Original Article

Dexmedetomidine versus ketamine in improving tolerance to noninvasive ventilation after blunt chest trauma: A randomized, double-blinded, placebo-controlled trial

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Abstract

Background and Aims: Even though patient tolerance is critical to the success of noninvasive ventilation (NIV), research on using sedation to improve tolerance to NIV after traumatic chest injuries is limited. We hypothesized that dexmedetomidine would be superior to ketamine in terms of patient tolerance and lengthening the NIV sessions after blunt chest trauma.

Material and Methods: This randomized, double-blinded, placebo-controlled trial included 45 patients of both genders aged 18–60 who needed NIV after blunt chest trauma. The patients were randomly assigned to one of three groups ($n = 15$) for receiving dexmedetomidine, ketamine, or placebo (0.9% sodium chloride solution) infusion to maintain a Richmond Agitation Sedation Scale (RASS) score between 0 and − 3 during two successive NIV sessions. Patients were evaluated for the duration of the NIV sessions, RASS, Visual Analog Scale (VAS), and the total amount of rescue analgesia consumed.

Results: The mean duration of the NIV sessions was significantly longer in patients who received dexmedetomidine ($P < 0.001$) or ketamine ($P < 0.001$) compared to placebo. However, the NIV durations did not differ significantly between the dexmedetomidine and ketamine groups ($P > 0.05$). The dexmedetomidine group had a significantly lower RASS score compared to the ketamine ($P < 0.001$) and placebo ($P < 0.001$) groups, whereas the ketamine group had a significantly lower VAS compared to the dexmedetomidine ($P = 0.005$) and placebo ($P = 0.022$) groups and required significantly less total morphine ($P = 0.001$) compared to the other groups.

Conclusion: The duration of the NIV sessions for patients with blunt chest trauma did not differ significantly between the dexmedetomidine and ketamine groups.

Keywords: Blunt chest trauma, dexmedetomidine, ketamine, non-invasive ventilation

Introduction

Blunt chest trauma accounts for nearly one-third of all acute trauma hospital admissions.[1] The official European Respiratory Society (ERS)/American Thoracic Society (ATS) clinical practice guidelines and other literature recommend early noninvasive ventilation (NIV) for chest trauma patients with acute respiratory failure to reduce the need for intubation, the incidence of nosocomial pneumonia, and the intensive care unit (ICU) length of stay.[2-4] Even though patient tolerance is critical to the success of NIV, research on the efficacy of sedative drugs to facilitate NIV in this target trauma population is limited.

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While studies have investigated the use of dexmedetomidine in nontrauma patients managed with NIV,[5,6] the effects of dexmedetomidine as a sedative in patients receiving NIV after blunt chest injuries have yet to be thoroughly studied. A recent randomized, crossover pilot trial involving 19 patients with blunt chest trauma who required NIV reported that dexmedetomidine extended the duration of the first NIV sessions and was associated with a lower Richmond Agitation Sedation Scale (RASS) and Visual Analog Scale (VAS) compared to placebo.[7] Likewise, ketamine is increasingly being used as a sedative in mechanically ventilated patients as well as nontrauma patients on NIV.[8] However, there is a paucity of data on the use of ketamine as a sedative in chest trauma patients receiving NIV. Ketamine was studied as a therapeutic modality for reducing the amount of opioids used to treat rib fracture pain.[9] Both dexmedetomidine and ketamine are unique among sedatives in that they preserve the respiratory function and maintain a patent airway.[10,11]

This double-blinded, randomized, placebo-controlled study was designed to investigate and compare the effects of dexmedetomidine and ketamine on patient tolerance for NIV after blunt chest injuries. We hypothesized that dexmedetomidine would be superior to ketamine in terms of patient tolerance and lengthening the NIV sessions after blunt chest trauma. The primary outcome was the length of the NIV sessions. The secondary outcomes were the mean RASS score for sedation, the mean VAS for pain assessment during each NIV session, and the total amount of morphine consumed.

