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Original Article

Standardization and Validation of Non-invasive Monitoring of End Tidal Carbon Dioxide in Neonates via Nasal Cannula: An Observational Study

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ABSTRACT

Background: Carbon dioxide (CO_2) is a by-product of cellular metabolism, which could be considered as a reflection of metabolism, circulation, and ventilation. Arterial blood gas analysis (ABG) is the gold standard of monitoring for CO_2. However, is an expensive method leading to blood loss and iatrogenic anemia. In addition, each sample is only a snapshot view of the sampling moment. End-tidal CO_2 ($ETCO_2$) measurement gives a non-invasive and continuous monitoring of exhaled CO_2. Therefore, this study aimed to validate the non-invasive CO_2 measurement performed by nasal cannula and evaluate the correlation with partial pressure of arterial CO_2 ($PaCO_2$) in neonates.
Methods: This single-center observational study was conducted in the Neonatal Intensive Care Unit (NICU), Kasturba Hospital, Manipal, India. $PaCO_2$ was reported on routine ABG within a 15-minute interval of ABG sampling. Moreover, partial pressure of end-tidal carbon dioxide ($PetCO_2$) was noted at continuous 30-sec intervals (i.e., 30, 60, 90, ..., 180) up to 3 minutes. The values of $PaCO_2$ and $PetCO_2$ were found to be correlated with Pearson correlation and were shown by scattered plot. Regression analysis was used to get the prediction equation and the variance.
Results: A total of 70 samples were taken in the initial phase to study the correlation between $PaCO_2$ and measured $PetCO_2$. Pearson correlation showed a moderate positive correlation (r= 0.589) between $PetCO_2$ and measured $PaCO_2$. Regression analysis demonstrated a variance of 33.8% between the measured $PetCO_2$ and $PaCO_2$, which was statistically significant (P<0.001). A prediction equation was obtained for $PaCO_2$. In the final phase, 20 samples were recruited to standardize and validate the prediction equation. The $PaCO_2$ was calculated using the predicted equation and a new prediction equation was obtained.
Conclusion: According to the findings of this study, there is a good correlation (r=0.681) between the non-invasively measured $PetCO_2$ and $PaCO_2$.

Keywords: Correlation, $ETCO_2$, Nasal cannula, Neonates, Non-invasive, $PaCO_2$

Introduction

Carbon dioxide (CO_2) is a by-product of cellular metabolism that is pumped to lungs where oxygen (O_2) and CO_2 diffuse across the alveolar-capillary membrane and CO_2 is exhaled out. Therefore, CO_2 is considered as a reflection of metabolism, circulation, and ventilation (1,2). Although ABG analysis is the gold standard for monitoring, it is expensive and leads to more complications and each sample is only a snapshot view of the sampling moment (3).

It is essential to monitor the partial pressure of CO_2 ($PaCO_2$) in blood because changes in $PaCO_2$ may give rise to serious complications, especially in neonates (4,5). End-tidal CO_2 ($ETCO_2$) sampling is a continuous non-invasive measurement of blood CO_2 levels with short response time and minimizes the complications associated with repeated arterial sampling (6).

The $ETCO_2$ in intubated pediatrics has been proven to have a good correlation with arterial CO_2 value (7,8). Certain studies have reported that non-invasive measurement of $PetCO_2$ by

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infrared capnometry via nasal cannula may provide a good approximation of $PaCO_2$ in non-intubated patients (9,10). Tai CC *et al.* found that $ETCO_2$ measurement by side-stream capnometry through nasal cannula could provide an accurate and non-invasive estimate of $PaCO_2$ levels in non-intubated neonates (11).

It is shown that $ETCO_2$ and venous blood gas carbon dioxide ($VpCO_2$) has a good correlation and level of agreement in non-intubated children with moderate to severe respiratory distress (12). It is also important to know the level of agreement between the non-invasively measured CO_2 with arterial blood CO_2 value to minimize the invasive procedures and related complications in neonates. The present study aimed to validate the non-invasive measurement of $PetCO_2$ through the nasal cannula and evaluate the correlation with $PaCO_2$ value in neonates in the NICU.

