

Surfactant Deficiency in Transient Tachypnea of the Newborn

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Objective To evaluate surfactant production and function in term neonates with transient tachypnea of the newborn (TTN).

Study design Samples of gastric aspirates collected within 30 minutes of birth from 42 term newborns with gestational age ≥ 37 weeks (21 patients with TTN and 21 control subjects), delivered via elective cesarean delivery, were analyzed with lamellar body count and stable microbubble test.

Results Results of lamellar body counts and stable microbubble tests were significantly lower in the TTN group than in control subjects ($P = .004$ and $.013$, respectively). Lamellar body counts were significantly lower in infants with TTN requiring oxygen for ≥ 24 hours after birth than in infants requiring oxygen for < 24 hours ($P = .029$). When the cutoff point was 48 hours, the stable microbubble count was significantly lower in the group requiring oxygen for ≥ 48 hours than in the group requiring oxygen for < 48 hours ($P = .047$).

Conclusions Term infants with TTN had low lamellar body counts associated with decreased surfactant function, suggesting that prolonged disease is associated with surfactant abnormalities. (*J Pediatr* 2011;159:750-4).

Transient tachypnea of the newborn (TTN) is a common cause of respiratory distress during the first days of life. Newborns with this syndrome have variable amounts of tachypnea soon after birth, sometimes associated with grunting, chest retraction, nasal flaring, and cyanosis, usually requiring low amounts of oxygen supplementation. Symptoms may persist for a few hours as long as 1 week.

This syndrome has been attributed to delayed resorption of fetal lung fluid. However, evidence has accumulated that the syndrome results from mild immaturity of the surfactant system. Low levels of phosphatidylglycerol and of phosphatidylcholine and phosphatidylinositol in lung fluid¹⁻³ and in amniotic fluid,⁴ reduction in bubble clicking on tracheal aspirates,⁵ and low stable microbubble count on gastric aspirates⁶ have been reported. These observations suggest surfactant deficiency, dysfunction, or both in TTN.

The objective of this study was to evaluate surfactant production and function in term newborn infants, delivered via elective cesarean delivery, with a clinical diagnosis of TTN.

Methods

This is a prospective study comparing surfactant production and function of 21 term newborns diagnosed with TTN with a group of 21 newborns of the same gestational age without a diagnosis of TTN. The study was conducted at Hospital São Lucas/Pontifícia Universidade Católica do Rio Grande do Sul and Hospital Moinhos de Vento in southern Brazil between September 2007 and September 2008.

The study group included term infants with gestational age ≥ 37 weeks, delivered via elective cesarean delivery, with a clinical diagnosis of TTN. The control group included age-matched newborns, also delivered via elective cesarean delivery, without respiratory distress. Gestational age was determined by the date of the last menstrual period confirmed with ultrasound scanning before 20 weeks' gestation. Exclusion criteria for both groups included meconium in the amniotic fluid, major congenital malformations, and specific respiratory disease other than TTN or respiratory distress syndrome (RDS). The criteria for the diagnosis of TTN were presence of tachypnea (respiratory rate > 60 breaths/min) and need of supplemental oxygen for at least 6 hours, associated with a radiological pattern compatible with the diagnosis of TTN.

The first chest radiographs were obtained during the first 12 hours of life and analyzed independently by two experienced neonatal radiologists, who were blinded to the clinical data. Perihilar streaking, pulmonary hyperaeration, or both and fluid in the minor fissure, pleural space, or both were considered to be typical TTN. RDS was diagnosed in the presence of homogeneous diffuse granular opacities or ground-glass appearance. Control subjects without respiratory distress did not undergo radiological examinations.

DTT	Dithiothreitol
RDS	Respiratory distress syndrome
TTN	Transient tachypnea of the newborn

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Gastric aspirates were collected from all infants within 30 minutes of birth by using a gastric tube and a 20-mL syringe. All samples received coded labels and were frozen at -20°C . Between 48 and 96 hours after birth, the samples were thawed at room temperature for analysis.

