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Can ketamine administration prevent intubation in patients who cannot comply with NIV due to agitation?

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Abstract

Background In patients presenting to the emergency department (ED) with acute respiratory failure, non-invasive mechanical ventilation (NIMV) is applied when conventional oxygen support is not sufficient. Patients who are agitated often have very low NIMV compliance and a transition to invasive mechanical ventilation (IMV) is often required. To avoid IMV, a suitable sedative agent can be utilized. The aim of this research is to investigate the relationship between ketamine administration to patients who are non-compliant with NIMV due to agitation and the outcome of their intubation.

Methods This retrospective study included patients with acute respiratory failure who were admitted to the ED from 2021 to 2022 and used Richmond Agitation Sedation Scale (RASS) to identify agitation level of patients. The relationship between ketamine administration in this patient group and NIMV compliance and intubation rate was evaluated.

Results A total of 81 patients, including 35 (43.2%) men and 46 (56.8%) women, were included in the study. Of these patients, 46 (56.8%) were intubated despite ketamine administration, while 35 (43.2%) were compliant with NIMV and were not intubated. When evaluating the RASS, which shows the agitation levels of the patients, the non-intubated group was found to be 2.17 ± 0.68, while the intubated group was 2.66 ± 0.73, and it was statistically significant that the NIMV intubated group was higher ($p = 0.003$).

Conclusion This study showed that agitation can impair NIMV compliance in patients with acute respiratory failure. However, a significant proportion of this patient group can be avoided through IMV with proper sedative agents.

Keywords Ketamine, Psychomotor agitation, Noninvasive ventilation, Respiratory insufficiency

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Introduction

Patients presenting with acute respiratory failure frequently require urgent intervention and are commonly referred to the emergency department. The management of these patients involves haemodynamic monitoring, the administration of necessary oxygen support and the development of a treatment plan directed at the underlying cause. In cases where conventional oxygen support is insufficient, non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation may be applied. Patients who are agitated often have very low NIMV compliance, and unfortunately, a transition to invasive mechanical ventilation is often required. Invasive mechanical ventilation is a costly approach compared to NIMV, as it increases the length of stay in the intensive care unit and the incidence of ventilator-associated pneumonia [1].

In patients who are indicated for NIMV but are unable to cooperate due to agitation, sedative agents can be used to ensure patient compliance [2]. Considering that ketamine has both analgesic and anxiolytic effects, it may be superior to other sedative agents [3] as it can be used as a sedative in patients presenting with acute respiratory failure without causing respiratory depression and with no negative effect on haemodynamics. The Richmond Agitation-Sedation Scale (RASS) can be used to measure the agitation levels of patients presenting to the emergency department [4].

This study investigated the likelihood of intubation in patients who presented to the emergency department with acute respiratory failure, who had an agitation level of +2 or higher according to the RASS score, and who received one or two 0.5 mg/kg doses of ketamine. The RASS scale is particularly advantageous in acute situations such as acute respiratory failure as it can be applied quickly and repeatedly to measure both the level of agitation and sedation.

Methods

This is a retrospective study conducted on patients admitted to our clinic with acute respiratory failure. Eighty-one patients who were given ketamine because they could not tolerate NIMV due to agitation were included in the study. In the Medeniyet University emergency department, NIMV is the first choice before intubation for acute respiratory failure. RASS was used to evaluate agitation, and a sedation protocol was applied when patients scored+2 or above. For agitated patients, our procedural sedation protocols include ketamine, midazolam, propofol or combinations of these agents [5]. The choice of sedative agent depends on the patient's clinical status. Among the patients who were admitted to the emergency department with acute respiratory failure, which is an indicator for NIMV, all patients who were administered ketamine because they could not comply with NIMV due to agitation were included in the study. Patients underwent NIMV according to the clinical practice guidelines on noninvasive ventilation for acute respiratory failure of the European Respiratory Society/American Thoracic Society (ERS/ATS) (2017), and all patients were evaluated by emergency medicine specialists [6]. No patient undergoing NIMV was previously denied for intubation. The dose of ketamine administered to patients for sedation was 0.5 mg/kg. The dose was repeated in patients whose RASS score was ≥2 and whose NIMV compliance was inadequate. If compliance was still not achieved, an induction dose of 1–1.5 mg/kg was administered, and the patient was intubated. Figure 1 summarizes the algorithm for agitated patients who are considered for NIMV. The study was carried out with the approval of the Clinical Research Ethics Committee of Medeniyet University Hospital (Approval Nos. 2022/0489 and 17.08.2022). The study analysed patients' gender, age, chronic diseases, vital signs, saturation and respiratory rates at admission, ketamine application and adverse effects, and intubation rate between June 1, 2021 and August 8, 2022. The purpose of this study was to investigate the intubation rate of patients who received ketamine because they could not tolerate NIMV due to agitation.

