, the SpO2 was monitored continuously, and for prevention of hypoxemia, FiO2 was equal to 0.6. Data were expressed as mean±SD and statistically significance was accepted at $p<0.05$ and they were analyzed with the use of SPSS (Student T-test) software.

RESULTS

The results are summarized in Tables 1-4 and Figures 1-3. The mean peak airway pressure significantly decreased from 75.36cmH2O, prior to administration of ketamine, to 50.27 and 39.63cmH2O, 15min and 2h after infusion, respectively ($p<0.05$) (Table 2 and Figure 1). Similarly, the mean PaCO2 considerably decreased from 70.90mmHg, prior to administration of ketamine, to 64.36 and 45.36mmHg, 15min and 2h after infusion, respectively (p<0.05) (Table 3 and Figure 2). Furthermore, the mean PaO2 increased from 63.09mmHg, prior to administration of ketamine, to 75.36 and 91.63mmHg, 15min and 2h after infusion, respectively (p<0.05) (Table 4 and Figure 3).

DISCUSSION

In the management of bronchospastic disease, b-2 agonists are the first line of therapy and the second line consists of theophylline, followed by inhaled or parenteral anticholinergics, corticosteroids, and other drugs if necessary.[14] However, in some patients these medications are non-satisfactory and therefore endotracheal intubation, mechanical ventilation, and the use of other drugs with potent bronchodilatory effects,

Table 1. Detail data of patients.

No.	Age (yrs)	Gender		Peak Airway Pressure (cm H2O)			PaCO2 (mmHg)			PaO2 (mmHg)		
				T0	T1	T2	T0	T1	T2	T0	T1	T2
1	28	Male		81	55	45	75	70	50	65	80	95
2	34	Male		69	45	35	67	60	40	58	68	85
3	30	Female		75	50	40	71	64	45	62	76	91
4	24	Male		78	53	43	76	72	51	61	77	93
5	18	Female		71	47	36	66	63	39	64	72	90
6	27	Female		77	52	39	70	64	46	68	78	94
7	32	Male		81	57	46	73	62	49	69	80	96
8	30	Male		71	43	33	67	60	41	59	72	87
9	29	Male		75	49	45	72	69	47	63	74	91
10	40	Female		78	57	35	70	61	48	65	79	96
11	38	Male		73	45	39	73	63	43	60	73	90
11	30	7	4	75.3636	50.2727	50.2727	70.9091	64.3636	45.3636	63.0909	75.3636	91.6364
Total	Mean	Male	Female	Means			Means			Means		

T0: Prior to ketamine administration, T1: 15 min, and T2: 2 hours after ketamine.

Table 2. Peak airway pressures (mean±SD and SE) at three times: prior to ketamine administration (T0), 15 min (T1); and 2 hours after ketamine (T2).

Times	N	Mean	Std. Deviation	Std. Error Mean
T0	11	75.3636*	4.0564	1.2231
T1	11	50.2727*	4.9415	1.4899
T2	11	39.6364*	4.5885	1.3835

*p<0.005 (p= 0.00)

are necessary.

It has been demonstrated that, ketamine decreases airway resistance and increases lung compliance in the asthmatic patients. Investigations on animal and human preparation have suggested one or more of following mechanisms of action: sympathomimetic effect, direct relaxant effect, antagonistic effect to histamine and acetylcholine, and membrane stabilizing

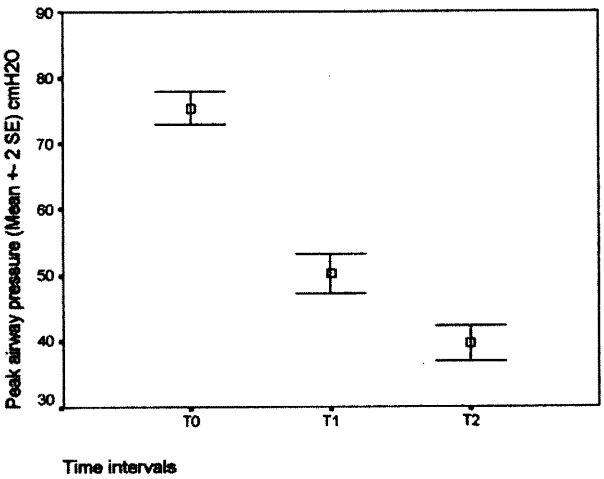

Figure 1. Peak airway pressure (mean±SD and SE) at three times: prior to ketamine administration (T0), 15min (T1); and 2 hours after ketamine (2).

