The Incidence and Severity of Hypocarbia in Neonates Undergoing General Anesthesia

Kristin Chenault, Mayuko Wakimoto, Rebecca Miller, and Joseph D Tobias

BACKGROUND: Extended periods of hypocarbia in preterm infants may be associated with intraventricular hemorrhage, periventricular leukomalacia, and bronchopulmonary dysplasia. To evaluate the current anesthetic practice in preterm neonates, we retrospectively reviewed the intraoperative course with regard to P_{aCO_2} and ventilation during non-cardiac surgical procedures in infants <60 weeks postmenstrual age. METHODS: This was a single-center, retrospective study during non-cardiac surgical procedures in neonates. Hyperventilation was defined as a $P_{aCO_2} \leq 35$ mm Hg, significant hyperventilation as a $P_{aCO_2} \leq 30$ mm Hg, and extreme hyperventilation as a $P_{aCO_2} \leq 25$ mm Hg. RESULTS: The study cohort included 112 neonates, with a median postnatal age of 40 weeks, median gestational age of 38 weeks, and median weight of 5 kg. Thirty-seven subjects (33%) had at least one arterial blood gas value that demonstrated hyperventilation. Thirteen (12%) were noted to have significant hyperventilation ($P_{aCO_2} \leq 30$ mm Hg) and 2 had extreme hyperventilation ($P_{aCO_2} \leq 25$ mm Hg). CONCLUSIONS: The incidence of at least one arterial blood gas that demonstrated inadvertent hyperventilation in neonates was high during intraoperative care. These data may provide the baseline for future studies that address more rigorous monitoring and control of P_{aCO_2} during intraoperative care. Although the duration of the anesthetic care and surgical procedure is brief compared with the neonatal ICU length of stay because there is no demonstrated benefit of hypocapnia and, in fact, well-documented harm associated with hyperventilation in neonates, care should be directed at limiting inadvertent hyperventilation. (ClinicalTrials.gov registration NCT03823716.) *Key words: infant; newborn; hyperventilation; respiratory therapy; anesthesia; general; hypercapnia; ventilation.*
[Respir Care 2020;65(8):1154–1159. © 2020 Daedalus Enterprises]

Introduction

Arterial P_{aO_2} is an important determinant of cerebral blood flow. Hypercapnia leads to cerebral vasodilation and an increase in cerebral blood flow, whereas hypocapnia leads to cerebral vasoconstriction and decreased cerebral blood flow.[1] Results of previous research demonstrated that inadvertent intraoperative hyperventilation in the pediatric population occurs.[2] The practice of intentionally providing a high minute ventilation during anesthetic care was founded on various misconceptions, including the premise that hypocarbia augmented systemic oxygen delivery through its effects on the alveolar P_{aO_2}.[3] This tenet focused only on the alveolar gas equation, in which a decline in the P_{aO_2} leads to an increased P_{aO_2}, provided that atmospheric pressure and water vapor pressure in the enclosed alveolus is maintained.

Drs Chenault, Wakimoto, Miller, and Tobias are affiliated with the Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio. Drs Chenault and Tobias are affiliated with the Department of Anesthesiology and Pain Medicine, The Ohio State University College of Medicine, Columbus, Ohio. Dr Tobias is affiliated with the Department of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio.

Dr Chenault presented a version of this paper at Anesthesiology annual meeting held October 13, 2018 in San Francisco, California.

The authors have disclosed no conflicts of interest.

Correspondence: Kristin Chenault MD, Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205. E-mail: Kristin.Chenault@Nationwidechildrens.org.