Material and Methods

The institutional ethical committee approved this double-blinded, randomized, placebo-controlled study (approval number: 494/12/20; approval date: 04/12/2020). Furthermore, the trial was registered at ClinicalTrial.gov (NCT05175781; 04/01/2022). The study was conducted between January 2022 and July 2022 in the surgical ICU at a university hospital and followed the Consolidated Standards of Reporting Trials guidelines. The participants were told about the study, and they signed a written informed consent or granted it through relatives. All methods were performed according to the 1964 Declaration of Helsinki's ethical standards and later amendments.

The study included all blunt chest trauma patients of both genders, aged 18–60 years, who had more than three rib fractures, pulmonary contusion, hypoxemia (SpO_2 90% on oxygen mask 8–10 L/min), or hypercapnia ($PaCO_2$ 45 mmHg) at the start of the study, or a respiratory rate of 25 breaths per minute or more despite receiving intravenous analgesia (paracetamol 1 g intravenous six hourly and ketorolac 30 mg intravenous eight hourly), and in whom invasive mechanical ventilation was not indicated. Patients under the age of 18 or older than 60, those on mechanical ventilation, those admitted more than 24 h after trauma, those with fewer than three rib fractures, those who did not have a chest computed tomography (CT) scan, and those who were contraindicated to NIV, dexmedetomidine, or ketamine were all excluded from the study. The authors used supplemental oxygen (8–10 L/min) via facial mask for all patients till randomization and enrollment in the study.

The patients were randomly assigned to one of the following three equal groups using computer-generated randomization tables: placebo (0.9% sodium chloride solution), dexmedetomidine, or ketamine. An investigator not involved in the outcome assessment received the serially numbered envelopes with group allocation, prepared the study drugs, and adjusted the infusion rate. The patients and those who assessed study outcomes were blinded to study group allocation.

During each NIV session, the participants received a continuous infusion of dexmedetomidine, ketamine, or a placebo to maintain a RASS score between 0 and −3. Dexmedetomidine infusions were begun at 0.7 μg/kg/h without a loading dose and then titrated every 60 min by 0.2 μg/kg/h (up to a maximum dose of 1.3 μg/kg/h). The continuous infusion of ketamine began at a dose of 0.20 mg/kg/h and it was titrated every 60 min at 0.2 mg/kg/h (up to a maximum dose of 0.5 mg/kg/h). The authors controlled pain with a morphine dose (0.05 mg/kg) throughout the study if the 10-cm VAS exceeded 3.

NIV was delivered using CARESCAPE R860, Model G1500197 (Datex-Ohmeda, Madison, USA) through a full face mask with initial settings as follows: inspiratory positive airway pressure at 8 cm H_2O, positive end-expiratory airway pressure (PEEP) at 4 cm H_2O, and a fraction of inspired oxygen to achieve pulse oximetry higher than 94%. During the 4-h gap between sessions, we gave no NIV or drug infusion.

The primary outcome was the duration of the NIV sessions. The mean, highest, and lowest levels of PEEP and FiO_2 during the NIV sessions, the arterial blood gases (PaO_2, $PaCO_2$), and the pH evaluated at the end of each session, as well as the hourly measurements of the RASS score for sedation and the 10-cm VAS for pain assessment during each NIV session, and the total amount of morphine consumed were all secondary outcomes. The NIV session was stopped if the patient was agitated, measured by a RASS score of more than 2, or if intubation was required for a life-threatening condition or emergency surgery.

The sample size was calculated using G*power, version 3.1.9.2. The primary outcome measure of this study was the duration of the NIV sessions. Based on a pilot of the current study involving 15 patients, we expected to find an effect size of 0.50 in the mean duration of NIV sessions among the three studied groups (306, 331, and 200 min). At a power of 80%, α of 0.5, and an additional 10% to compensate for any unanticipated technical issues, we estimated the sample size for the study to be 45 patients (15 in each group).