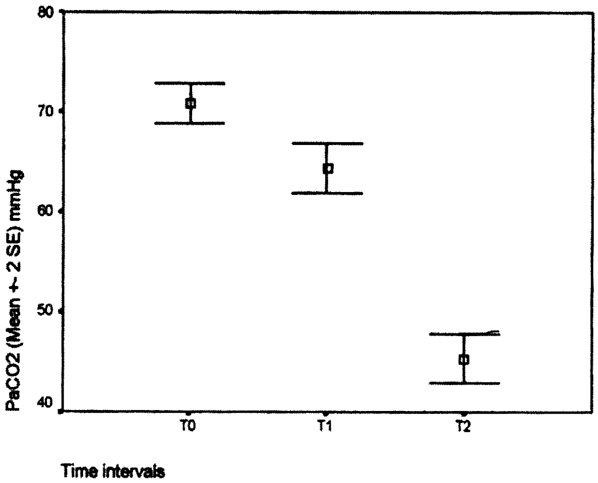

Figure 2. PaCO2 (mean±SD and SE) at three times: prior to ketamine administration (T0), 15min (T1); and 2 hours after ketamine (T2).

Table 3. PaCO2 (mean±SD and SE) at three times: prior to ketamine administration (T0), 15 min (T1); and 2 hours after ketamine (T2).

Times	N	Mean	Std. Deviation	Std. Error Mean
T0	11	70.9091*	3.3001	.9950
T1	11	64.3636*	4.1297	1.2452
T2	11	45.3636*	4.1297	1.2452

*$p<0.005$ ($p= 0.00$)

Table 4. PaO2 (mean±SD and SE) at three times: prior to ketamine administration (T0), 15 min (T1); and 2 hours after ketamine (T2).

Times	N	Mean	Std. Deviation	Std. Error Mean
T0	11	63.0909*	3.5342	1.0656
T1	11	75.3636*	3.8800	1.1699
T2	11	91.6364*	3.5853	1.0810

*$p<0.005$ (p= 0.00)

effect as with local anesthetics.[15] Furthermore, it has been shown that, ketamine increases plasma concentrations of catecholamines and directly relaxes bronchial smooth muscles.[16] Petrillo et al. evaluated the effects of adding ketamine to standard emergency department therapy for patients with status asthmaticus. They evaluated clinical asthma score (CAS), vital signs, peak expiratory flow (PEF), in 10 children with an acute exacerbation of bronchial asthma unresponsive to standard therapy, before and after administration of ketamine. Patients were not intubated. It has been shown that, the addition of ketamine to conven-

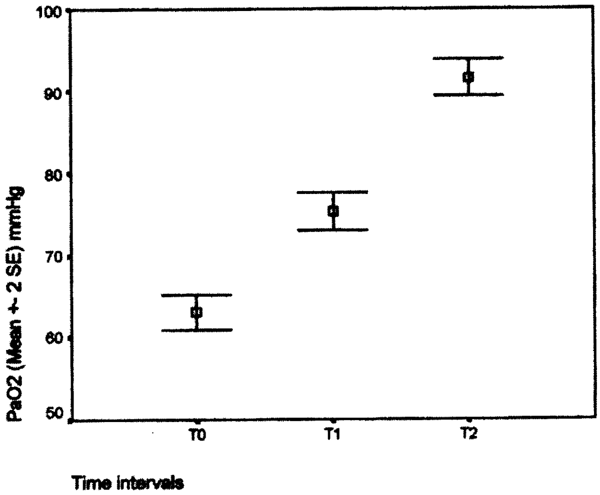

Figure 3. PaO2 (mean±SD and SE) at three times: prior to ketamine administration (T0), 15min (T1); and 2 hours after ketamine (T2).

tional therapy is associated with statistically significant improvement of CAS, respiratory rate, oxygen saturation, and statistically non-significant improvement of PEF.[13] In other study, ketamine has been used for emergency intubation and ventilation in 30 patients with severe bronchial asthma. Simon et al. found that, ketamine produces immediate and unequivocal improvement of respiratory global insufficiency and resolution of bronchospasm. They concluded that ketamine is an efficient complement to conventional emergency treatment of severe asthma.[17] On the other hand, evaluation of five patients with status asthmaticus whose respiratory acidosis (increased PaCO2) persisted despite conventional therapy, showed that intubation with ketamine and mechanical ventilation can cause immediate improvement of respiratory acidosis (similar to present study). This improvement immediately after intubation is in contrast to previous reports of asthmatics whose respiratory acidosis and bronchospasm worsened immediately after intubation.[18] Finally, it has been suggested that, because of bronchodilatory, analgesic and sedative effects of ketamine, administration of this drug during long-term ventilatory support, is useful, and it is recommended, that the use of ketamine with benzodiazepines and other sympathomimetics is suitable during life-threatening situations of patients with status asthmaticus.[19]

Although, in this study we did not have a control group, we compared patient's respiratory variables prior to and after administration of ketamine. Decreasing of peak airway pressure shows an increase in dynamic compliance and decrease in airway resistance. Due to these changes, ventilation is improved, followed by an improvement in the levels of PaCO2 and PaO2. Except for increased secretions during the ketamine infusion, our patients did not show any immediate or long-term complications related to ketamine administration. We conclude that ketamine is a useful drug for intensive treatment of status asthmaticus. However, it should only be used for asthmatics, whose respiratory failure does not respond to conventional management and mechanical ventilation. Finally, other double-blinded randomized (and case-control) clinical trials need to be conducted to further determine the effects of ketamine on patients with status asthmaticus.

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