DOI: 10.4187/respcare.07382

Studies conducted in neonatal ICUs demonstrated that extended periods of hypocarbia in preterm infants is associated with an increase in severe intraventricular hemorrhage, periventricular leukomalacia, and bronchopulmonary dysplasia.[4,5] As such, close attention to factors that control the arterial pressure of carbon dioxide in the blood (P_{aCO_2}) may be indicated during the perioperative period. To evaluate current anesthetic practice in the care of preterm infants and neonates, we retrospectively reviewed the intraoperative course with regard to P_{aCO_2} and ventilation during non-cardiac surgical procedures in infants who were <60 weeks postmenstrual age. Our primary aim was to determine the incidence of inadvertent hyperventilation, investigate the minute ventilation required to provide a normocarbic state, and to evaluate characteristics associated with an increased risk of inadvertent and significant hyperventilation.

QUICK LOOK

Current knowledge

Extended periods of hypocarbia have been shown to be associated with an increased risk of poor neurologic outcomes in the neonatal ICU population. Although close control of P_{aCO_2} is generally recommended during ICU care, there has been less attention to these issues during intraoperative care.

What this paper contributes to our knowledge

In this single-center retrospective observational study, the incidence of intraoperative hyperventilation ($P_{aCO_2} \leq 35$ mm Hg) was high. The subjects who had a lower body weight were more likely to have significant hyperventilation. Given the retrospective nature of the study, no impact on clinical outcome could be attributed to these findings. Although it is unknown if limited periods of hyperventilation are detrimental, further evaluation of intraoperative ventilation strategies and CO_2 monitoring for this population is warranted.

Methods

This study was approved by institutional review board at Nationwide Children's Hospital (17-00032) and registered at clinicaltrials.gov. We retrospectively identified non-cardiac surgical procedures performed over a 3-y period in neonates <60 weeks postmenstrual age. Procedures were selected for analysis if they were performed with the patients under general anesthesia with pressure-controlled mechanical ventilation with invasive arterial access, and if arterial blood gas (ABG) samples were obtained during surgery. All intraoperative ABG results were obtained for each case, and ventilator parameters were determined at the time of each ABG sample. Patients were excluded from the study if mechanical ventilation was not in use during any of the available ABG samples.

Hyperventilation was defined based on the identification of a $P_{aCO_2} \leq 35$ mm Hg and was considered significant if the P_{aCO_2} was ≤ 30 mm Hg. Extreme hyperventilation was defined as $P_{aCO_2} \leq 25$ mm Hg. Independent variables in the analysis included tidal volume, peak inspiratory pressure, PEEP, F_{IO_2}, and breathing frequency. Minute ventilation was calculated as the product of the tidal volume and breathing frequency. Additional data extracted from the ABG results included P_{aO_2}, pH, and base deficit or excess. Subject and procedure characteristics obtained for the study included subject gestational age, postnatal age, sex, weight, comorbidities (congenital heart disease, respiratory disease, neurologic disease, renal disease, and hematologic disease), and procedure type (general pediatric surgery, neurosurgery, or other).

In the initial descriptive analysis, the occurrence of hyperventilation was examined at any available time point (ABG sample) during each procedure when mechanical ventilation was in use. Categorical data were summarized as counts with percentages, and continuous data were summarized as means ± SDs, or medians with interquartile ranges (IQR). Ventilator settings (averaged across available ABG observations from each procedure), ABG results (averaged across available observations), and other subject and procedure characteristics were compared between procedures according to whether hyperventilation had occurred.

Data were compared between these groups by using unpaired *t* tests or rank-sum tests for continuous measures, and chi-square tests for categorical measures. In further analysis, multivariable mixed effects regression was used to predict significant hyperventilation at the time of a given ABG sample, as a function of ventilator parameters at that time. In this analysis, a procedure-level random effect was included to capture residual variation in the risk of significant hyperventilation according to subject and procedure characteristics.[6] ABG samples with incomplete data on minute ventilation, peak inspiratory pressure, PEEP, or oxygen saturation were excluded from this portion of the analysis. Data analysis was performed in Stata/IC 14.2 (StataCorp, College Station, Texas), and 2-tailed $P < .05$ was considered statistically significant.

