Effect of doxapram on the electrical activity of the diaphragm waveform pattern of preterm infants

Araki, Ryosuke; Tomotaki, Seiichi; Akita, Mitsuyo; Motokura, Kouji; Tomobe, Yutaro; Shimotsuma, Taiki; Hanaoka, Shintaro; ... Niwa, Fusako; Takita, Junko; Kawai, Masahiko

Effect of doxapram on the electrical activity of the diaphragm waveform pattern of preterm infants

Ryosuke Araki MD; Seiichi Tomotaki MD, PhD; Mitsuyo Akita MD; Kouji Motokura MD; Yutaro Tomobe MD; Taiki Shimotsuma MD; Shintaro Hanaoka MD, PhD; Hiroko Tomotaki MD; Kogoro Iwanaga MD; Fusako Niwa MD, PhD; Junko Takita MD, PhD; Masahiko Kawai MD, PhD

Department of Pediatrics, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

Corresponding Author: Ryosuke Araki, Department of Pediatrics, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

E-mail: r_araki@kuhp.kyoto-u.ac.jp; Tel: +81-75-751-3291; Fax: +81-75-751-2361

Conflicts of Interest and Source of Funding: None declared.

Keywords: bronchopulmonary dysplasia; neonatal intensive care units; Respiratory system agents

Running Head: Doxapram for electrical activity of the diaphragm

Abstract

Objective

This study aimed to evaluate the change in the waveform pattern of the electrical activity of the diaphragm (Edi) following the administration of doxapram in extremely preterm infants ventilated with neurally adjusted ventilatory assist (NAVA).

Study Design

We conducted this retrospective cohort study in our neonatal intensive care unit between November 2019 and September 2021. The study participants were extremely preterm infants under the gestational age of 28 weeks who were ventilated with NAVA and administered doxapram. We collected the data of the Edi waveform pattern and calculated the proportion. To analyze the change in the proportion of the Edi waveform pattern, we compared the proportion of the data for 1 hour before and after doxapram administration.

Results

Ten extremely preterm infants were included. Almost all the patients' respiratory condition improved after doxapram administration. The ventilatory parameters—Edi peak, Edi minimum, peak inspiratory pressure, time in backup ventilation, and number of switches to backup ventilation—did not change significantly. However, the proportion of phasic pattern significantly increased (before: 46% vs. after: 72%; $p < 0.05$), whereas the central apnea pattern significantly decreased after doxapram administration (before: 31% vs. after: 8.3%; $p < 0.05$). The proportion of irregular low-voltage patterns tended to decrease, albeit with no significant changes.

Conclusion

Our results indicated that the proportion of Edi waveform patterns changed following

doxapram administration. Edi waveform pattern analysis could be a sensitive indicator of effect with other intervention for respiratory conditions.

INTRODUCTION

Recently, an increasing number of studies have reported on the effect of neurally adjusted ventilatory assist (NAVA) to prevent brochopulmonary dysplasia (BPD) [1-4]. Successful ventilation with NAVA depends on the patients' spontaneous breathing. However, as extremely preterm infants have only poor spontaneous breathing [5], there were some cases in which NAVA did not work effectively even though the ventilator settings were adjusted precisely [6].

Doxapram has been known to be effective for reducing apneic spell and invasive mechanical ventilation days by stimulating peripheral and central chemoreceptors in the respiratory center [7]. Many studies on doxapram have focused on preventing apnea in infants supported with noninvasive mechanical ventilation [8-10]. However, we speculated that doxapram could also be effective in infants supported with intubation and invasive mechanical ventilation, particularly NAVA.

Previously, we reported that the electrical activity of the diaphragm (Edi) waveform pattern was associated with peripheral oxygen saturation (SpO_2) of the infants ventilated with NAVA [11]. In that report, we did not consider the effect of any medications, such as caffeine citrate or doxapram. Furthermore, no reports have described the association between doxapram and Edi waveform pattern. Hence, in this study, we analyzed the Edi waveform patterns and evaluated the mechanism of the effect of doxapram on the Edi waveform pattern of infants ventilated with NAVA. We hypothesized that in addition to stimulating the respiratory center, altering the Edi waveform pattern could be a mechanism underlying the effect of doxapram.

This study aimed to evaluate the change in the proportion of the Edi waveform pattern following doxapram administration.