Statistical analysis

Data were collected, tabulated, and statistically analyzed using a Statistical Package of the Social Sciences (SPSS Statistics for Windows, Version 26.0 software program; IBM Corporation, Armonk, NY, USA). Descriptive statistics are expressed as number and percentages for categorical variables. All quantitative data are expressed as mean ± standard deviation (SD) for parametric data or median [25th, 75th percentile] for nonparametric data. When appropriate, the mean difference among the three treatment groups was calculated and compared with the one-way analysis of variance (ANOVA) test or nonparametric Kruskal–Wallis test. *Post hoc* Tukey's test was run to confirm where the differences occurred between groups. The association between the session duration results and different study variables was investigated using Pearson correlation analyses, and Pearson correlation coefficients (r) were calculated. The confidence interval (CI) was set at 95% for all tests, and P values less than 0.05 were considered statistically significant.

Results

Fifty-three patients were considered for participation in the trial. Eight patients were excluded because they did not meet the inclusion criteria (two were below 18 years, four were mechanically ventilated on admission, and two were admitted to ICU more than 24 h after trauma). Finally, 45 patients were enrolled in this study and randomly assigned (intent-to-treat patients) to one of three groups for a continuous intravenous infusion of dexmedetomidine, ketamine, or a placebo (0.9% sodium chloride solution) throughout two successive NIV sessions [Figure 1]. The baseline clinical characteristics of the study population are shown in Table 1.

The mean duration of the first and second NIV sessions was longer in patients who received an intravenous infusion of dexmedetomidine (309.6 ± 63.5 and 290.5 ± 43.2 min, respectively, $P < 0.001$) or ketamine (291.0 ± 56.2 and 288.8 ± 59.6 min, respectively, $P < 0.001$) compared to the placebo (200.7 ± 46.9 and 187.0 ± 76.7 min,

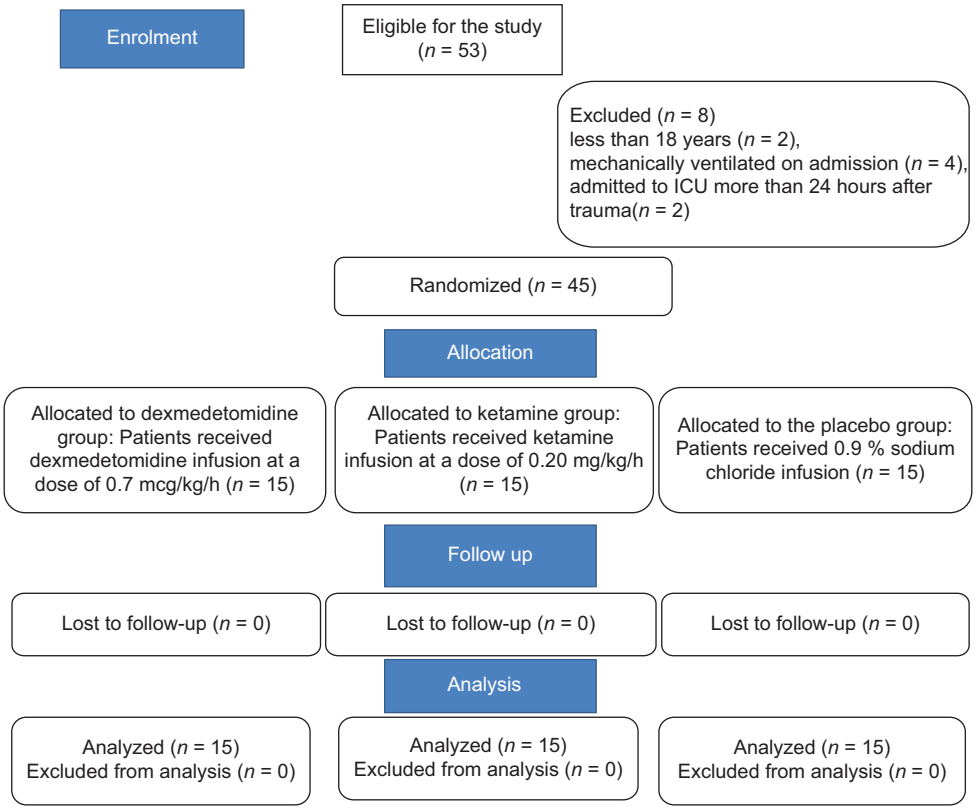

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow chart provides the number of patients at each study stage