Results

We identified 4,268 patients who were <60 weeks postmenstrual age and who, in 2014–2017, underwent non-cardiac surgical procedures with the patient under general anesthesia. Of these patients, 154 had ABG samples obtained during surgery. In this group, 33 patients were excluded for not having an arterial line placed, and 9 were excluded because mechanical ventilation was not in use

Table 1. Subject and Ventilation Characteristics According to the Occurrence of Significant Hyperventilation

Characteristics	Significant Hyperventilation ($n = 13$)*	No Significant Hyperventilation ($n = 99$)	P
Subject characteristics			
Female, *n* (%)	6 (46)	41 (41)	.75
Postnatal age, median (IQR) d	40 (36–48)	40 (37–50)	.81
Gestational age, median (IQR) d	37 (36–38)	38 (36–39)	.12
Weight, median (IQR) kg	4 (3–4)	5 (4–7)	.046
Comorbid conditions, *n* (%)			
Congenital heart disease	5 (38)	40 (40)	>.99
Respiratory	7 (54)	65 (66)	.40
Neurologic	3 (23)	50 (51)	.08
Renal	3 (23)	16 (16)	.46
Hematologic	6 (46)	38 (38)	.76
Procedure type, *n* (%)			.52
General surgery	8 (62)	73 (74)	
Neurosurgery	4 (31)	19 (19)	
Other	1 (8)	7 (7)	
Average ventilation characteristics			
Minute ventilation, median (IQR) mL	757 (548–1,141)	1,185 (896–1,380)	.01
Tidal volume, median (IQR) mL	37 (29–48)	41 (34–62)	.20
Tidal volume/weight, median (IQR) mL/kg	3 (2–3)	2 (1–3)	.07
Frequency, median (IQR) breaths/min	20 (15–22)	25 (20–30)	.030
pH, mean ± SD	7.4 ± 0.1	7.3 ± 0.1	.008
Base deficit, median (IQR)	5 (2–6)	4 (1–6)	.60
Peak inspiratory pressure, median (IQR) cm H_2O	19 (17–20)	20 (18–24)	.09
PEEP, median (IQR) cm H_2O	5 (4–5)	5 (4–6)	.25
Oxygen saturation, median (IQR) %	100 (99–100)	99 (94–100)	.09
P_{ETCO_2}, median (IQR) mm Hg	27 (21–32)	34 (28–37)	.007
V_D phys, median (IQR)	0.20 (0.04–0.34)	0.30 (0.16–0.41)	.13

$N = 112$.
* Defined as $P_{aO_2} \leq 30$ mm Hg.
IQR = interquartile range
P_{ETCO_2} = end-tidal carbon dioxide pressure
V_D phys = physiologic dead space calculated as $(P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$

when the ABG samples were collected, which resulted in a study cohort of 112 subjects (47 females, 65 males). The median (IQR) postnatal age was 40 (37–50) weeks, median (IQR) gestational age was 38 (36–39) weeks, and median (IQR) weight was 5 (4–6) kg. Comorbidities included congenital heart disease (45 [40%]), respiratory disease (72 [64%]), neurologic disease (53 [47%]), renal disease (19 [17%]), and hematologic disease (44 [39%]). Most subjects were undergoing general pediatric surgery procedures (81 [72%]), followed by neurosurgery (23 [21%]), and other surgery types (8 [7%]). Within general pediatric surgery, the most common procedure was exploratory laparotomy ($n = 19$), followed by bronchoscopy ($n = 11$) and diaphragmatic hernia repair ($n = 9$). Thirty-seven subjects (33%) had at least one ABG value that demonstrated hyperventilation ($P_{aCO_2} \leq 35$ mm Hg). Thirteen (12%) were noted to have significant hyperventilation ($P_{aCO_2} \leq 30$ mm Hg) and 2 had extreme hyperventilation ($P_{aCO_2} \leq 25$ mm Hg), both with gestational ages of 38 weeks and postnatal ages of 48 and 49 weeks.