For lamellar body count, diluted dithiothreitol (DTT, Invitrogen, Carlsbad, California) was prepared in advance in distilled water (10 mg/mL) and kept frozen at -20°C in Eppendorf tubes until its use. The amount of gastric aspirate used for each lamellar body count ranged from 50 to 100 μL . The samples were placed in test tubes containing diluted DTT (1 part gastric aspirate and 6 parts DTT). The diluted sample was mixed for 10 seconds with a Vortex mixer (Phoenix AP-56, Araraquara, Brazil), and the material was then aspirated into an automated cell counter (Sysmex XT-1800i, Sysmex, Kobe, Japan). Lamellar body count was performed by using the platelet channel of the cell counter.⁷

We validated the use of frozen samples with analyses of fresh and 72-hour frozen samples diluted with DTT and saline. The Spearman correlation co-efficients were ≥ 0.95 .

The stable microbubble test was carried out according to Pattle et al⁸ with slight modifications.⁶ We also previously had analyzed in our laboratory whether the frozen gastric fluids were adequate for the microbubble count.⁶

Infants with TTN were observed until the disappearance of respiratory symptoms. Perinatal data, respiratory interventions, total duration of supplemental oxygen, and inspired fraction of oxygen were recorded.

The study was approved by the research ethics committees of the Pontificia Universidade Católica do Rio Grande do Sul and Hospital Moinhos de Vento, with informed consent from the mothers to collect gastric fluid from infants.

To detect a difference ≥ 0.9 units SD (effect size ≥ 0.9) with 80% statistical power and a 5% significance level, 21 patients would be required in each group.

Descriptive statistics were used for the quantitative variables. The Kruskal-Wallis test was used to compare groups for lamellar body count and stable microbubble test results. Sensitivity and specificity rates of the tests were determined.

Results

Infants with the same gestational ages (median, 38 weeks; minimum, 37 weeks; maximum, 39 weeks) were examined,

21 term newborn infants with a clinical diagnosis of TTN and 21 healthy infants. In both groups, 14 infants were 37 weeks' gestation, 6 infants were 38 weeks' gestation, and one infant was 39 weeks' gestation. In the TTN group, 16 patients with respiratory distress exhibited chest radiographs typical of TTN, and 5 patients had non-typical radiographs that were compatible with the diagnosis of TTN. The 21 patients were not considered to have RDS by the radiologists.

The groups had similar birth weight (TTN group: 3168 ± 408 g; control group: 3122 ± 413 g; $P = .597$), and 1- and 5-minute Apgar scores were not different (TTN group: 8 [range, 2-9] and 9 [range, 7-10]; control group: 8 [range, 8-9] and 9 [range, 9-10], respectively). There were 12 male infants in the TTN group and 11 male infants in the control group.

Two infants in the TTN group required mechanical ventilation, one for 24 hours and the other for 2 hours. These two patients who underwent ventilation and one non-ventilated patient received a dose of surfactant. Two of these infants had low lamellar body counts and stable microbubbles, and one of them had high counts in both tests. None of the 5 patients with non-typical TTN was intubated or received surfactant.

There was a statistically significant difference in lamellar body counts and stable microbubble tests between the TTN and control groups (Table I). Even when the 3 patients who received surfactant were not included in the analysis, the difference persisted (lamellar body count, $P = .012$; stable microbubble test, $P = .017$). When the analysis included only the 16 patients with typical TTN compared with control subjects, the statistical difference persisted for lamellar body count ($P = .006$), and the P value for stable microbubble test was .051.

Considering a cutoff point of 70 000 lamellar bodies/ μL and 35 stable microbubbles/ mm^2 , the sensitivities and specificities of the tests to diagnose TTN were 71 and 71% for lamellar body count and 71 and 91% for stable microbubble test, respectively. The area under the receiver operating characteristic curve was 0.746 for lamellar body count and 0.739 for stable microbubble test.

