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Comparative Study on the Clinical Characteristics of Transient Tachypnea of Newborns according to the Need for Invasive Mechanical Ventilation

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ABSTRACT

Purpose: Transient tachypnea of the newborn (TTN) is the most prevalent respiratory disease worldwide. Many neonates with TTN generally demonstrate spontaneous improvement. However, only few patients present with severe complications. This study aimed to investigate the differences in clinical features to identify neonates at risk for further complications.

Methods: Between January 2015 and December 2020, 267 neonates who developed dyspnea within 6 h of birth were delivered at a gestational age of at least 37 weeks. The experimental group (group E) included 44 neonates who required invasive mechanical ventilation, whereas the control group (group C) included 223 neonates who required only observation or non-invasive respiratory support. We analyzed the differences in clinical and perinatal factors between the two groups.

Results: Gestational age and pH on arterial blood gas analysis at admission were significantly lower in group E (P<0.05). Clinical findings, such as moaning, tachypnea (>90 breaths/min), and pneumothorax, were more frequently observed in group E (P<0.05).

Conclusion: Moaning, tachypnea (>90 breaths/min), and need for respiratory assistance (fraction of inspired oxygen concentration ≥0.25) are predictive factors for increased risk of progression to a more severe disease course in neonates with TTN. Additional studies are needed to identify definitive factors that can differentiate TTN that improves spontaneously from TTN that requires intensive care.

Key Words: Transient tachypnea of the newborn; Cesarean section; Noninvasive ventilation

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INTRODUCTION

Transient tachypnea of the newborn (TTN) is the most prevalent respiratory distress condition in full-term neonates, accounting for 1% to 2% of all neonates[1]. The mechanism

underlying delayed fetal lung fluid absorption and associated clinical symptoms was first described by Avery et al.[2] in 1966. The pathophysiology of TTN is as follows: when the total ventilated air volume through the alveoli decreases owing to delayed pulmonary fluid absorption, the exchange of gas in the lungs decreases. Impaired gas exchange leads to a reduced oxygen supply and increased carbon dioxide accumulation in tissues.

TTN is a self-limiting condition that commonly improves spontaneously within the first 24 to 72 hours after delivery, without serious complications. However, a few cases in which patients present with serious complications such as hypoxia, respiratory distress, and air leaks have been reported[3]. To prevent these complications, certain neonates with TTN may require oxygen supplementation or non-invasive respiratory support (e.g., a nasal cannula, heated humidified high-flow nasal cannula [HHHFNC], and nasal continuous positive airway pressure [CPAP]). One study has reported that using a T-piece resuscitator CPAP shortly after birth reduced the duration and severity of TTN[4]. TTN treatment is critical as it may require invasive mechanical ventilation to maintain appropriate oxygen saturation, and TTN can progress to "malignant TTN" with severe persistent pulmonary hypertension of the newborn (PPHN)[5].

This study aimed to investigate the differences in clinical features of neonates with TTN to identify those at risk of further complications.

MATERIALS AND METHODS

We retrospectively evaluated electronic medical records of neonates admitted to the neonatal intensive care unit (NICU) of Wonkwang University Hospital between January 2015 and December 2020. The study included only neonates who developed dyspnea within 6 hours of birth and delivered at a gestational age of ≥37 weeks. Neonates with congenital infections, malformations of the respiratory or circulatory system, chromosomal abnormalities, or other respiratory diseases (such as air leaks, neonatal respiratory distress syndrome requiring surfactant use, and meconium aspiration syndrome, which could be suspected based on meconium staining) were excluded from the study.

TTN was diagnosed by expert radiologists using chest radiographs taken during hospitalization, which confirmed interlobar lung fluid deposition, hyperinflation, and evident vascular/perihilar markings[6] in addition to typical clinical findings such as tachypnea, moaning, nasal flaring, and chest retraction. espiratory failure, including apnea, inadequate oxygenation, and hemodynamic instability, necessitates tracheal intubation[7]. The experimental group (group E) included 44 neonates who required invasive ventilation, whereas the control group (group C) included 223 neonates who either did not require treatment or only required non-invasive mechanical ventilation.