Subject and procedural characteristics are compared by occurrence of significant hyperventilation in Table 1 and by occurrence of any hyperventilation in Table 2. The subjects who experienced significant hyperventilation had a lower minute ventilation (median, 757 vs 1,185 mL; $P = .01$) and a lower breathing frequency (median, 20 vs 25 breaths/min; $P = .030$), compared with infants who did not experience significant hyperventilation. These differences were attenuated when comparing any versus no hyperventilation (Table 2). Among subject characteristics, weight was slightly lower in the subjects who experienced significant hyperventilation (median, 4 vs 5 kg; $P = .040$), but no other characteristics varied according to whether the subjects developed significant hyperventilation. The multivariable analysis included 249 ABG samples with complete data on minute ventilation, peak inspiratory pressure, PEEP, and O_2 saturation (Table 3) (between 1 and 7 ABG samples per subject). A higher minute ventilation at the time of a given ABG sample was associated with lower odds of significant hyperventilation, but this association did not reach statistical significance (odds

Table 2. Subject and Ventilation Characteristics According to the Occurrence of Hyperventilation

Characteristics	Hyperventilation ($n = 37$)*	No Hyperventilation ($n = 75$)	*P*
Subject characteristics			
Females, *n* (%)	13 (35)	34 (45)	.30
Postnatal age, median (IQR) d	40 (37–49)	40 (38–51)	.70
Gestational age, median (IQR) d	37 (36–38)	38 (36–39)	.17
Weight, median (IQR) kg	5 (4–6)	5 (4–7)	.86
Comorbid conditions, *n* (%)			
Congenital heart disease	15 (41)	30 (40)	.96
Respiratory	20 (54)	52 (69)	.11
Neurologic	15 (41)	38 (51)	.31
Renal	9 (24)	10 (13)	.15
Hematologic	18 (49)	26 (35)	.15
Procedure type, *n* (%)			.78
General surgery	26 (71)	55 (73)	
Neurosurgery	9 (24)	14 (19)	
Other	2 (5)	6 (8)	
Average ventilation characteristics			
Minute ventilation, median (IQR) mL	1092 (760–1358)	1187 (840–1368)	.32
Tidal volume, median (IQR) mL	41 (36–57)	41 (33–59)	.50
Tidal volume/weight, median (IQR) mL/kg	2 (1–3)	2 (1–3)	.34
Frequency, median (IQR) breaths/min	22 (17–27)	25 (20–31)	.07
pH, mean ± SD	7.4 ± 0.1	7.3 ± 0.1	<.001
Base deficit, median (IQR)	4 (0–6)	4 (2–6)	.23
Peak inspiratory pressure, median (IQR) cm H_2O	20 (18–22)	20 (17–24)	.67
PEEP, median (IQR) cm H_2O	5 (4–5)	5 (4–6)	.65
Oxygen saturation, median (IQR) %	100 (97–100)	99 (96–100)	.21
P_{ETCO_2}, median (IQR) mm Hg	29 (25–33)	34 (29–39)	.001
V_D phys, median (IQR)	6 (2–12)	12 (7–28)	<.001

N = 112.
* Defined as $P_{aO_2} \leq 35$ mm Hg.
IQR = interquartile range
P_{ETCO_2} = end-tidal carbon dioxide pressure
V_D phys = physiologic dead space calculated as $(P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$

Table 3. Hierarchical Logistic Regression of Ventilation Characteristics Associated With Significant Hyperventilation at Each Time Point Clustered by Procedure (249 arterial blood gas measurements)

Ventilation Characteristics	Odds Ratio	95% CI	*P*
Minute ventilation, 100 mL	0.8	0.7–1.0	.054
Peak inspiratory pressure, cm H_2O	1.1	1.0–1.4	.16
PEEP, cm H_2O	0.6	0.3–1.2	.14
Oxygen saturation, %	1.4	0.9–2.4	.15

ratio 0.8, 95% CI 0.7–1.0; $P = .054$). Peak inspiratory pressure, PEEP, and O_2 saturation were not associated with the risk of significant hyperventilation on this analysis.