MATERIALS AND METHODS

Patients

We conducted this retrospective cohort study in a single level III neonatal intensive care unit (Kyoto University Hospital, Kyoto, Japan). We included extremely preterm infants born at our hospital between November 2019 and September 2021 who were under the gestational age of 28 weeks, ventilated with NAVA delivered by Servo-n® (Maquet, Critical Care AB, Solna, Sweden), and administered doxapram.

Indication and dosing of doxapram

The ventilator settings of NAVA were adjusted according to the methods described in our previous study [11]. When the infants demonstrated any instability in their respiratory function despite being supported with precisely adjusted ventilator settings of NAVA, we resorted to administering doxapram. In addition, we administered doxapram a few days before extubation to prevent reintubation due to the patients' poor spontaneous breathing.

Accorting to our unit protocol based on pharmaceutical reference in Japan, doxapram was administered intravenously with 0.3–0.4 mg/kg/hour (as nearly as close to 0.4 mg/kg/hour). At our institution, we routinely administer caffeine citrate on the 4th or 5th days of life in extremely preterm infants; hence, all patients were already administered caffeine citrate before doxapram administration.

Data collection

Patient characteristics and clinical course were collected from medical records. Edi waveforms and pressure and flow supplied from the ventilator were recorded

continuously using the software SERVO CONNECT (Fukuda Denshi Co. Ltd., Tokyo, Japan). We defined the valid timing for analysis when the infants had not been manipulated and the ventilator setting had not been changed for at least 3 hours. The collected data were analyzed for 1 hour before and after doxapram administration in each patient. For the data collected before doxapram administration, we analyzed the data just before doxapram administration in those who met the abovementioned valid timing. For the data collected after doxapram administration, we analyzed the data of the first hour after at least 3 hours had passed since doxapram administration in those who met the abovementioned valid timing. No interventions, including changing ventilator settings and prescribing medication, were performed in the time between the two data collection points.

We collected the ventilatory parameters at the same time points as mentioned above from the data stored in the ventilator. These parameters were Edi peak, Edi minimum, peak inspiratory pressure, time in backup ventilation, and the number of switches to backup ventilation.

SpO_2 was recorded using a central monitoring system (Phillips Information Management System®; Phillips Japan, Japan) every minute. We defined desaturation as a decrease in $SpO_2 < 85\%$ because our setting of the lower limit of SpO_2 was routinely 85% as part of our respiratory strategy.

Data analysis

To evaluate the clinical effect of doxapram, we compared median SpO_2, frequency of desaturation, and fraction of inspired oxygen concentration (FiO_2) before and after doxapram administration in each patient.

As described in a previous report, the collected data of Edi waveform patterns were classified into four patterns as follows: 1) phasic pattern, 2) central apnea pattern, 3) irregular low-voltage pattern, and 4) tonic burst pattern [11] (as shown in Figure 1). Edi waveforms were indicated in 1 window every 10 seconds. The classification of Edi waveform patterns shown in each window was performed by one investigator (blinded clinical data). We calculated the proportion of each waveform pattern for every collected hour.

To evaluate the change in the proportion of Edi waveform pattern caused by doxapram administration, we compared the proportion of each waveform pattern before and after doxapram administration. In addition, we compared the collected ventilatory parameters before and after doxapram administration.

The study protocol was approved by the local medical ethics committee (reference number R2154).

Statistical analysis

Statistical analysis was performed using R statistical software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) using the EZR application. Collected data were expressed as median (interquartile range [IQR]) and n (%). Continuous variables were analyzed using Mann–Whitney U test. A p-value of <0.05 indicated statistical significance.

RESULTS

Patient characteristics

Ten extremely preterm infants ventilated with NAVA and administered doxapram were included. The patient characteristics are shown in Table 1 (detailed data of each patient are presented in E-table 1). The median gestational age and birth weight of the included infants were 25.1 weeks (IQR: 24.4–25.4 weeks) and 631 g (IQR: 521–747 g), respectively. The median day and postconceptional age at the initiation of doxapram administration on ventilation with NAVA were 26 days (IQR: 22–29 days) and 29.1 weeks (IQR: 28.6–29.5 weeks), respectively. The median dose of doxapram was 0.38 mg/kg/hour (IQR: 0.37–0.4 mg/kg/hour).