Table 1: Baseline clinical characteristics of the study population (*n*=45)

Variables	Value
Age in years, median [25th, 75th percentile]	36 [24.5, 47.5]
Sex, *n* (%)	
Male	43 (95.6)
Female	2 (4.4)
Mechanism of injury, *n* (%)	
Road traffic accident	40 (88.9)
Fall from height	5 (11.1)
Chest wall injuries	
Hemo/pneumothorax, *n* (%)	
Yes	35 (22.2)
No	10 (77.8)
Lung contusion, *n* (%)	
Yes	28 (62.2)
No	17 (37.8)
Emphysema, *n* (%)	
Yes	2 (4.4)
No	43 (95.6)
Chest tube, *n* (%)	
Used	21 (46.7)
Not drained	24 (53.3)
Rib fractures, *n* (%)	
3–6	25 (55.6)
>3 bilateral	20 (44.4)
Baseline physiology/variables on admission, median [25th, 75th percentile]	
Heart rate, beats/min	99 [87, 107]
Mean arterial blood pressure, mmHg	78 [75, 84]
Respiratory rate, cycles/min	29 [26, 32]
SpO_2 pulse oximetry	90 [86.5, 93.5]
PaO_2, mmHg	61 [57, 73]
$PaCO_2$, mmHg	38 [36, 42]
PaO_2/FiO_2	164.0 [149.5, 182.5]
Arterial pH	7.40 [7.36, 7.42]
VAS on admission, median [25th, 75th percentile]	6 [4, 7]
ICU length of stay in days, mean±SD	6.0±2.0
Secondary respiratory complications, *n* (%)	
Yes	5 (11.1)
No	40 (88.9)

All patients obtained data under supplemental oxygen (8–10 L/min). All data are reported as median (IQR) [25th, 75th percentile] unless otherwise stated; some values are in number (%) and mean±SD. ICU=intensive care unit, IQR=interquartile range, $PaCO_2$=partial pressure of arterial carbon dioxide, PaO_2=partial pressure of arterial oxygen, PaO_2/FiO_2=partial pressure of arterial oxygen/fraction of inspired oxygen, SD=standard deviation, SpO_2=oxygen saturation, VAS=Visual Analog Scale

respectively). However, there was no significant difference in the duration of the NIV sessions between the dexmedetomidine and ketamine groups [Figure 2]. There was also a significant negative correlation between the session durations and the measured VAS and RASS scores during the first ($r^2 = -0.483$ and $r^2 = -0.635$, respectively, $P < 0.001$) and second ($r^2 = -0.544$ and $r^2 = -0.643$, respectively, $P < 0.001$) sessions. The

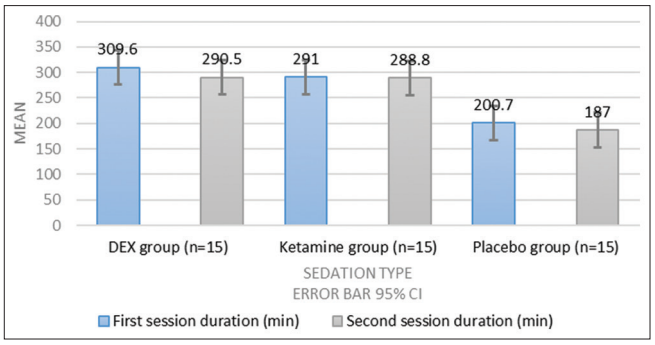

Figure 2: The clustered error bars (95% CI) for the mean duration of the NIV sessions (min) by the sedation type. The time of the NIV sessions was longer in patients who received an intravenous infusion of dexmedetomidine or ketamine compared to the placebo group. However, the NIV sessions' duration did not differ significantly between the dexmedetomidine and ketamine groups. CI = confidence interval, NIV = noninvasive ventilation

lengths of the first and second sessions were significantly and strongly correlated ($r^2 = 0.71$, $P < 0.001$).