Discussion

Our study identified that the incidence of any hyperventilation and significant hyperventilation in neonates during general anesthesia was 33% and 12%, respectively. There were only 2 subjects in the study cohort with extreme hyperventilation ($P_{aCO_2} \leq 25$ mm Hg). The subjects who had a lower body weight were more likely to have significant hyperventilation. All the subjects were managed by a pressure control ventilation mode, and multivariate analysis did not confirm any statistical significance with regard to subject or ventilation characteristics.

In recent years, significant data have emerged from neonatal ICUs with regard to the potential deleterious effects of hyperventilation on the central nervous and pulmonary systems. Two major determinants of long-term morbidity in preterm infants are intraventricular hemorrhage/periventricular leukomalacia and bronchopulmonary dysplasia. Hypocapnia in the neonate has been shown to be a risk factor for periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy, cognition development disorder, and auditory deficits.[7] The duration of hypocapnia has also been demonstrated to play a role in the incidence of periventricular leukomalacia, intraventricular hemorrhage, and

bronchopulmonary dysplasia. Ikonen et al[8] demonstrated that an increasing duration of hypocapnia ($P_{aCO_2} < 30$ mm Hg) in the first 72 h of life was associated with an increased severity of periventricular leukomalacia and subsequent development of neurologic impairment and cerebral palsy. A subsequent study by Erickson et al[4] demonstrated that an increasing duration of hypocarbia was associated with an increased incidence of bronchopulmonary dysplasia.

A decrease in the P_{aCO_2} will lead to cerebral vasoconstriction and to decreased cerebral blood flow and decreased cerebral oxygen delivery. These effects on the neonatal brain may be exaggerated or exacerbated in the operating room by other variables, such as hypotension, hyperoxia, hypoglycemia, anemia, and hyperthermia. As these data have emerged, there has been a shift in ventilation strategies in the neonatal ICU, with a focus on permissive hypercapnia guiding ventilation. However, these strategies may not be well known by anesthesia providers and have not necessarily been adopted during intraoperative anesthetic care.

During intraoperative care, even in previously intubated and mechanically ventilated neonates, patients are transported to the operating room. During an anesthetic procedure, ventilation parameters and requirements may be changed as an intraoperative ventilator is used or there may be variations in basal metabolic rate related to anesthetic agents or physiologic stresses imposed by the surgical procedure. The issues of intraoperative mechanical ventilation are compounded by difficulties with the accurate measurement of tidal volume and minute ventilation, especially in the neonatal population. This can be related to many factors, including the use of a cuffed versus uncuffed endotracheal tube, dead space in the anesthesia circuit, and the type of anesthesia ventilator used. Chambers et al[9] demonstrated that, not only do uncuffed endotracheal tubes exhibit a higher leak, independent of the mode of ventilation, but the delivered tidal volumes and leak percentage change over time, particularly when pressure-controlled ventilation is used. It is not unusual for flexible elbow connectors or heat-and-moisture exchangers to be added to a circuit, both of which contribute to an increase in circuit dead space.[10] Anesthesia ventilators equipped with compliance compensation have been shown to accurately deliver small tidal volumes, whereas those without this technology are far less accurate.[11]

A small percentage of neonates presenting to the operating room have an arterial line in situ or require one for the surgical procedure. ABG measurements only provide a single snapshot of ventilation, which makes following trends more difficult. End-tidal carbon dioxide pressure (P_{ETCO_2}) monitoring is standard in the operating room but is not standard in all neonatal intensive care settings. Various factors, including high fresh gas flows, sampling errors, small tidal volumes, ventilation-perfusion inequalities, and changes in dead space affect the accuracy of P_{ETCO_2} monitoring.[12] These factors affect the correlation between the P_{aCO_2} and P_{ETCO_2}, which makes the gradient variable during prolonged cases. Transcutaneous CO_2 monitoring has been shown to be as accurate as P_{ETCO_2} monitoring in patients with normal respiratory function and may be more accurate in patients with shunts or ventilation perfusion abnormalities; however, transcutaneous CO_2 is not readily available in most pediatric operating rooms.[12]