Effect of doxapram on SpO_2, FiO_2, and frequency of desaturation

A comparison of SpO_2, frequency of desaturation, and FiO_2 before and after doxapram administration is shown in Figure 2. In 8 of the 10 patients, SpO_2 increased, frequency of desaturation decreased, and FiO_2 decreased after doxapram administration. Unfavorable changes in SpO_2 and frequency of desaturation were observed in two and one patients, respectively (detailed data are shown in E-table 2)

We did not observe any severe adverse reactions with doxapram, such as necrotizing enterocolitis. But, eight of ten infants had presented hypokalemia and needed correction with oral potassium preparation administration.

Comparison of the proportion of Edi waveform pattern

A comparison of the proportion of Edi waveform pattern before and after doxapram administration is shown in Table 2. The proportion of phasic pattern was significantly

increased after doxapram administration [before: 46% (IQR: 40%–63%) vs. after: 72% (IQR: 64%–76%); p = 0.006]. Conversely, the proportion of central apnea pattern was significantly decreased after doxapram administration [before: 31% (IQR: 9.7%–43%) vs. after: 8.3% (IQR: 8.3%–15%); p = 0.03]. The proportion of irregular low-voltage pattern was also decreased, albeit not significantly [before: 3.8% (IQR: 0%–5.6%) vs. after: 0% (IQR: 0%–4.2%); p = 0.28]. A comparison of the proportion of each Edi waveform pattern in each patient is shown in Figure 3 (detailed data are shown in E-table 3).

Comparison of ventilatory parameters

A comparison of the ventilatory parameters before and after doxapram administration is shown in Table 3. Time in backup ventilation was decreased, albeit not significantly. Other parameters showed only a slight difference before and after doxapram administration.

DISCUSSION

We indicated that the proportion of phasic pattern was significantly increased, whereas that of central apnea pattern was significantly decreased after doxapram administration. Our previous report highlighted the association between the proportion of Edi waveform pattern and SpO_2. Stable SpO_2 was represented by a high frequency of the phasic pattern. This pattern was increased after doxapram administration. Conversely, unstable SpO_2 was represented by a high frequency of the central apnea pattern or irregular low-voltage pattern, which may ultimately result in failure to ventilate with NAVA [11]. These patterns were decreased after doxapram administration in the present study. Therefore, it can be assumed that the improvement in the respiratory conditions following doxapram administration resulted from the associated changes in the proportion of Edi waveform pattern.

In a previous report, the effects of doxapram were analyzed via transcutaneous electromyography of the diaphragm [12]. However, this study did not report a significant difference in diaphragmatic activity following doxapram administration. Thus, the report concluded that doxapram only regulates respiratory drive and does not affect respiratory muscle activity. In our study, although there was no significant difference, the proportion of irregular low-voltage pattern tended to decrease after doxapram administration. We considered that the decreased proportion of irregular low-voltage pattern could have changed to the phasic pattern. Therefore, doxapram administration significantly affected the respiratory drive (as demonstrated by the decreased central apnea pattern) and Edi waveform patterns (as evidenced by the increased phasic pattern and decreased irregular low-voltage pattern).

Ventilatory parameters did not reveal any significant difference before and after

doxapram administration. This suggests that evaluating Edi waveform patterns could be a sensitive indicator of the effect of interventions to improve the respiratory condition. However, the other parameters, including Edi peak, Edi minimum, peak inspiratory pressure, time in backup ventilation, and number of switches to backup ventilation, may not serve as substitute indicators.

In our study, there were only two patients who were not improved their respiratory conditions with doxapram administration (case1 and 9). They had some notable features in the proportion of Edi waveform pattern. The proportion of phasic pattern before doxapram administration was relatively higher in these patients than in others who showed improvement in respiratory conditions. The proportion of central apnea pattern before doxapram administration was relatively lower in these patients than in others who showed improvement in respiratory conditions. These results indicated that the favorable effect of doxapram is more evident in patients who had a lower proportion of phasic pattern or higher proportion of central apnea pattern. However, although some patients had a high proportion of phasic pattern and low proportion of central apnea pattern, they showed improvement in their respiratory conditions following doxapram administration. Therefore, there is a need for further research to evaluate the different effects of doxapram administration. This may facilitate the prediction of the effect of doxapram before its administration. In addition, the effects of other interventions on respiratory conditions could be evaluated by analyzing the Edi waveform pattern.