The perinatal parameters of the neonates included in the study were sex, gestational age, birth weight, height (including percentiles), delivery method, Apgar score (at 1 and 5 minutes), premature rupture of membranes (PROM), *in vitro* fertilization and embryo transfer (IVF-ET), gestational diabetes mellitus (DM), place of delivery (in-born/out-born), and period from birth to admission. Hemoglobin level, total white blood cell (WBC) count, neutrophil percentage, platelet count, C-reactive protein (CRP) level, and arterial blood pH were compared, and laboratory tests were performed at admission. Thyroid function tests (TFT), such as those for thyroid-stimulating hormone (TSH) and free thyroxine (T4), as well as the neonatal screening test were performed 7 days after admission. The clinical parameters included moaning, nasal flaring, peak respiratory rate measured 72 hours after birth, pneumothorax, oxygen supplementation via nasal cannula, or respiratory support (e.g., nasal CPAP, HHHFNC, or tracheal intubation).

The collected data were analyzed using SPSS version 21.0 (IBM Corp.). The chi-square test or Fisher's exact test for categorical data was used to compare anthropometric and demographic factors between the two groups. For continuous variables, the Student's *t*-test and Mann–Whitney *U*-test were used. The predictive factors were determined using logistic regression analysis. Sensitivity and specificity were determined using receiver operating characteristic curves. Significance was set at $P<0.05$.

RESULTS

Overall, 267 neonates (171 males and 96 females) were included in groups E and C. A comparison of the clinical characteristics of the study participants is presented in Table 1. The number of neonates delivered outside our hospital was significantly higher in group E (n=40 [90.9%]) than in group C (n=157 [70.4%]). Comparing the perinatal characteristics between the two groups, the gestational age (weeks) in group E was 37.97± 0.67, which was marginally lower than that in group C (38.37± 1.00, $P=0.001$). No

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significant differences in weight or height, including the percentiles at birth, were observed between the two groups. The 1-minute Apgar score was significantly higher in group E at 8.70±0.63 than in group C at 8.11±1.34 (P=0.005). Meanwhile, no significant difference in the 5-minute Apgar score was noted between the two groups. Further, no significant differences in other parameters such as PROM, IVF-ET, and gestational DM were observed between the two groups. In the laboratory data obtained at the time of admission, no significant differences in hemoglobin level, total WBC count, neutrophil percentage, platelet count, CRP level, partial pressure of oxygen (PaO_2; P=0.057), and partial pressure of carbon dioxide ($PaCO_2$; P=0.063) were observed between the two groups, although a difference in the pH on the arterial blood gas analysis (ABGA) was noted (P=0.026) (Table 1). A TFT was performed on day 7 after admission; however, no significant differences in the TSH level and free T_4 were observed between group E (3.17±2.26 μIU/mL and 1.72± 0.43 ng/dL, respectively) and group C (3.12±3.45 μIU/mL and 1.68±0.29 ng/dL, respectively).

Significant differences in moaning, nasal flaring, pneumothorax, inotropes administered, and non-invasive respiratory assistance before invasive mechanical ventilation in various physical examinations at admission were observed between the two groups (P<0.05). In group E, 15 neonates presented with pneumothorax before tracheal intubation and six with pneumothorax on both sides of the lung. The respiratory rate with an adequate level of sensitivity (77%) and specificity (65%) to distinguish between groups E and C was approximately 90 breaths/min. A significant difference in the number of neonates with a maximum respiratory rate of >90 breaths/min between the two groups was observed. The peak fraction of inspired oxygen concentration (FiO_2) with sufficient sensitivity (82%) and specificity (83%) to differentiate groups E and C was approximately 0.25. The number of neonates with a maximal FiO_2 level ≥0.25 was significantly different between the two groups (Table 2). We performed a logistic regression analysis to identify aspects that clinicians should pay attention to among several parameters that were statistically significant. A maximum respiratory rate of >90 breaths/min and an FiO_2 level of ≥0.25 had an odds ratio of 5.938 (95% confidence interval, 1.743 to 20.221; P=0.004) and and 3.774 (95% confidence interval, 1.386 to 10.275; P=0.009), respectively.