A previous prospective study from the neonatal ICU with a large cohort in Europe showed that the incidence of hypocapnia ($P_{CO_2} < 30$ mm Hg or 4 kPa) is relatively uncommon (4% of blood gases).[13] The most recent retrospective study from a single-center, neonatal ICU also demonstrated a very low incidence of hypocapnia ($P_{CO_2} < 30$ mm Hg), which is <2% of all the ABG samples.[14] Analysis of our data demonstrated that this incidence is higher during intraoperative care in the neonatal population. Our cohort of neonates revealed that one third had at least one ABG that demonstrated inadvertent hyperventilation, and 12% experienced significant hyperventilation with a $P_{aCO_2} \leq 30$ mm Hg. With the increasing volume of literature emerging with regard to deleterious effects of hypocapnia, continuous monitoring of ventilation in neonates during an anesthetic may be warranted.[14]

With our data, we were not able to compare the modes of ventilation and the incidence of hyperventilation because all the subjects were ventilated by using a pressure-control mode of ventilation. This strong preference for use of pressure control is likely institution-dependent and related to problems with measuring small tidal volumes with current anesthesia-based ventilators and flow meters. However, data from neonatal ICU studies does clearly demonstrate several advantages of volume-targeted modes of ventilation compared with pressure-limited modes of ventilation. Two different meta-analyses that compared volume-targeted to pressure-limited ventilation in preterm infants showed reductions in incidence of bronchopulmonary dysplasia, hypocarbia, grade III/IV intraventricular hemorrhage, pneumothorax, and duration of mechanical ventilation.[15,16] It is possible that, by decreasing the variability of delivered tidal volumes by using a volume-targeted mode of ventilation, there may be a decrease in volutrauma and lung injury. Reducing the incidence of hypocarbia and large variations in P_{aCO_2} may lead to more stable cerebral perfusion and, subsequently, less neonatal brain injury.[15]

Interestingly, we noted that the subjects in our study who experienced significant hyperventilation had a lower minute ventilation and breathing frequency than those who were not hyperventilated. This may be due to active adjustments made during surgery by anesthesia providers in response to ABG values. Without demonstrating a clear relationship between increased minute ventilation and decreased P_{aCO_2}, other factors may be playing a role in

determining P_{aCO_2} during the intraoperative period, including changes in dead space or ventilation-perfusion matching, depth of anesthesia, and metabolic rate (CO_2 production).

Permissive hypercapnia has become a commonly used ventilation strategy in neonatal intensive care settings.[17] However, analysis of our data demonstrates that inadvertent hyperventilation is common during intraoperative anesthetic care. Although it is unknown if these limited periods of hyperventilation are detrimental, when combined with other potential complications of surgery and anesthesia, including hypotension, bleeding and resultant anemia, and hypoglycemia, unintentional harm may occur in our youngest and most vulnerable population. Combined with the potential for anesthetic-induced neurotoxicity, it may be time to reevaluate our intraoperative ventilation strategies and CO_2 monitoring devices for this population.

The potential limitations of this study should be acknowledged. First, because we evaluated P_{aCO_2} data, we only included subjects who had an arterial line and ABG data during surgery. This might suggest that our patient population was comparatively sicker or the procedure was more invasive compared with the patients who did not require intraoperative arterial line or ABG sampling, thereby impacting the incidence of hyperventilation if it is more common in this subset of patients. Second, subject and ventilation characteristics data were limited in this study because we used a retrospective design. Therefore, other possible confounding factors related to hyperventilation, such as leak, type of endotracheal tube, and exact ventilation parameters, were not able to be captured. However, with these limitations in mind, this was the first study to our knowledge that investigated the incidence of inadvertent hyperventilation during intraoperative care in neonates.

