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Antibiotics For Transient Tachypnea of Newborn; are Comorbidities Reasons or Results?

Yenidoğanın Geçici Takipnesinde Antibiyotikler; Komorbiditeler Sebep mi Sonuç mu?

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ÖZ

Amaç: Yenidoğanın geçici takipnesi(YDGT) tanısı alan, antibiyotik tedavisi verilen ve konservatif tedavi uygulanan geç pematüre ve term yenidoğanların, enfeksiyöz komplikasyonlar, pulmoner hava kaçağı ve hastanede kalış süresi açısından karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu prospektif çalışma, Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Sağlık Bilimleri Üniversitesi, Tıp Fakültesi'nde yürütüldü. İki yüz doksan bir bebek çalışmaya dahil edildi ve 101'ine (% 34.7) antibiyotik tedavisi verildi ve 190' ına (% 65.3) konservatif tedavi uygulandı.

Bulgular: Antibiyotik ile tedavi edilen bebeklerde, konvansiyonel tedavi ile izlenen bebeklerle karşılaştırıldığında daha fazla non-invaziv solunum desteği gereksinimi (% 57 -% 21, p <0.0001), daha uzun hastanede kalış süresi (7.8 ± 3.6 ve 5.5 ± 3.1 gün, P <0.0001), daha fazla enfeksiyöz komplikasyon (%16.8 ve -% 0.5, p <0.0001) ve pulmoner hava kaçağı komplikasyonları (% 8.9 -% 0.5, p <0.01) olduğu görüldü.

Sonuç: Antibiyotik ile tedavi edilen YDGT'li bebeklerde enfeksiyöz komplikasyonlar ile birlikte pulmoner hava kaçağı komplikasyonu da daha fazla olduğu görülmüştür. Antibiyotik tedavisi görmeyen YDGT'li bebeklerin hastanede yatış sürelerinin daha kısa olması nedeni ile hastanede uzun süre yatış nedeni ile ortaya çıkabilecek komplikasyonların da önüne geçmesini sağlamıştır. Elde ettiğimiz sonuçlar ışığında, YDGT'li bebeklerin çoğunun gereksiz antibiyotik aldığını düşünmekteyiz.

Anahtar Kelimeler: Geçici takipne, yenidoğan, antibiyotik, komplikasyon

ABSTRACT

Aim: To compare late preterm and term newborns administered antibiotic treatment and conservative management with the diagnosis of TTN including infectious complications, pulmonary air leak and length of hospital stay.

Materials and methods: This prospective study was carried out at Zekai Tahir Burak Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences. Two hundred and ninety one infants were included in the study and 101 (34.7%) were given antibiotic treatment and 190 (65.3%) were followed with conservative treatment.

Results: Infants treated with antibiotics required more noninvasive respiratory support (57% vs 21%, p<0.0001), had a longer duration of hospital stay (7.8±3.6 vs 5.5±3.1 days, P<0.0001), more infectious complications (16.8% vs 0.5%, p<0.0001) and pulmonary air leak complications (8.9% vs 0.5%, p<0.01) than untreated infants.

Conclusions: Infants with TTN treated with antibiotics have not only more infectious complications but also more pulmonary air leak than untreated infants. Infants with TTN not treated with antibiotics have a shorter length of hospital stay possibly preventing complications related to longer hospital stay. In the light of our results we emphasize that most infants with TTN receive unnecessary antibiotics.

Keywords: Transient tachypnea , newborn, antibiotics, complications

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INTRODUCTION

Transient tachypnea of the newborn (TTN) is a common self-limited respiratory disorder of the term and late preterm newborns(1). Newborns with TTN develop respiratory distress soon after birth, due to inadequate pulmonary fluid clearance related to immature epithelial sodium channel function and/or lack of intrapartum mechanical forces aiding lymphatic drainage(2,3). Supportive care with close monitoring of these infants in the neonatal intensive care unit (NICU) is important for resolution of the symptoms and preventing complications.

Transient tachypnea of newborn is presented at or shortly after birth with grunting, retractions, and an increased respiratory rate. The symptoms of TTN are nonspecific and can be seen in many neonatal disorders including, pneumonia, sepsis, surfactant deficiency and meconium aspiration. Consequently most infants with TTN are evaluated for infection and are treated with broad-spectrum antibiotics pending a definitive diagnosis. Although short-term antibiotic therapy does not pose obvious morbidity to neonates, the provision of any unnecessary treatment should be avoided.