Infants with a clinical diagnosis of TTN who required supplemental oxygen for ≥ 24 hours had lamellar body counts significantly lower than infants requiring oxygen for < 24 hours (Table II). A significant lower microbubble count was observed in infants with TTN requiring oxygen for ≥ 48 hours. In patients with TTN and lamellar body count ≥ 70 000, one of 8 infants required supplemental oxygen

Table I. Lamellar body count and stable microbubble test on gastric aspirates from term infants with clinical diagnosis of transient tachypnea of the newborn compared with a normal control group

	n	Median	IQR	Minimum	Maximum	P value
Lamellar body count/ μL						
TTN	21	63 000	28 000-84 000	7000	203 000	.004
Control	21	119 000	56 000-182 000	28 000	259 000	
Stable microbubble test (microbubbles/ mm^2)						
TTN	21	29	17-89	4	122	.013
Control	21	80	65-97	22	156	

Table II. Lamellar body count and stable microbubble test according to time on oxygen and maximum inspired fraction of oxygen

	n	Median	IQR	Minimum	Maximum	P value
Lamellar body count/ μ L						
<24 hours	9	105 000	70 000-140 000	7000	203 000	.029
\geq 24 hours	12	31 5000	24 500-63 000	7000	84 000	
Stable microbubble test (microbubbles/ mm^2)						
<24 hours	9	65	25-95	4	122	.255
\geq 24 hours	12	28	14-62	8	102	
Lamellar body count/ μ L						
<48 hours	15	70 000	28 000-133 000	7000	203 000	.055
\geq 48 hours	6	24 500	14 000-63 000	7000	77 000	
Stable microbubble test (microbubbles/ mm^2)						
<48 hours	15	35	25-98	4	122	.047
\geq 48 hours	6	14	11-29	8	89	
Lamellar body count/ μ L						
$\text{FiO}_2 < 0.40$	11	73 500	42 000-133 000	7000	203 000	.129
$\text{FiO}_2 \geq 0.40$	10	28 000	21 000-84 000	7000	140 000	
Stable microbubble test (microbubbles/ mm^2)						
$\text{FiO}_2 < 0.40$	11	51	29-98	4	122	.139
$\text{FiO}_2 \geq 0.40$	10	25	12-65	8	105	

FiO_2 , inspired fraction of oxygen.

for ≥ 24 hours, whereas 9 of 13 patients with lamellar body counts $< 70\,000$ required supplemental oxygen for ≥ 24 hours ($P = .024$). In infants with a stable microbubble count ≥ 35 , only two of 8 infants required oxygen for ≥ 24 hours, whereas 8 of 13 infants with a stable microbubble count < 35 required oxygen for ≥ 24 hours ($P = .182$).

Discussion

With the analysis of gastric fluid soon after birth, term neonates with TTN, delivered via elective cesarean delivery, were revealed to have a low production of lamellar bodies from their lungs and abnormal surfactant function. This study also revealed that infants with TTN who needed supplemental oxygen for a longer period had significantly lower lamellar body and microbubble counts, suggesting that low counts may be associated with more prolonged respiratory distress.

After Dubin⁷ showed that lamellar body count in amniotic fluid could predict RDS, numerous studies have evaluated the performance of this method in amniotic fluid,⁹⁻¹⁷ which is currently widely used by obstetricians. According to a consensus on lamellar body count in amniotic fluid, lung maturity is suggested by a count $\geq 50\,000/\mu\text{L}$.¹⁸

Lamellar body counts were assessed with gastric aspirates of preterm infants soon after birth. The test had a good performance for diagnosing RDS.¹⁹ However, gastric aspirates are more thick and non-homogeneous than amniotic fluid, which hinders processing by the cell counter without centrifugation, even when the fluid is diluted in saline. Because centrifugation significantly affects lamellar body count,^{7,20} in this study gastric fluid was diluted with a liquefying agent (DTT solution). Tests performed in our laboratory showed that this agent and freezing the samples for 72 hours did not affect lamellar body count significantly.¹⁹

Results of the stable microbubble test can predict RDS with amniotic fluid,^{21,22} tracheal aspirates,²³⁻²⁵ and gastric aspirates.^{21,26,27} The test was previously used with gastric aspirates from infants with TTN with gestational age ≥ 34 weeks.⁶ Our findings confirmed the low microbubble count in TTN, which is consistent with the low lamellar body count.