Patients who met the following criteria were included in the study:

- Patients who were 18 years of age or older.
- Patients with hypoxia despite standard oxygen support (Sao2 < 92).
- Patients with a respiratory rate of > 25 tachypneic.
- Patients with hypercapnia (Paco 2 > 45).
- Patients using assistive respiratory muscles/abdominal breathing.
- Patients with an RASS score of + 2 or higher.
- Patients who received one or two 0.5 mg/kg doses of ketamine.
- Patients who met any of the following criteria were excluded from the study:
- Patients with cardiopulmonary arrest.
- Patients with NIMV unsuitability due to craniofacial trauma.
- Patients with mask incompatibility due to anatomical abnormalities.
- Patients in whom complications were expected or mortality may increase in the case of a delay in invasive mechanical ventilation.
- Patients who could not undergo NIMV due to clouding of consciousness.
- Patients with active upper gastrointestinal bleeding.
- Patients who recently underwent head and neck or esophageal surgery.

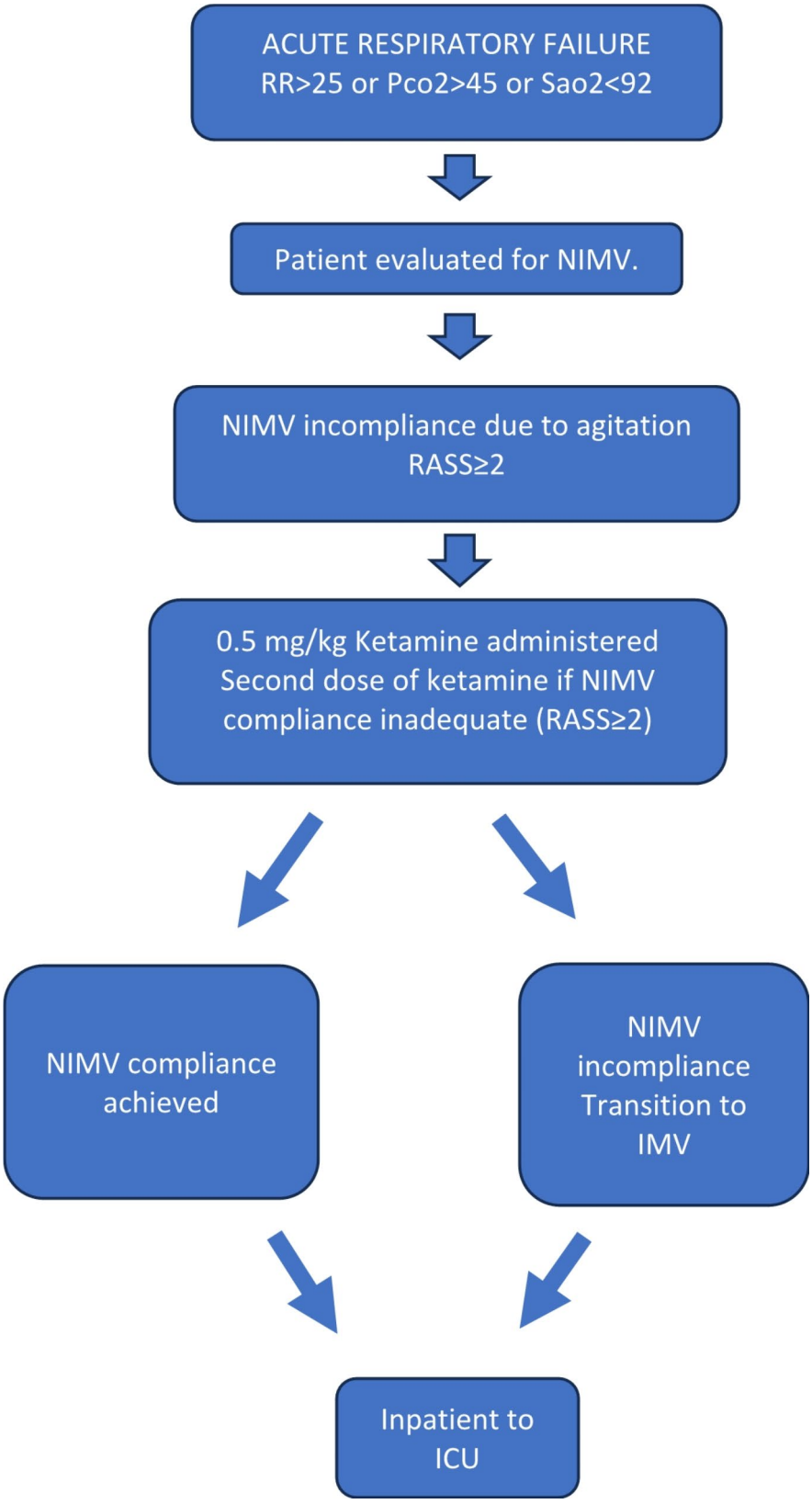

Fig. 1 Ketamine protocol for acute respiratory failure

The patients in the study population were managed by emergency medicine specialists and residents in the resuscitation section of the emergency department, who recorded their findings and the patients' outcomes. The data were collected from our hospital's data management system and patient files.

Statistical analyses