Our study had several limitations. The small number of patients was the main limitation. Furthermore, because this was a retrospective study and we defined the valid timing for the analysis, we could only collect and analyze the data for each participant at two time points only: 1 hour before and after doxapram administration. To increase the reliability

of our results, more patients should be analyzed. There is a need to conduct a prospective study. Also, the study population was limited to only infants supported with invasive ventilation (NAVA). Infants who were supported with noninvasive NAVA (NIV-NAVA) were not included. Hence, the study results may not be generalizable to all infants under ventilatory support. Considering that the frequency of doxapram administration in infants supported with noninvasive ventilation is greater, there is a need for the same analysis in infants supported with NIV-NAVA.

Conclusion

Our results indicated that the proportion of Edi waveform patterns changed following doxapram administration. This change may demonstrate improvement in the respiratory condition of extremely preterm infants. We concluded that the Edi waveform pattern analysis could serve as a sensitive indicator of the effect with other interventions in patients ventilated with NAVA.

Acknowledgement

We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Conflict of interest

No conflict of interest declared

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Rong X, Liang F, Li YJ, Liang H, Zhao XP, Zou HM, Lu WN, Shi H, Zhang JH, Guan RL, et al. Application of neurally adjusted ventilatory assist in premature neonates less than 1,500 grams with established or evolving bronchopulmonary dysplasia. Front Pediatr 2020;24:110.
2. Jung YH, Kim HS, Lee J, Shin SH, Kim EK, Choi JH. Neurally adjusted ventilatory assist in preterm infants with established or evolving bronchopulmonary dysplasia on high-intensity mechanical ventilatory support: A single-center experience. Pediatr Crit Care Med 2016;17:1142-1146.
3. Rossor TE, Hunt KA, Shetty S, Greenough A. Neurally adjusted ventilatory assist compared to other forms of triggered ventilation for neonatal respiratory support. Cochrane Databese Syst Rev 2017;27:10:CD012251.
4. Kallio M, Koskela U, Peltoniemi O, Kontiokari T, Pokka T, Suo-Palosaari M, Saarela T. Neurally adjusted ventilatory assist (NAVA) in preterm newborn infants with respiratory distress syndrome-a randomized controlled trial. Eur J Pediatr 2016;175:1175-1183.
5. Eichenwald EC, Committee on Fetus and Newborn, American Academy of Pediatrics. Apnea of Prematurity. Pediatrics 2016;137:e20153757.
6. Stein H, Howard D. Neurally adjusted ventilatory assist in neonates weighing < 1500 grams: A retrospective analysis. J Pediatr 2012;160:786-789.
7. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. J Pediatr 1990;116:648-653.

8. liegenthart RJ, Ten Hove CH, Onland W, van Kaam AH. Doxapram treatment for apnea of prematurity: A systematic review. Neonatology 2017;111:162-171.
9. Henderson-Smart D, Steer P. Doxapram treatment for apnea in preterm infants. Cochrane Databese Syst Rev 2004;18:CD000074.
10. Ten Hove CH, Vliegenthart RJ, Te Pas AB, Brouwer E, Rijken M, van Wassenaer-Leemhuis AG, van Kaam AH, Onland W. Long-term neurodevelopmental outcome after doxapram for apnea of prematurity. Neonatology 2016;110:21-26.
11. Araki R, Tomotaki S, Akita M, Motokura K, Tomobe Y, Yamauchi T, Hanaoka S, Tomotaki H, Iwanaga K, Niwa F, et al. Effect of electrical activity of the diaphragm waveform patterns on SpO_2 for extremely preterm infants ventilated with neurally adjusted ventilatory assist. Pediatr Pulmonol 2021;56:2094-2101.
12. de Waal CG, Hutten GJ, Kraaijenga JV, de Jongh FH, van Kaam AH. Doxapram treatment and diaphragmatic activity in preterm infants. Neonatology 2019;115:85-88.

Image legends

Figure 1. Representative waveforms for four Edi waveform patterns.

Pressure curves are shown in each upper row and Edi waveforms are shown in each lower row. A: Phasic pattern, B: central apnea pattern, C: tonic bursts pattern, D: irregular low-voltage pattern.

Figure 2. Comparison of SpO_2, frequency of desaturation, and FiO_2 before and after doxapram administration.

(a) SpO_2 (%), (b) frequency of desaturation (/hour), and (c) FiO_2 (%).

Figure 3. Change in the proportion of each Edi waveform pattern before and after doxapram administration in each patient.

(a) Phasic pattern, (b) central apnea pattern, (c) irregular low-voltage pattern, and (d) tonic burst pattern.