RASS scores were significantly lower in the dexmedetomidine group compared to the ketamine (dexmedetomidine vs. ketamine, $P < 0.001$) and placebo (dexmedetomidine vs. placebo, $P < 0.001$) groups during the first and second sessions [Table 2]. The pain scores (measured by a VAS) were ≤3 using the multimodal analgesic regimen augmented by intravenous morphine as rescue analgesia. VAS was significantly lower in the ketamine group compared to the dexmedetomidine and placebo groups ($P = 0.005$ and $P = 0.012$) during the first and second sessions, respectively. The total morphine requirement was lowest in the ketamine group compared to the dexmedetomidine ($P = 0.001$) and placebo ($P = 0.001$) groups [Table 2].

Mean blood pressure was significantly lower in the dexmedetomidine group than in the ketamine ($P = 0.001$) and placebo ($P < 0.001$) groups during the NIV sessions. However, the heart rate of the dexmedetomidine group was significantly lower than that of the ketamine group ($P = 0.005$) only during the second session. The respiratory rate of the dexmedetomidine group was considerably lower ($P = 0.041$) than that of the placebo group during the first session [Table 2].

At the end of the first and second sessions, the PaO_2 values were significantly higher in the dexmedetomidine ($P = 0.032$, $P = 0.004$) and ketamine ($P = 0.029$, $P = 0.015$) groups than in the placebo group. Likewise, the PaO_2 / FiO_2 ratio at the end of the first and second sessions were significantly higher in the dexmedetomidine ($P = 0.030$, $P = 0.035$) and ketamine ($P = 0.033$, $P = 0.022$) groups than in the placebo group [Table 2].

All study groups had comparable lengths of stay in the ICU; patients were discharged from the ICU after a mean

Table 2: Secondary outcome variables of the study population

Parameters	Measurement time	Dexmedetomidine group (*n*=15)	Ketamine group (*n*=15)	Placebo group (*n*=15)
Heart rate	During the first NIV session	91.13±8.05	95.73±6.23	95.53±8.35
	During the second NIV session	88.47±7.54[a]	95.53±4.71	92.60±4.79
Mean blood pressure	During the first session	74.00±5.90[a,b]	82.73±3.65	84.47±8.09
	During the second session	70.67±4.10[a,b]	83.87±4.68	83.60±6.20
Respiratory rate	During the first session	22.60±3.46[b]	23.20±3.68	25.87±3.52
	During the second session	21.60±2.32	21.40±2.69	23.55±5.34
Arterial PH	At the end of the first session	7.39±0.06	7.41±0.03	7.39±0.03
	At the end of the second session	7.40±0.04	7.38±0.06	8.30±3.51
$PaCO_2$	At the end of the first session	37.00±4.92	35.87±2.722	38.20±3.09
	At the end of the second session	37.53±3.99	37.47±3.54	39.53±5.91
PaO_2	At the end of the first session	98.13±14.39[b]	98.33±14.10[b]	85.53±10.76
	At the end of the second session	98.20±10.00[b]	96.27±14.45[b]	84.40±7.64
PaO_2 / FiO_2 ratio	At the end of the first session	246.53±37.54[b]	246.00±35.5[b]	213.93±27.07
	At the end of the second session	239.00±32.02[b]	241.13±36.322[b]	210.60±19.47
RASS	During the first session	0 [0,1][a,b]	1 [0,1]	2 [1,2]
	During the second session	0 [−1,0][a,b]	1 [0,1]	2 [2,2]
VAS	During the first session	3 [2,4]	2 [2,3][b,c]	3 [3,4]
	During the second session	3 [3,3]	3 [2,3][b,c]	3 [3,5]
Total morphine consumption (mg)		12 [6,18]	6 [0,9][b,c]	18 [16,23]