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 package (Utah, USA). Descriptive statistical methods (mean, standard deviation) were used to evaluate the data, and the Shapiro–Wilk normality test was used to examine the distribution of variables. For variables showing normal distribution, the independent t-test was used to compare the two groups, and the chi-square and Fisher's exact test were used to compare categorical data. Logistic regression analysis was performed to determine the factors affecting intubation rate. Findings of $p<0.05$ were considered statistically significant.

In the power analysis performed with the G*power 3.1 program regarding our study, the effect size for Respiratory rate>30 in the study groups was found to be 0.34 (Early detection of non-invasive ventilation failure among acute respiratory failure patients in the emergency department) (alpha error probability=0.05); in the sample width analysis performed by taking the power value as 0.8, the total number of samples to be taken was found to be a minimum of 68.

Results

The study included 81 patients – 35 (43.2%) male and 46 (56.8%) female – who could not tolerate NIMV due to agitation caused by acute respiratory failure. The group in which NIMV was unsuccessful and resulted in intubation was defined as NIMV Intubation (+), while the group in which the patients were cooperative and intubation was not necessary was defined as NIMV Intubation (-) (Table 1). Of these 81 patients who presented with acute respiratory failure but could not tolerate NIMV, 46 (56.8%) tolerated NIMV with ketamine administration and avoided intubation which is NIMV Intubation (-) group but significant portion of patients still required intubation (n:35, 43.2%).

