The Efficacy of Dexmedetomidine in Patients with Noninvasive Ventilation: A Preliminary Study

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BACKGROUND: Agitation is associated with failure of noninvasive ventilation (NIV). We investigated the effect of dexmedetomidine in patients with NIV.
METHODS: This was a prospective clinical investigation in an intensive care unit. Dexmedetomidine was infused in 10 patients in whom NIV was difficult because of agitation.
RESULTS: Ramsay and Richmond Agitation-Sedation Scale scores were maintained at 2.94 ± 0.94 and -1.23 ± 1.30, respectively. All patients were successfully weaned from NIV, and the respiratory state was not worsened.
CONCLUSION: This study shows that dexmedetomidine is an effective sedative drug for patients with NIV.
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Noninvasive ventilation (NIV) is extremely effective for treatment of respiratory failure associated with acute cardiogenic pulmonary edema and exacerbation of chronic obstructive pulmonary disease.[1–4] Its usefulness has also been suggested for other acute respiratory failures, such as in postoperative[5] and immunocompromised patients.[6]

However, delirium and agitation cause serious complications,[7,8] and even if indicated, NIV sometimes fails with these complications.[9] In this study, we hypothesized that dexmedetomidine would be effective as a sedative during NIV, and investigated whether dexmedetomidine can be used without adversely affecting the respiratory state of patients on NIV.

METHODS

The study was approved by the Committee on Human Subjects of Nippon Medical School. Although all patients received information about this study as a part of the process of informed consent, their understanding was insufficient because of agitation. Therefore, the information was provided to the patient's next of kin, whose consent was obtained before study entry.

The study population consisted of 10 patients with acute respiratory failure who were given NIV because of dyspnea of sudden onset, typical findings on chest radiograph (e.g., bilateral infiltrates, perihilar bat wing appearance, Kerley B lines, etc.), or signs of acute respiratory distress defined by hypoxemia (Pao_2/Fio_2 <200 mm Hg), and who were admitted to the intensive care unit (ICU). Inclusion criteria were patients receiving NIV who were subsequently uncooperative rated as 1 on the Ramsay score and +1 or more on the Richmond Agitation-Sedation Scale (RASS) (Tables 1 and 2).[10,11] Exclusion criteria were poor respiratory state requiring immediate intubation, severe hemodynamic instability, hepatic failure, renal failure, digestive tract hemorrhage, or a do-not-resuscitate or do-not-intubate order. NIV was performed using a BiPAP Vision respiratory support system (Respironics Inc., Murrysville, PA).

Table 1. Ramsay Score[10]

1.	Anxious and agitated or restless or both
2.	Cooperative, oriented, and tranquil
3.	Responding to commands only
4.	Brisk response to light glabellar tap
5.	Sluggish response to light glabellar tap
6.	No response to light glabellar tap

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Table 2. Richmond Agitation-Sedation Scale[11]

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator asynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, in response to voice
−2	Light sedation	Briefly (less than 10 s) awakens with eye contact in response to voice
−3	Moderate sedation	Any movement (but no eye contact) in response to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Table 3. Patients' Clinical Characteristics

Patient	Age (yr)	Sex	Indication	NIV mode (cm H_2O)	NIV setting	NIV duration (h)	ICU length of stay (d)
1	68	M	Postoperative respiratory failure	CPAP	10	18	28
2	72	F	Postoperative respiratory failure	CPAP	6	16	16
3	68	F	Postoperative respiratory failure	CPAP	8	36	8
4	78	M	Postoperative respiratory failure	CPAP	6	13	2
5	79	M	Acute cardiogenic	CPAP	10	10	7
6	63	M	Kyphoscoliosis	CPAP	8	72	13
7	80	F	Acute cardiogenic pulmonary edema	CPAP	8	19	24
8	46	M	Acute cardiogenic pulmonary edema	CPAP	12	45	9
9	76	M	Postoperative respiratory failure	Bilevel-PAP	IPAP8/EPAP4	15	2
10	80	M	Postoperative respiratory failure	CPAP	8	31	4

NIV = noninvasive ventilation; ICU = intensive care unit; CPAP = continuous positive airway pressure; Bilevel-PAP = bilevel positive airway pressure; IPAP = inspiratory positive airway pressure; EPAP = expiratory positive airway pressure.