In this study with gastric aspirates from a term population, the best cutoff points for the diagnosis of TTN were higher than those established for RDS in amniotic fluid. The only study with a stable microbubble test comparing gastric and amniotic fluid to diagnose RDS showed a higher cutoff point when gastric fluid was used.²¹

TTN has been attributed to delayed clearance of lung fluid, and, in some cases, chest radiographs clearly showed excess of lung fluid. Patients with TTN had low lamellar body count and low microbubble count, supporting earlier data showing phospholipid abnormalities and abnormal physical test results in the lung fluid and amniotic fluid of patients with a diagnosis of TTN. Surfactant abnormality may be considered a primary problem in TTN, as suggested in 1984 by James et al.³ Lack of surfactant increases alveolar surface tension, causing epithelial damage and consequent alveolar flooding and pulmonary edema.²⁸ Difficulty in clearing lung water may be caused by low pulmonary expression of the activity of airway epithelial sodium channels.^{29,30}

Preterm infants with RDS have lower amiloride-sensitive nasal transepithelial potential difference than normal and infants with TTN, suggesting significant abnormalities of the lung epithelial sodium channel.^{29,30} However, administration of exogenous surfactant promotes a dramatic clinical response in these patients, and most of them do not need supplemental oxygen after surfactant therapy. Another observation indicating surfactant abnormality as the primary cause of TTN is that this is a very rare disease in infants > 38 weeks' gestation.³¹

TTN, as clinically defined, may be a multifactorial disease, including delayed absorption of lung fluid and surfactant abnormalities in variable degrees. Alternatively, within the diagnosis of TTN two different diseases may occur (surfactant deficiency and excess of lung fluid), which many times are overlapping. In this study, 3 patients had a more serious disease, and most neonatologists would consider these cases as RDS despite the initial picture of TTN. However, the analysis performed without these patients did not change the interpretation of test results.

Lamellar body count and stable microbubble test are not as sensitive and specific for the diagnosis of TTN as for the diagnosis of RDS, and, for this purpose, they have limited clinical application. However, in patients with an initial diagnosis of TTN, lamellar body count $<70\ 000/\mu\text{L}$ suggests a probable prolonged disease.

Some term infants with an initial diagnosis of TTN have progressive and severe respiratory distress. In clinical practice, these "term infants" with a radiological diagnosis of TTN generally do not receive surfactant replacement therapy because their respiratory distress is not attributed to surfactant deficiency. We believe that these patients, with evidence of surfactant abnormalities with low lamellar body counts, microbubble counts, or both should be examined in controlled studies for a possible clinical benefit of surfactant replacement therapy. Lamellar body count and stable microbubble test on gastric aspirates are rapid and inexpensive tests, which may be performed not only in preterm babies, but also in term infants who exhibit some respiratory symptoms during the first minutes of life. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Congenital Abnormalities of the Urinary System II: Renal Cortical and Medullary Necrosis

Bernstein J, Meyer R. *J Pediatr* 1961;59:657-68

This article was a companion to another report¹ that was the subject of an earlier 50 Years Ago piece in *The Journal*, which focused on a detailed description of such abnormalities that continue to be important developmental and acquired kidney problems in pediatric patients today.²

This article, however, is a detailed description of renal cortical and medullary necrosis in neonates, including 4 described in the earlier study and an additional 7 neonates observed subsequently. The authors found that neonates with cortical necrosis, medullary necrosis, or both had a history of severe shock caused by severe asphyxia, blood loss, or both. Several neonates had evidence of utero-placental hemorrhage, and most neonates had severe anemia. Gross or microscopic hematuria was common, but not universal, and oliguria/anuria was present in many neonates. Similarly, pathologic lesions of microthrombi were common, but not universal. Cortical necrosis, medullary necrosis, or both usually occurred in the absence of congenital malformations. Focal, ischemic necrosis, and petechial hemorrhage were commonly present in other organs including focal areas of necrosis in the brain, liver, adrenal glands, and in the gastrointestinal tract. The few neonates who survived had the later development of hypertension and renal scarring. In addition, primitive structures developed in association with the healing process and were thought to be a reaction to healing.

This article was an important early description of the clinical features and pathologic of renal cortical and medullary necrosis in neonates. The authors also documented the strong association with asphyxia and blood loss and they also demonstrate that extra-renal lesions were common as well. As described in the report, cortical necrosis remains an important cause of acute kidney injury and frequently leads to substantial chronic kidney disease in the neonate.

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