Conclusions

These data may provide the baseline for future studies, addressing more rigorous monitoring and control of P_{aCO_2} during intraoperative care. Although the duration of the anesthetic care and surgical procedure is brief compared with the neonatal ICU length of stay because there is no demonstrated benefit of hypocapnia, care should be directed at limiting inadvertent hyperventilation.

REFERENCES

1. McCann ME, Schouten A. Beyond survival; influences of blood pressure, cerebral perfusion and anesthesia on neurodevelopment. Paediatr Anaesth 2014;24(1):68-73.
2. Rozmiarek A, Taghon T, Tobias JD. Inadvertent hyperventilation during intraoperative anesthetic care in the pediatric population. ICU Director 2012;3(4):172-175.
3. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care 2010;14(2):220.
4. Erickson S, Grauaug A, Gurrin L, Swaminathan M. Hypocarbia in the ventilated preterm infant and its effect on intraventricular haemorrhage and bronchopulmonary dysplasia. J Paediatr Child Health 2002;38(6):560-562.
5. Fabres J, Carlo WA, Phillips V, Howard G, Ambalavanan N. Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. Pediatrics 2007;119(2):299-305.
6. Froyshteter AB, Tumin D, Whitaker EE, Martin DP, Hakim M, Walia H, et al. Changes in tissue and cerebral oxygenation following spinal anesthesia in infants: a prospective study. J Anesth 2018;32(2):288-292.
7. Zhou W, Liu W. Hypercapnia and hypocapnia in neonates. World J Pediatr 2008;4(3):192-196.
8. Ikonen RS, Janas MO, Koivikko MJ, Laippala P, Kuusinen EJ. Hyperbilirubinemia, hypocarbia and periventricular leukomalacia in preterm infants: relationship to cerebral palsy. Acta Paediatr 1992;81(10):802-807.
9. Chambers NA, Ramgolam A, Sommerfield D, Zhang G, Ledowski T, Thurm M, et al. Cuffed vs. uncuffed tracheal tubes in children: a randomised controlled trial comparing leak, tidal volume and complications. Anaesthesia 2018;73(2):160-168.
10. Feldman JM. Optimal ventilation of the anesthetized pediatric patient. Anesth Analg 2015;120(1):165-175.
11. Bachiller PR, McDonough JM, Feldman JM. Do new anesthesia ventilators deliver small tidal volumes accurately during volume-controlled ventilation. Anesth Analg 2008;106(5):1392-1400.
12. Tobias JD. Transcutaneous carbon dioxide monitoring in infants and children. Paediatr Anaesth 2009;19(5):434-444.
13. van Kaam AH, De Jaegere AP, Rimensberger PC; Neovent Study Group. Incidence of hypo- and hyper-capnia in a cross-sectional European cohort of ventilated newborn infants. Arch Dis Child Fetal Neonatal Ed 2013;98(4):F323-F326.
14. Brown MK, Poeltler DM, Hassen KO, Lazarus DV, Brown VK, Stout JJ, et al. Incidence of hypocapnia, hypercapnia, and acidosis and the associated risk of adverse events in preterm neonates. Respir Care 2018;63(8):943-949.
15. Wheeler KI, Klingenberg C, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Neonatology 2011;100(3):219-227.
16. Peng W, Zhu H, Shi H, Liu E. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2014;99(2):F158-F165.
17. Thome UH, Genzel-Boroviczeny O, Bohnhorst B, Schmid M, Fuchs H, Rohde O, et al; PHELBI Study Group. Permissive hypercapnia in extremely low birthweight infants (PHELBI): a randomised controlled multicentre trial. Lancet Respir Med 2015;3(7):534-543.