Table 1. Comparison of Perinatal Characteristics between Two Groups

Variable	Group C (n=223)	Group E (n=44)	*P*-value
Male sex	142 (63.7)	29 (65.9)	0.778
Gestational age (wk)	38.37±1.00	37.97±0.67	0.001*
Birth weight (kg)	3.23±0.48	3.16±0.39	0.303
Height (cm)	49.46±2.30	49.55±2.29	0.815
Cesarean section	170 (76.2)	38 (86.4)	0.139
Apgar score (1 min)	8.11±1.34	8.70±0.63	0.005*
Apgar score (5 min)	9.17±1.20	9.45±0.90	0.072
PROM	7 (3.1)	0	0.234
IVF-ET	2 (0.9)	0	0.528
Gestational DM	16 (7.2)	4 (9.1)	0.657
Out-born	157 (70.4)	40 (90.9)	0.005*
Between birth to admission (hr)	9.27±15.94	8.70±10.46	0.177
Laboratory findings (at admission)			
Hb (g/dL)	16.34±1.87	15.83±1.90	0.384
WBC ($\times10^3$/μL)	18.22±7.36	20.09±7.31	0.868
Neutrophil (%)	63.75±21.58	71.19±13.06	0.207
PLT ($\times10^3$/μL)	271.10±62.03	269.25±53.31	0.104
CRP (mg/L)	2.30±9.89	4.34±12.26	0.075
pH	7.32±0.08	7.27±0.06	0.026*

Values are expressed as number (%) or mean±standard deviation.
*P<0.05.
Abbreviations: PROM, premature rupture of membrane; IVF-ET, in vitro fertilization and embryo transfer; DM, diabetes mellitus; Hb, hemoglobin; WBC, white blood cell; PLT, platelets; CRP, C-reactive protein.

Table 2. Comparison of Clinical Features between Two Groups

Variable	Group C (n=223)	Group E (n=44)	*P*-value
Moaning	101 (45.3)	28 (63.6)	0.026*
Nasal flaring	12 (5.4)	12 (27.3)	<0.001*
RR >90 breaths/min	80 (35.9)	34 (77.3)	<0.001*
Pneumothorax	10 (4.5)	17 (38.6)	<0.001*
One side	9	11	
Both	1	6	
Inotropes use	0	17 (38.6)	<0.001*
Respiratory support			<0.001*
None	47 (21.1)	0	
Cannular	111 (49.8)	7 (15.9)	
HHHFNC	30 (13.5)	4 (9.1)	
Nasal CPAP	35 (15.7)	33 (75.0)	
FiO_2 ≥0.25	28 (12.6)	30 (68.2)	<0.001*

Values are expressed as number (%).
*P<0.05.
Abbreviations: RR, respiratory rate; HHHFNC, heated humidified high-flow nasal cannula; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen.

DISCUSSION

Although TTN is often a benign condition, previous research has been conducted to identify significantly associated risk factors because the risk of morbidity increases when hypoxia, respiratory failure, and air leakage are present[8]. Cesarean section, large-for-gestational-age, twins, male sex, and maternal history of diabetes or asthma are all well-known primary risk factors for TTN[9]. Delivery by Cesarean section has been identified as a crucial predisposing risk factor for TTN[10]. This study included 208 neonates (78%) born by Cesarean section. The risk of neonates developing TTN should receive more attention because Cesarean section rates have demonstrated an increasing trend[11].

Pirjani et al.[10] discovered that neonates born at 38 to 39 weeks gestation by Cesarean section had greater rates of TTN and NICU admission than neonates born at ≥39 weeks gestation. In our study, the gestational age of neonates in group E was considerably lower than that of neonates in group C (P=0.001). This is similar to the results of Tutdibi et al.[1], who have reported that Cesarean section and low gestational age were critical contributors to TTN development in neonates aged >37 weeks. Consequently, even in full-term neonates (gestational age, 37 to 42 weeks) born by Cesarean section, physicians should be aware that those with a lower gestational age may experience a more severe course.