ANOVA=analysis of variance, $PaCO_2$=partial pressure of arterial carbon dioxide, PaO_2=partial pressure of arterial oxygen, PaO_2/FiO_2=partial pressure of arterial oxygen/fraction of inspired oxygen, RASS=Richmond Agitation Sedation Scale, SD=standard deviation, VAS=Visual Analog Scale. All data reported as mean±SD; parametric ANOVA F test was used to analyze normally distributed variables. [a]Statistical significance compared to the ketamine group. [b]Statistical significance compared with the control group. [c]Statistical significance compared to the dexmedetomidine group

stay of 6 ± 2 days. Furthermore, the PEEP data collected during the NIV sessions were comparable across all study groups ($P > 0.05$), including the highest, lowest, and mean values. Two patients in the dexmedetomidine group, two in the placebo group, and one in the ketamine group developed secondary respiratory complications (chest infection) while in the ICU.

Discussion

Blunt chest wall injury is attributed to 20%–25% of all trauma deaths. It impairs ventilation and causes acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[12] Furthermore, the increase in the proinflammatory cytokines after blunt chest trauma may also result in apoptosis.[13] Even though NIV is recommended as the standard of care for patients with blunt chest trauma,[4,14] there is no consensus on the appropriate drugs that provide sedation and analgesia for blunt chest trauma patients and enhance their tolerance to NIV. Wu *et al.*,[15] in an experimental study, discovered that dexmedetomidine suppresses the proinflammatory cytokine response and decreases the levels of tumor necrosis factor and interleukin-1 in blunt chest trauma–induced pulmonary contusion in rats. Ketamine also has a strong anti-inflammatory effect,[16] and a combination of dexmedetomidine–ketamine could mitigate pulmonary inflammatory response in rats.[17]

Our clinical trial is the first to compare the effects of dexmedetomidine and ketamine on improving patient tolerance to NIV after blunt chest trauma. We found that patients who received a dexmedetomidine or ketamine intravenous infusion could tolerate NIV for longer periods than those who received a placebo. The duration of the NIV sessions, however, did not differ significantly between the dexmedetomidine and ketamine groups. Patients in the dexmedetomidine group had a deeper level of sedation and a lower RASS score than those in the ketamine and placebo groups. In contrast, the ketamine group had better pain control, a lower VAS score, and less total morphine requirement than the dexmedetomidine and placebo groups. The mean duration of NIV sessions had a significant negative correlation with the measured VAS and RASS scores.

Our results are generally in line with an earlier study on 40 patients with acute respiratory failure due to acute exacerbations of chronic obstructive pulmonary disease undergoing NIV, which reported that both dexmedetomidine and midazolam were effective sedatives for patients with NIV.[6] Moreover, a recent meta-analysis found that ketamine can be used as a sedation-sparing agent in mechanically ventilated patients,[18] and also in a case study, ketamine facilitated NIV in acute decompensated heart failure.[8]

We found that the NIV sessions were significantly longer in the dexmedetomidine group than in the placebo group. These

results are consistent with a crossover, placebo-controlled pilot study that included 19 patients who were treated with NIV after blunt chest trauma.[7] The study reported that dexmedetomidine prolonged the duration of NIV compared to placebo during the first session only, as patients who had received dexmedetomidine first were less likely to tolerate NIV for an extended period during their second placebo exposure. Furthermore, a recent meta-analysis of six randomized controlled trials (RCTs; $N = 307$ patients) found that dexmedetomidine reduced the duration of NIV when compared to benzodiazepines (Mean Difference - MD, –35.90 h; 95% CI, –42.69 to –29.11 h), but not when compared to placebo (MD, –6.10 h; 95% CI, –22.56 to 10.36 h) or antipsychotics (MD, –4.40 h; 95% CI, –9.08 to 0.28 h).[19] Also, a previous study compared the efficacy and safety of dexmedetomidine sedation versus midazolam sedation in patients with acute cardiogenic pulmonary edema during NIV treatment. The study concluded that dexmedetomidine resulted in a higher level of desired waking sedation, and that the duration of study drug treatment was shorter in the dexmedetomidine group because dexmedetomidine-treated patients were weaned from NIV more rapidly.[20] In the same context, a previous research found that ketamine infusion in a mechanically ventilated adult surgical ICU reduced both opioid consumption and propofol use while maintaining adequate sedation.[21]