Methods

This single-center observational study was conducted in the NICU of the Kasturba Hospital, Manipal as a tertiary academic hospital during January 2015-June 2016. We included both term and preterm neonates who were managed with oxygen therapy, high flow nasal cannula (HFNC), nasal continuous positive airway pressure (NCPAP), and room air in the NICU. The intubated neonates and neonates with congenital anomalies were excluded from the study. The study was approved by the Institutional Ethics Committee, Kasturba hospital, Manipal, India with the code of IEC 69/2015.

The recorded demographic data included the gestational age, baby gender, birth weight, primary diagnosis, Downes Score, and method of ventilation. The ABG was analyzed by GEM premier 3000, USA and $PetCO_2$ was recorded by capnocheck plus BCI®9004, US within an interval of 15 minutes after documentation of $PaCO_2$ through ABG sampling. $PetCO_2$ sampling was performed using a microstream processing sidestream sampling nasal cannula.

Exhaled CO_2 value was obtained by placing the nasal prongs of the cannula inside the nostril of the neonate and keeping the mouth closed. $PetCO_2$ was recorded continuously using 90-cm long cannula and values were documented on 30, 60, 90, and 120 sec up to 300 seconds with a stable value of not differing more than 4-5 mmHg in 30-sec interval. All the neonates were placed in the supine position and no unusual events, including apnea, hypopnea, and bradycardia were observed during the $PetCO_2$ measurement.

All the data were analyzed using SPSS software version 16, South Asia, Bangalore, India. The continuous and categorical variables of all the demographic parameters were analyzed by descriptive statistics. The correlation between $PaCO_2$ and $PetCO_2$ was analyzed using Pearson 2-tailed correlation and was depicted by scatter plot. The linear regression analysis was used to get a prediction equation, as well as the variance between the measured $PaCO_2$ and actual $PaCO_2$.

The sample size of 70 was calculated with the correlation factor of 0.7 between the two methods, power of 80%, and confidence interval of 95%. The correlation between $PetCO_2$ and $PaCO_2$ was evaluated and a standardized prediction equation was obtained. To validate the prediction equation, 20 more subjects were required with the power of 80% and a confidence interval of 95%. The $PaCO_2$ was calculated using the standardized prediction equation. In addition, the correlated between $PaCO_2$ and measured $PaCO_2$ was analyzed.

Results

A total of 70 samples were analyzed in the initial phase to study the correlation between the $PaCO_2$ and measured $PetCO_2$. Out of 70 samples, 46 (65.7%) neonates were males and 24 (34.3%) neonates were females. The mean gestational age of these neonates was 35.07±3.72 weeks and the mean bodyweight was 2294.35±863 gr. Overall, 27 (38.57%) and 43 (61.43%) neonates were preterm and term, respectively.

Complications of the neonates were documented, namely respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), and birth asphyxia in about 34.3%, 5.7%, 14.3%, and 5.7% of the newborns, respectively. Other diagnoses included abdominal distention and seizure disorders which indirectly affect the respiratory system were reported in about 40% of the subjects.

The method of ventilation used during $PetCO_2$ monitoring was as 28.6% room air and 28.9% on minimum oxygen support with the fraction of inspired oxygen (FiO_2) of 26.3±2.73%. Moreover, 18.6% of the newborns were on HFNC and 30% of the neonates were managed with non-invasive ventilation, in which 73% of the subjects were on room air oxygen and 27% were on FiO_2 of 25.4±2.7%. All the basic characteristics of the 70 neonates are summarized in Table 1.

Two-tailed Pearson correlation for the measured $PetCO_2$ and $PaCO_2$ value showed a moderate positive correlation (r=0.589, P<0.001).

The scatter diagram plotted to represent the relationship between $PetCO_2$ and $PaCO_2$ by expressing $PaCO_2$ in X-axis and $PetCO_2$ in Y-axis demonstrating the positive correlation (Figure 1).

Regression analysis showed the variance between the $PetCO_2$ and $PaCO_2$ as 33.8%, which was statistically significant ($P<0.001$). Furthermore, the prediction equation for $PaCO_2$ was $9.2+0.99*(PetCO_2)$. No significant difference was found between the $PetCO_2$ and $PaCO_2$ when gestational age, weight, gender, and diagnosis were checked as confounding factors.

In the final phase, we standardized and validated the prediction equation obtained by the 70 subjects. For validation of the prediction equation, a sample size of 20 was calculated. The $PetCO_2$ measured through sidestream cannula was computed in the above-predicted equation and was denoted as the calculated $PaCO_2$. The measured $PaCO_2$ was obtained from the ABG sample.