The mean age of the NIMV Intubation (-) group was 75.93±11.39, while for the NIMV Intubation (+), the

Table 1 Demographic structures of patients, chronic diseases, other findings and their relationship with intubation

		No intubation *n* :46 (56.8%)		Intubation *n*:35 (43.2%)		*p*
Age		75.93±11.39		78.51±12.49		0.336*
Gender	**Male**	18	39.13%	17	48.57%	0.395+
	Female	28	60.87%	18	51.43%	
Present clinical situation	**Asthma Attack**	2	4.35%	0	0.00%	0.503ǂ
	Decompensated cardiac failure	19	41,30%	7	20.00%	0.073+
	Hypertensive pulmonary edema	4	8.70%	8	22.86%	0.144+
	Interstitial lung disease	0	0.00%	1	2.86%	0.890ǂ
	COPD Attack	15	32.61%	13	37.14%	0.849
	Malignant effusion	one	2.17%	0	0.00%	0.890ǂ
	Pneumonia	5	10.87%	6	17.14%	0.625+
Hypertension		38	82.61%	21	60.00%	**0.023+**
Diabetes Mellitus		15	32.61%	11	31.43%	0.910+
Congestive heart failure		17	36.96%	5	14.29%	**0.023+**
Coronary artery disease		15	32.61%	9	25.71%	0.501+
Chronic renal failure		4	8.70%	2	5.71%	0.612+
Chronic obstructive pulmonary disease + Asthma		24	52.17%	17	48.57%	0.748+
Cerebrovascular accident		5	10.87%	7	20.00%	0.252+
Chronic kidney disease		2	4.35%	3	8.57%	0.434+
Alzheimer's		3	6.52%	one	2.86%	0.451ǂ
Malignity		3	6.52%	2	5.71%	0.881+
Under The Mask Spo2		88.46±5.55		78.4±10.97		**0.0001***
Respiration Rate		38.28±4.55		38.63±5.35		0.754*
RASS Agitation Score		2.17±0.68		2.66±0.73		**0.003***
A second administration of ketamine necessary?	**No**	46	100.00%	one	2.86%	**0.0001** ǂ
	Yes	0	0.00%	34	97.14%	
Adverse effect of ketamine	**No**	39	84.78%	33	94.29%	0.178+
	Yes	7	15.22%	2	5.71%	

*Independent t test + Chi-square test ǂFisher's Reality Test

mean age was 78.51±12.49. Seventeen males (43.57%) were intubated, and 18 (51.43%) females were intubated. There was no statistically significant difference between the NIMV Intubation (-) and NIMV Intubation (+) groups in terms of mean age or gender distribution ($p=0.336$, $p=0.395$, respectively). Of the patients, 46 (56.8%) required intubation despite ketamine, while 35 (43.2%) were able to tolerate NIMV following ketamine administration (Table 1).

The distribution of the patients' presentations was as follows: two patients (2.4%) had asthma attack, 26 patients (32%) had decompensated heart failure, 12 patients (14.8%) had hypertensive pulmonary oedema, one patient (1.2%) had interstitial lung disease, 28 patients (34.5%) had COPD attack, one patient (1.2%) had malignant effusion and 11 patients (13.5%) had pneumonia. There was no statistically significant correlation between the clinical background of the patients and the intubation rate ($p>0.05$) (Table 1).

In terms of chronic diseases, 59 patients (72.8%) had hypertension, 26 (32%) had diabetes mellitus, 22 (27.1%) had chronic heart failure, 24 (29.6%) had coronary artery disease, six (7.4%) had chronic kidney failure and 41 (50.6%) had COPD or asthma. The presence of hypertension was statistically significantly lower in the NIMV Intubation (+) group compared with the NIMV Intubation (-) group ($p=0.023$). The presence of CHF in the NIMV Intubation (+) group was also statistically significantly lower compared to the NIMV Intubation (-) group ($p=0.023$). No differences were found between the two groups in terms of the presence of other chronic diseases (Table 1).

The oxygen saturation level under the masks of patients in the NIMV Intubation (+) group were found to be 78.4±10.97, while in the NIMV Intubation (-) group, it was 88.46±5.55, and it was found that patients with more desaturation were statistically more likely to be intubated ($p=0.0001$). However, no statistically significant relationship was found between the number of breaths the patients took and the intubation rate ($p=0.754$) (Table 1).

The RASS scores of the patients, which show their level of agitation, were as follows: in the NIMV Intubation (-) group, patients' scores were 2.17±0.68, while in the NIMV Intubation (+) group, patients scores were 2.66±0.73; the scores of the NIMV intubation (+) group were found to be statistically significantly higher than those of the NIMV Intubation (-) group($p=0.003$) (Table 1).