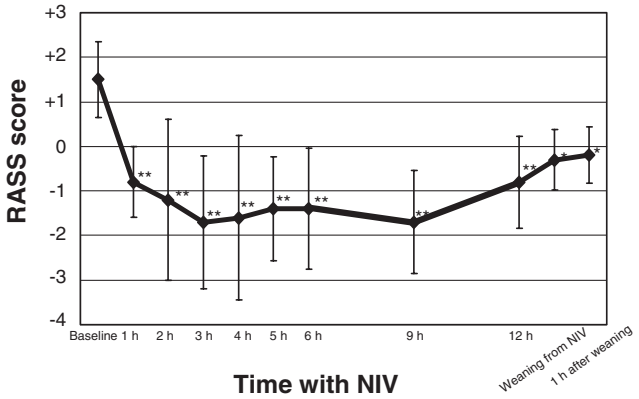

Figure 1. Change in Richmond Agitation-Sedation Scale score. Differences from baseline: $*P < 0.01$, $**P < 0.001$.

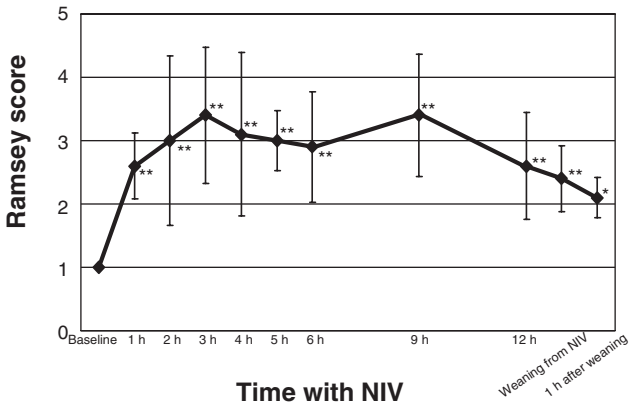

Figure 2. Change in Ramsay score. Differences from baseline: $*P < 0.05$, $**P < 0.001$.

After confirmation of response level (as measured by both Ramsay score and RASS score), administration of dexmedetomidine was started either at an initial loading dosage of 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ over 5 min, followed by continuous infusion at a dosage range of 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ to 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$, or by continuous infusion at a dosage of 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$. The infusion rate was adjusted to maintain a target sedation level of Ramsay score 2–3 and RASS score 0 to −2. The following evaluation

Table 4. Changes in Arterial Blood Gas Values, Respiratory Rate, and Hemodynamics (*Continued on page 170*)

Variable	Baseline	1 h	2 h	3 h	4 h
pH	7.38 ± 0.05	7.40 ± 0.05	7.40 ± 0.03	7.40 ± 0.03	7.41 ± 0.03*
Pao_2/Fio_2	219 ± 107	256 ± 116	272 ± 122	273 ± 78	270 ± 103
$Paco_2$ (mm Hg)	45.8 ± 15.3	42.5 ± 12.9	42.2 ± 11.8	42.3 ± 11.5	42.2 ± 12.5
Respiratory rate (breaths/min)	29.0 ± 3.5	24.8 ± 6.4	23.7 ± 6.4*	22.5 ± 3.6*	25.5 ± 7.9
Heart rate (bpm)	95.4 ± 15.2	82.2 ± 11.1†	78.3 ± 10.6†	76.9 ± 7.6†	77.8 ± 11.9†
Systolic blood pressure (mm Hg)	142 ± 25	121 ± 28*	116 ± 22†	116 ± 27†	123 ± 20
Diastolic blood pressure (mm Hg)	65 ± 15	52 ± 17*	50 ± 12*	56 ± 11	63 ± 12

Data are expressed as mean ± sd.

Differences from baseline: * $P < 0.05$, † $P < 0.01$.

items were recorded: presence of tracheal intubation; presence of complications of sedation; Ramsay score; RASS score; vital signs including arterial blood pressure, heart rate, and respiratory rate; and arterial blood gas analysis data. These variables were measured immediately before the start of administration of dexmedetomidine, every hour from 1 to 6 h after the start of administration, then every 3 h until 12 h after the start, and at NIV weaning. Criteria for NIV weaning were disappearance of dyspnea: Fio_2 ≤0.4, continuous positive airway pressure (CPAP) ≤4 cm H_2O, and Pao_2 ≥100 mm Hg for CPAP mode; or Fio_2 ≤0.4, pressure support level ≤4 cm H_2O, positive end-expiratory pressure ≤4 cm H_2O, and Pao_2 ≥100 mm Hg for bilevel-positive airway pressure (Bilevel-PAP) mode; plus no infiltrative shadow on the chest radiograph.