Out of the 20 samples, 40% of the neonates were males and 60% were females. The mean gestational age of these neonates was 36.00±3.96 weeks and the mean body weight was 2410±696.6 gr. All the demographic data of the 20 newborns are summarized in Table 1.

Pearson 2-tailed correlation was used and mean of the differences between the measured $PaCO_2$ and calculated $PaCO_2$ was estimated. At the 210-sec time interval the calculated $PaCO_2$ showed a minimum mean deviation of -2.3325 and a maximum stable correlation of 0.681 with actual measured $PaCO_2$. The correlation coefficients and the mean deviations are shown in Table 2.

Linear regression analysis for the 210-sec time interval calculated $PaCO_2$ showed a variance of 46.4% with the measured $PaCO_2$. Afterwards, the prediction equation for $PaCO_2$ was obtained as

Table 1. Basic characteristics of the neonates

Basic Characteristics	Initial phase n=70	Final phase n=20
Gestational age (weeks) (mean±SD)	35.07±3.72	36.00±3.96
Body weight (grams) (mean±SD)	2294.35±863.45	2410±696.6
Gender (%)		
Male	65.7	40
Female	34.3	60
Diagnosis (%)		
Respiratory distress syndrome	34.3	25
Meconium aspiration syndrome	5.7	15
Congenital diaphragmatic hernia	14.3	10
Birth Asphyxia	5.7	10
Others	40	40
Mode of ventilation (%)		
Room air	28.6	40
Oxygen	22.9	10
High flow nasal cannula	18.6	25
NCPAP/NIPPV*	30	25

* NCPAP: nasal continuous positive airway pressure, NIPPV: nasal intermittent positive pressure ventilation

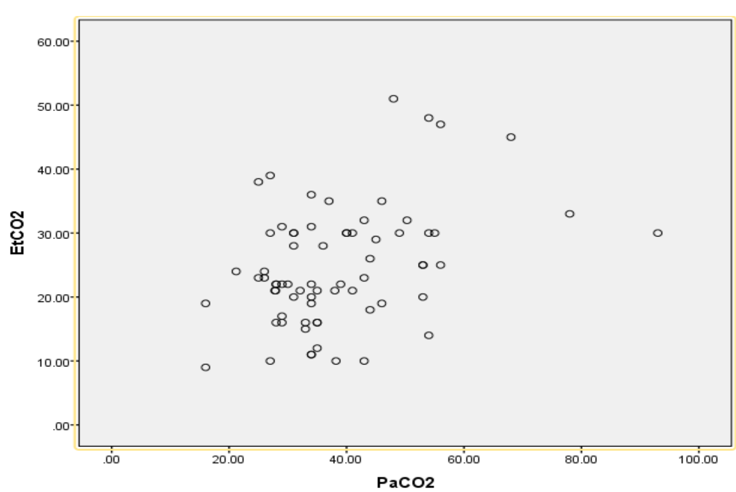

Figure 1. Scatter plot showing correlation between $PetCO_2$ and $PaCO_2$

Table 2. Correlation between the measured $PaCO_2$ and calculated $PaCO_2$ at different 30-sec intervals

Different time points of correlation (sec)	Correlation coefficient (r) (P<0.05)	Mean deviation	50th percentile of the mean deviation
30	0.627	-5.748	-3.97
60	0.638	-5.2035	-5.555
90	0.654	-4.6095	-4.13
120	0.612	-5.847	-7.06
150	0.641	-5.5995	-7.065
180	0.649	-4.4115	-3.73
210	0.681	-2.3325	-1.125
240	0.63	-5.0055	-4.13
270	0.649	-3.6195	-3.19
300	0.651	-4.602	-3.16

Table 3. Regression analysis of the 210th second calculated $PaCO_2$

R value	R^2 (%)	Adjusted R^2(%)	Prediction equation	P-value
0.681	46.4	43.4	8.6+0.83*$PetCO_2$ (210)	<0.001