The administration of a second dose of ketamine when the first dose was found to be insufficient was significantly higher in the NIMV intubation (+) group compared to the NIMV intubation (-) group ($p=0.0001$). All patients who required a second dose of ketamine were intubated, while only one patient was intubated without a second dose of ketamine. No second dose of ketamine was given to patients who were not intubated.

Table 2 Relation of adverse effect of ketamine with intubation

Adverse effect of ketamine	NIMV Intubation (-) *n*:46		NIMV Intubation (+) *n*:35	
3 consecutive ventricular extrasystole on ECG	2	33.33%	0	0.00%
Hypersalivation	one	16.67%	0	0.00%
Blood Pressure 20 mm HG drop	0	0.00%	2	100.00%
Heart rate 20 increase	3	50.00%	0	0.00%

Table 3 Logistic regression analysis

	OR	95% OR	*p*
Hypertension	1.4	0.36–5.43	0.627
Congestive heart failure	1.05	0.27–4.15	0.943
SpO2 under the mask	**0.86***	**0.79–0.94***	**0.0001***
RASS Agitation Score	2.45	1.08–5.55	**0.033***

The adverse effects of ketamine included the following:

- Three or more consecutive ventricular ectopic beats in ECG.
- Hypersalivation.
- A decrease in systolic blood pressure of more than 20 mm Hg.
- An increase in heart rate of 20 beats or more.

Of the 81 patients included in the study, adverse effects of ketamine were detected in eight patients (9.8%). Hypersalivation was seen in only one (1.2%) patient. No statistically significant difference was observed in the distribution of ketamine adverse effects between the NIMV intubation (-) and NIMV intubation (+) groups ($p=0.178$) (Table 2).

A logistic regression analysis was conducted to determine the factors affecting intubation using the hypertension, congestive heart failure, under-mask SpO2 and RASS score variables. The hypertension ($p=0.627$) and congestive heart failure ($p=0.943$) variables were found to be insignificant, while a decrease in under-mask SpO2 ($p=0.0001$) and an increase in RASS score ($p=0.033$) were identified as factors associated with intubation following unsuccessful ketamine application (Table 3).

Discussion

Non-invasive mechanical ventilation (NIMV) has been shown to be effective in avoiding intubation and improving survival in patients with acute hypoxemic respiratory failure compared to conventional oxygen therapy [7]. However, a patient's inability to adapt to mechanical ventilation or the occurrence of agitation due to respiratory distress can significantly reduce the success of NIMV. There are some case reports in the literature indicating

that the application of ketamine in patients who cannot tolerate NIMV due to agitation can be successful [8, 9]. In our study, intubation was successfully avoided in patients with COPD exacerbation, decompensated heart failure, hypertensive pulmonary oedema and pneumonia. The reason for the preference for ketamine over other sedatives is due to its anxiolytic effect and the absence of negative effects on respiration and hemodynamics.

The clinical cases mentioned in the case reports in the literature are asthma attack and acute cardiogenic pulmonary oedema [3]. At present, ketamine is used in our emergency medicine clinic for procedural sedation, deep sedation for intubation preparation, and sedation of agitated patients who cannot tolerate NIMV. Adverse effects of ketamine were evaluated to determine whether it affected NIMV intolerance due to ventricular tachycardia, hypersalivation, or other possible side effects and to distinguish impaired NIMV tolerance due to agitation. The patient may become unstable due to a possible adverse effect of ketamine or may need to be directly intubated for reasons other than agitation, such as hypersalivation and vomiting. A meta-analysis found that, among the adverse effects of ketamine, serious cardiopulmonary adverse effects were rare, and in our study, no serious adverse effects were observed. Our study found that 9.8% of patients experienced adverse effects, which is in line with the literature [10]. However, higher doses of ketamine may lead to the occurrence of dissociative effects, which are not compatible with ventilator use, and in the presence of these effects, invasive ventilation may be required. In our study, hypersalivation, which can disrupt ventilation compatibility, was observed in only one patient (1.2% of patients) and did not result in intubation. The dissociative effects of ketamine start at doses above 1–1.5 mg/kg. In our study, patients were administered up to two 0.5 mg/kg doses of ketamine, so no dissociative effects were observed. Other side effects of ketamine can include a systolic blood pressure increase of 20 mm Hg or more, three or more consecutive ventricular ectopic beats on the ECG, and a heart peak rate increase of 20 beats or more, which did not affect patients' intubation rate. The side effects caused by ketamine at low doses do not prevent the successful use of NIMV [11].