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL). The results are expressed as mean ± sd. Analysis of differences among the 11 time periods was performed with the general linear model module-repeated measures test, with the variable "time" as within factor. The residual variance was used as test factor and Dunnett's multiple comparison as *post hoc* test. Probabilities of <0.05 were considered significant.

RESULTS

Patient baseline characteristics are shown in Table 3. At baseline, all patients showed response levels of Ramsay score 1 and RASS score 1.5 ± 0.8. Maintenance of Ramsay scores at 2.94 ± 0.94 and RASS scores at −1.23 ± 1.30 and obtainment of effective sedation were demonstrated in all cases during dexmedetomidine infusion (Figs. 1 and 2).

Baseline measures were taken within 5.7 ± 7.6 h (range: 10 min to 16.5 h) from the time NIV was started. The total infusion time of dexmedetomidine was 16.5 ± 9.7 h (range: 9.3–43.7 h). Start settings of NIV were nine in CPAP and one in Bilevel-PAP mode at the time of dexmedetomidine start (Table 3). One of nine patients managed in CPAP mode was switched to Bilevel-PAP (30 min after the start of dexmedetomidine infusion), and one patient managed in Bilevel-PAP mode was switched to CPAP mode 30 min after the start of dexmedetomidine infusion. Although heart rate and arterial blood pressure decreased as intended, neither bradycardia nor excessively low arterial blood pressure was induced (Table 4). Respiratory rate decreased as intended 2 h after the start of dexmedetomidine infusion. The Pao_2/Fio_2 ratio and $Paco_2$ improved significantly (Table 4). All patients were successfully weaned from NIV, with none intubated, and all were discharged from the ICU alive. Other types of sedatives and analgesics were administered in two patients during dexmedetomidine infusion. One patient strongly wished to sleep in the night, and was infused with propofol at 20 mg/h for 6 h. Another patient was treated with 2 mg morphine for cardiogenic pulmonary edema.

All patients could cough and expectorate without assistance. None developed pneumonia during their stay in the ICU.

DISCUSSION

The present study used dexmedetomidine in patients who became agitated during NIV, and demonstrated its efficacy for sedation. In this study, all patients were successfully weaned from NIV and discharged from the ICU without experiencing aggravation of the respiratory state. All patients satisfied the target criteria of a Ramsay score of 2 or more and a RASS score of 0 or less within 1 h, experiencing adequate sedation even at low initial loading dose or without an initial loading dose. Although the present study showed no substantial changes in hemodynamics in any patient, an initial loading dose of dexmedetomidine may cause cardiovascular adverse drug reactions such as hypertension, hypotension, or bradycardia.[12] Results of this study suggest that for agitation at the level of severity seen in the present population, dexmedetomidine initiated at a low initial loading dose followed by continuous infusion can provide adequate sedation and safer control, compared with conventional sedatives. In conclusion, the present study demonstrates that dexmedetomidine, a sedative unlikely to cause respiratory depression, provides the possibility of achieving effective sedation

Table 4. *Continued*

5 h	6 h	9 h	12 h	Weaning from NIV	1 h after weaning
7.42 ± 0.03†	7.42 ± 0.03†	7.43 ± 0.02†	7.42 ± 0.02†	7.43 ± 0.03†	7.42 ± 0.05†
275 ± 106	294 ± 103*	295 ± 116*	281 ± 97	298 ± 93*	238 ± 95
41.5 ± 13.7*	41.7 ± 13.2	41.2 ± 14.4*	41.9 ± 13.1	41.5 ± 13.4*	42.6 ± 19.6
22.9 ± 3.0†	24.7 ± 6.7	23.8 ± 4.4*	24.6 ± 4.7	23.6 ± 3.8*	23.3 ± 4.2*
75.6 ± 8.3†	76.1 ± 10.1†	76.0 ± 12.2†	74.2 ± 7.4†	74.2 ± 7.5†	74.5 ± 8.4†
115 ± 25†	117 ± 17†	113 ± 20†	109 ± 17†	113 ± 13†	111 ± 14†
59 ± 10	59 ± 11	51 ± 8*	54 ± 11	54 ± 11	52 ± 13*

during NIV, ultimately leading to an increase in the rate of NIV success.

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