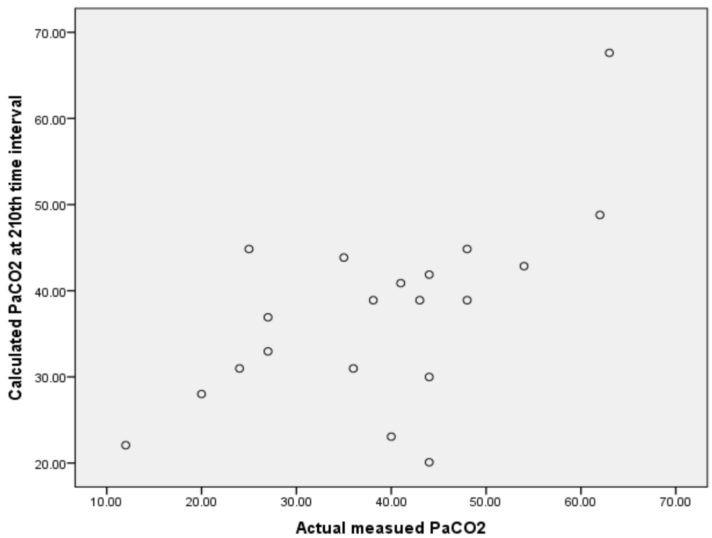

Figure 2. Scatter plot showing the correlation between calculated $PaCO_2$ at the 210-sec interval and measured $PaCO_2$

8.6+0.83*$PetCO_2$(210). The summarized values are demonstrated in Table 3.

A scattered diagram was plotted to show the relationship between the calculated $PaCO_2$ and measured $PaCO_2$. The calculated $PaCO_2$ was plotted on the Y-axis and the measured $PaCO_2$ was plotted on the X-axis showing a good positive correlation (Figure 2).

Discussion

The need for monitoring exhaled CO_2 values in adult patients has been considered as important over the years for various physiologic and diagnostic purposes. In neonates use of non-invasive $PetCO_2$ monitoring helps to reduce the complications related to the invasive arterial puncture.

Certain studies on intubated newborn have shown a good correlation between $PaCO_2$ and $PetCO_2$ (7,8). This may be because in intubated patients the sample of whole exhaled gas is taken through the artificial airway but in non-intubated patients may be a leakage or dead space, which can disturb an accurate correlation. This study focused on the neonatal group to find out whether the non-invasive measurement of the CO_2 value would correlate with or predict the blood CO_2 value in order to avoid an invasive investigation.

Coates BM et al. assessed ventilation status in non-intubated infants in PICU by comparing transcutaneous and arterial blood gas CO_2 value with exhaled sidestream CO_2. The authors found that the correlation of sidestream CO_2 with ABG was significant (r^2 = 0.907) and better than correlation with Partial pressure of transcutaneous CO_2 (r^2 = 0.649) (13).

Tai CC et al. revealed a significant correlation between $PetCO_2$ and $PaCO_2$ ($r=0.809$, $P<0.001$) and concluded that the $PetCO_2$ measured by sidestream nasal cannula has a good agreement with arterial CO_2 value. (11) Similarly, in our study, the $PetCO_2$ measurement at 210-sec time interval showed the maximum correlation ($r=0.681$, $P<0.001$) with a minimum deviation and the maximum variance explained by 46.4%. This study was performed prospectively whereas the study conducted by Tai CC et al. (11) included retrospective data.

Therefore, the $PetCO_2$ measured at the 210-sec time interval by sidestream nasal cannula gives an explanation of the 46.4% variance with the measured $PaCO_2$ which was found to be clinically significant ($P<0.001$). Prediction equation for $PaCO_2$ was found to be $8.6+0.83*ETCO_2(210)$ which could be practiced in the NICU of the same setup.

Continuous non-invasive monitoring of CO_2 is a good tool and can be performed easily in the neonatal population to avoid invasive blood gas sampling. It was revealed to have a good correlation with the arterial CO_2. However, to include it as a standardized clinical tool, studies with larger sample sizes are required. Utilizing cannulas with similar lengths and sizes in all the neonates might have caused some degree of difference in the correlation.

Conclusion

This study was performed to find the correlation between $PaCO_2$ and $PetCO_2$ in order to avoid frequent blood gas analysis in neonates. There was a good correlation ($r=0.681$) between the non-invasively measured $PetCO_2$ and measured $PaCO_2$. The prediction equation for $PaCO_2$ was obtained as $8.6+0.83*ETCO_2(210)$. It should be noted that to use it as a clinical tool instead of $PaCO_2$, we would require larger clinical trials that focus on varied sizes of nasal prongs in neonates. Using further studies, all the confounding factors could be investigated in details.

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Conflicts of interests

The authors declare no conflict of interest for the present study.

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