NIMV cannot be initiated unless the required comfort and ventilation compliance are achieved; if adequate oxygenation cannot be achieved, direct invasive ventilation is necessary. The RASS is used to measure levels of agitation and sedation in patients. In critically ill patients with acute respiratory failure, the measurement tool used must be rapid, reliable and repeatable. In a study that compared the RASS with the Ramsay Sedation Scale, the RASS was found to be more reliable [12]. In our study, patients with RASS scores of +2 or higher were included, and patients with higher levels of agitation were more frequently intubated. Most of the patients who were eventually intubated had to be given a second dose of ketamine, probably because their agitation levels were higher. Moreover, considering that the need for a second dose of ketamine arose from agitation levels or an inability to achieve sufficient compliance with NIMV with one dose of ketamine, it may be more appropriate to proceed directly to invasive ventilation with these patients instead of administering a second ketamine dose. A study conducted on high-flow nasal oxygen (HFNO) showed that the failure of HFNO increased mortality by causing a delay in intubation, which is why waiting to give a patient a second dose of ketamine prolongs the period of inadequate oxygen support, which may negatively impact the outcome [13].

Our study included 81 patients who were unable to tolerate NIMV due to agitation and who would have required invasive mechanical ventilation if ketamine had not been administered. In 43.2% of this patient group, intubation was avoided. A widespread epidemiological study in the United States showed that mechanical ventilation is correlated with mortality and represents a significant economic burden on the health system [14]. In a study of 180,326 hospitalized patients, 2.7% required mechanical ventilation, and the total cost was estimated to be 2.7 billion US dollars [14]. Therefore, cost-saving measures should be implemented where possible. In a study on complications related to mechanical ventilation, 9.3% of 597 patients developed ventilator-associated pneumonia [15]. The expected mortality rate for ventilator-associated pneumonia is in the range of 10% and is expected to be higher in critically ill patients. Although the patient group unable to tolerate NIMV due to agitation is small, using ketamine to prevent the transition to invasive ventilation may be significant in terms of both cost savings and patient survival [16].

Between 40% and 60% FiO2 can be delivered with simple mask oxygenation. In our study despite this oxygen support, lower So2 values were found in a group of intubated patients. In this context, sedating critically ill patients with lower oxygen saturation using ketamine makes it more difficult to avoid intubation. A previous study that analysed the predictors of intubation showed that having a high respiratory rate under conventional oxygen support increased the likelihood of ending with intubation [17]. In our study, the administration of ketamine did not result in a statistically significant difference in the incidence of intubation as judged by the respiratory rate. This could be attributed to the fact that all the patients included in the study were monitored, and patients whose respiratory rate increased to more than 25 breaths per minute were not necessarily intubated. Our study did not find a statistically significant difference in the intubation rate of patients admitted to the emergency

department based on their presenting clinical features. A previous meta-analysis of 25 randomized controlled trials with a total of 3,804 patients evaluated the relationship between NIMV and mortality in acute respiratory failure [18]. Studies have found a significant decrease in mortality with NIMV compared to standard oxygen support, regardless of the severity of the clinical presentation. Offering NIMV to patients prior to intubation can be positive in terms of patient survival, regardless of the clinical status of patient. The literature also demonstrates the positive effect of NIMV implementation on chronic respiratory failure in patients with COPD exacerbation, who make up a significant portion of patients [19].