Shamim *et al.*[5] reported in a cross-sectional, prospective study on 110 intubated and 101 nonintubated patients in a medical ICU that the mean RASS before starting dexmedetomidine infusion was $+2.2 \pm 0.8$ and decreased to -2.0 ± 1.00 after starting dexmedetomidine. This sedation score that allowed the patients to remain calm and cooperative was achieved after 1 h with a mean dose of 0.7 μg/kg/h of dexmedetomidine infusion. These findings are consistent with ours, in which RASS was significantly lower in the dexmedetomidine group compared to the ketamine and placebo groups. However, in another study comparing the effectiveness of dexmedetomidine and midazolam for sedation in 49 patients with acute respiratory failure undergoing NIV, Senoglu *et al.*[6] found that the level of sedation did not differ significantly between the dexmedetomidine and midazolam groups, but dexmedetomidine required fewer dosing adjustments to maintain adequate sedation than midazolam.

Pain control is a critical part of care for patients who have experienced blunt chest trauma. In the 2018 guidelines, it is mentioned for the first time that multimodal analgesia, including nonopioid analgesics, contributes to ameliorating pain management and decreasing opioid use in adult ICU.[22] A meta-analysis of opioid consumption as an outcome in postoperative critically ill patients randomly assigned to ketamine or saline infusions found that the mean cumulative morphine consumption at 48 h was significantly lower in the ketamine group (58 ± 35 mg) compared to the placebo group (80 ± 37 mg, $P < 0.05$).[23] Buchheit *et al.*[21] recently demonstrated that ketamine administration significantly reduced opioid needs in mechanically ventilated surgical ICU patients. Furthermore, Kugler *et al.*[24] reported that low-dose ketamine infusion reduced oral morphine equivalent utilization in elderly patients with multiple rib fractures and injury severity score ≥15 at the 12–24-h period. Our clinical trial found similar results of less total morphine requirement in the ketamine group.

Dexmedetomidine use increased the risk of bradycardia (Relative Risk - RR, 2.80; 95% CI, 1.92–4.07; I^2 14 0%; moderate certainty) and hypotension (RR, 1.98; 95% CI, 1.32–2.98; I^2 14 11%; moderate certainty) compared to other sedation strategies (midazolam, antipsychotic, and placebo), according to a meta-analysis of seven studies on 494 patients using NIV.[19] Senoglu *et al.*[6] compared dexmedetomidine and midazolam infusion for sedation in noninvasive, mechanically ventilated ICU patients. They noticed that patients who received dexmedetomidine infusion had significantly lower heart rate levels than the midazolam group patients throughout the study period. Also, in our patient populations, the dexmedetomidine group had a significantly lower heart rate than the ketamine group during the second session. This can be explained by the dexmedetomidine-mediated central inhibition of sympathetic outflow and the circulating level of catecholamines.[11]

Patients in the current study were discharged from the ICU after a mean length of stay of 6.0 ± 2.0 days, with no significant difference between groups. Another study found that the length of stay in critical care for all intubated and nonintubated patients receiving dexmedetomidine infusion ranged from 3 to 8 days.[5] None of our patients needed invasive ventilation due to signs of respiratory depression or deeper sedation.

Our study has some limitations. First, it is a single-center study with a small sample size limited to patients with chest trauma. Second, the RASS scoring system was used to ensure patients received the appropriate sedative dose, while the bispectral index monitoring was unavailable. Third, the lack of statistically significant differences in secondary complications between groups could be explained by the fact that our study was not powered to detect statistically significant differences in secondary side effects.

Conclusions

Dexmedetomidine and ketamine infusions improved patient tolerance and prolonged NIV session durations

compared to placebo in patients receiving NIV after blunt chest injuries. However, the length of the NIV sessions did not differ significantly between the two groups. The dexmedetomidine group experienced more profound sedation and had a lower RASS score than the ketamine and placebo groups. In contrast, the ketamine group had better pain control, a lower VAS score, and a lower total morphine requirement than the dexmedetomidine and placebo groups.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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