The main pathophysiology cited for Cesarean delivery as a significant risk factor for developing TTN is delayed discharge and resorption of postnatal lung fluid, and studies to support these pathological hypotheses have been conducted[12]. According to Alhassen et al.[13], symptoms may develop depending on the quantity of lung fluid present in the airways at birth. Respiratory support, such as nasal CPAP, improves respiratory function and prevents further deterioration of the TTN. Celebi et al.[14] have suggested that the prophylactic use of positive pressure ventilation in the delivery room reduced NICU admission rates. If respiratory support such as oxygen via a nasal cannula or mechanical ventilation is not provided during an acute illness, respiratory failure may occur because of fatigue and exhaustion of the respiratory muscles[15]. All neonates received supplemental oxygen therapy to maintain oxygen saturation (≥90%) during hospitalization. When comparing the respiratory support methods used before tracheal intubation in group E, appropriate oxygen saturation could only be maintained by employing methods that provided higher positive pressure support (P<0.001).

Moreover, considering the oxygen concentration administered as well as the respiratory support pressure is crucial. However, data to determine the exact FiO_2 administered through the nasal cannula, which is widely used in infants and neonates, are insufficient. When administering 1 L/min of oxygen through the nasal cannula, the FiO_2 was calculated as 0.24[16], When data that validated the FiO_2 (such as HHHFNC or nasal CPAP) were compared, group E had a higher FiO_2 value. A significant difference in the number of neonates with a maximum FiO_2 level of ≥0.25 was observed between the two groups (P<0.001).

TTN commonly improves spontaneously; however, if it escalates and worsens to tachypnea, chest retraction, stridor, or cyanosis, NICU admission may be required. In rare cases, TTN may progress to hypoxic respiratory failure such as PPHN[17,18]. In our study, group E had a considerably higher incidence of clinical observations indicating distress (such as moaning and nasal flaring), increased requirement for inotropes, and the occurrence of pneumothorax (P<0.05). Pneumothorax was more common in group E than in group C, with 15 cases occurring before tracheal intubation for invasive mechanical ventilation and six cases occurring on both sides of the lungs. Eight neonates in group E had PPHN; however, statistical analysis was impossible because of the small sample size. Similar to a previous study[19], the number of neonates with a maximum respiratory rate >90 breaths/min was significantly different between groups E and C. Therefore, specific care and management are required for neonates with a malignant course.

No significant difference in the TFT was identified between all the neonates in our study at 7 days after admission compared to that in a previous study demonstrating a link between TTN and thyroid hormones[20]. However, various external factors, such as stress caused by respiratory failure and discordance in TFT sampling timing after birth, can influence the TFT results. As mentioned above, prophylactic respiratory support should be provided during the early stages of respiratory symptoms[15]. In a study by Hirata et al.[21], the time from birth to admission to the NICU was considered important. Although the rate of outbirths was high (90.9%) in group E, the time from birth to admission to the NICU was not significantly different between the two groups in our study. Because both groups included out-born neonates, no significant difference was observed between both groups. However, because the pH on ABGA performed at admission in group E was low, immediately transferring the neonate may minimize the damage caused by respiratory difficulties.

One limitation of this study is that the Apgar scores reported by

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each delivery hospital for newborn neonates were inconsistent. Although laboratory blood tests were performed immediately upon admission, the blood sampling times of the study participants were inconsistent because of varying elapsed time intervals after birth. In our study, tracheal intubation was performed only in cases of low oxygen saturation and severe hypercapnia ($PaCO_2$ ≥60 mm Hg); however, it may be used in other cases, depending on the neonate's condition.

In conclusion, to prevent the progression of TTN to a severe course, appropriate positive pressure ventilation should be provided at birth or shortly after birth when symptoms of respiratory failure are observed in newborns with a relatively low gestational age. When assessing neonates with TTN, physicians should closely monitor clinical parameters, such as moaning, tachypnea (>90 breaths/min), and features of pneumothorax. Special attention is required if respiratory assistance with an FiO_2 level of ≥0.25 is needed. If invasive mechanical ventilation is required, TTN-related complications requiring aggressive treatment should be evaluated. Additional research regarding the factors that may distinguish severe from non-severe TTN is warranted.

ARTICLE INFORMATION

Ethical statement

This study proposal was approved by the Institutional Review Board of Wonkwang University Hospital (WKUH 2021-08-007). Written informed consent by the patients was waived due to a retrospective nature of our study.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conception or design: H.J.Y., S.H.L.

Acquisition, analysis, or interpretation of data: H.J.Y., S.H.L.

Drafting the work or revising: H.J.Y., S.H.L.

Final approval of the manuscript: All authors read and approved the final manuscript.

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