Logistic regression analysis in our study showed that the presence of hypertension and congestive heart failure did not significantly affect the likelihood of intubation. No significant relationship was found between other chronic illnesses and intubation rate. This suggests that, in patients with acute respiratory failure, the administration of ketamine may be beneficial in avoiding intubation, regardless of the patient's existing chronic illnesses.

When compared to other sedative agents used during NIMV, ketamine has been found to be more effective than midazolam, propofol and the opioid group but less effective than dexmedetomidine [20]. Dexmedetomidine is another agent that may have positive effects on NIMV tolerability due to its analgesic effect for short- and long-term sedation, prevention of delirium, and the absence of respiratory depression [21]. In a prospective study on procedural sedation, midazolam and ketamine were compared and ketamine was shown to be safer on the respiratory system [22]. A meta-analysis has shown that the combined use of propofol with ketamine has more hemodynamic and respiratory protection and less adverse effects than using it alone [23]. While ketamine is commonly found in emergency departments, dexmedetomidine is typically unavailable in these settings in Turkey. For this reason, ketamine is the best choice among sedative drugs for NIVM. Due to its hemodynamically benign properties, it is considered a more favorable option compared to propofol and midazolam [24]. Furthermore, ketamine exhibits a lower rate of respiratory depression compared to opioids, propofol and midazolam. Ketamine is commonly used in the emergency department for intubating patients who are experiencing haemodynamic instability, such as those with sepsis or hypovolemic shock. Since ketamine is also an induction agent, transition to mechanical ventilation is easy.

Limitations

The retrospective nature of the study precluded the display of changes in values such as Sp02 and patients' RASS scores following ketamine administration. We were able to obtain only admission data, which we routinely record to determine the indication for NIMV and sedative agent administration. These data are not sufficient to definitively state that ketamine is a suitable sedative agent to improve NIMV tolerance. Its efficacy would be better demonstrated through larger-scale studies in the future that involved working with multiple centres prospectively, which would increase methodological confidence. In our study, the exclusion of patients who were administered sedative agents other than ketamine for agitation prevented the evaluation of ketamine compared to other agents. Mortality analysis could not be performed because the group included in the study was very heterogeneous and relatively small. Future studies should investigate the effects of avoiding intubation on mortality in this patient group as an important outcome. Another limitation is that the retrospective nature of the study prevents the detection of physician selection bias. A prospective study on this subject, conducted with a control group and, if possible, with larger groups including other sedative agents, will provide more accurate scientific data.

Clinical implications

In patients with acute respiratory failure, agitation can disrupt NIMV compliance, but a proper sedative agent can help ensure NIMV compliance in a significant proportion of this patient group, thereby avoiding the need for invasive mechanical ventilation. Considering the known effects of ketamine, it may be considered a suitable agent. Given that ketamine applications at doses greater than 0.5 mg/kg do not prevent the need for intubation, delaying invasive mechanical ventilation with a second dose of ketamine may not be appropriate. To reduce the costs of invasive mechanical ventilation and its adverse effects on patient outcomes, sedation with ketamine may be a suitable option.

Conclusion

Ketamine is a promising agent for avoiding intubation and providing appropriate sedation in patients who cannot tolerate NIMV due to agitation. Future studies may shed more light on the subject.

Abbreviations

ED	Emergency Department
NIMV	Non-invasive mechanical ventilation
IV	Invasive ventilation
IMV	Invasive mechanical ventilation
RASS	Richmond Agitation Sedation Scale

Supplementary Information

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Supplementary Material 1

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Author contributions
CN: Conceptualization (lead); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal)., data collecting.GAS: Software (lead); writing – review, and editing (equal). FA: Methodology (lead); writing – review, and editing (equal), data collecting. ÖFG: Methodology (lead); writing – review, and editing (equal), data collecting. KOD: Methodology (lead); writing – review, and editing (equal), data collecting.

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Data availability
Data is provided within supplementary information files.

Declarations

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Not Applicable.

Competing interests
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Consent to participate
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