Based on these reasons we have conducted a prospective study to compare late preterm and term newborns administered antibiotic treatment and conservative management with the diagnosis of TTN including infectious complications and length of hospital stay.

METHODS

Newborns having a diagnosis of TTN with a gestational age (GA) 34-0/7 and 41-6/7 weeks who were delivered in Zekai Tahir Burak Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences (Ankara, Turkey) between January 2014 and December 2014 were enrolled in the study. Parental informed consent was obtained from all individual participants included in the study. The study was approved by Ethics committee at Zekai Tahir Burak Maternity Teaching Hospital.

Gestational age was based on the menstrual dating. 34-0/7 weeks was chosen to exclude lung immaturity as being a potential cause of respiratory distress. The diagnosis of TTN was established based on the following clinical and laboratory criteria: (1) onset of tachypnea (respiratory rate exceeding 60/min) within 6 hours after birth; (2) persistence of tachypnea for at least 12 hours; (3) chest X-ray indicating at least one of the following: prominent central vascular markings, widened interlobar fissures of pleural fluid, symmetrical perihilar congestion, hyperaeration as evidenced by flattening and depression of the diaphragmatic domes or increased anteroposterior diameter, or both and (4) exclusion of all other known respiratory disorders (meconium aspiration, respiratory distress syndrome, pneumonitis, congenital cardiac disease) and non-respiratory disorders (metabolic disorders, polycythemia) likely to cause tachypnea, based on radiologic and laboratory findings(4). Patients with transient respiratory distress of <6 hours duration were classified as having a delayed transition and were excluded.

Maternal and newborn demographics, clinical characteristics and details were extracted from the medical record between 1 January 2014 and 31 December 2014 prospectively. Newborns who received antibiotics during hospital stay were recorded for the type of antibiotics used, length of treatment, perinatal risk factors. Determination of treatment and evaluation of chest X-rays were made by a single experienced neonatologist. Perinatal risk factors for sepsis included: maternal urinary infection, premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), peterm labor and maternal intrapartum antibiotic prophylaxis. PROM was defined as membrane rupture >18 hours prior to delivery.

All newborns included in the study were evaluated for maternal diseases, complications including early-onset sepsis, late-onset sepsis, pneumonia, and air leak. Air leaks were right pneumothorax, left pnemothorax and pneumomediastinum. Type of respiratory support used were either supplemental oxygen therapy or nasal continuous positive airway pressure (nCPAP). Neonatal blood C-reactive protein(CRP) and interleukin-6(IL-6) levels at 6 hours postdelivery were analyzed. Enzyme-linked immunosorbent assay kits were used to measure IL-6 (R&D Systems, Minneapolis, MN, USA) and levels of IL-6 >50 pg/ml was considered elevated. CRP was measured with the Behring BN II Nephelometer (Dade Behring, Marburg, Germany) and levels of CRP > 5 mg/dl was considered elevated.

STATISTICAL ANALYSIS

All data was analyzed using SPSS Statistics version 20 (IBM, Armonk, N.Y., USA). Group comparisons between patients who did and did not receive antibiotics were made by t-test and chi-square test. Data were expressed as mean ± SD. Differences in the means of variables were tested using both parametric and non-parametric tests depending on the distribution of the variables. A probability value of less than 0.05 was considered significant. T-test, Mann-Whitney U and chi-square tests were used for comparing indexes between groups. All data was analyzed using SPSS Statistics version 20 (IBM, Armonk, N.Y., USA).

RESULTS

Two hundred and ninety one infants were included in the study and 101 (34,7%) were given antibiotic treatment and 190 (65,3%) were followed with conservative treatment. Maternal and newborn demographics and clinical characteristics are shown in table 1.

Table 1. Characteristics of the study population

Variables	Received antibiotics (n=101)	Did not receive antibiotics (n=190)	p value
Gestational age, weeks	36.1 ± 1.6	36.2 ±1.7	0.50
Birth weight, g	2654 ± 527	2714 ± 626	0.054
Male	48	101	0.9
Median Apgar score,IQR			
1 min	7 (7, 8)	7 (7, 8)	0.4
5 min	9 (8, 9)	9 (9, 9)	0.17
Cesarean section	74 (73)	154(81)	0.125
Multiple gestation	11 (10)	29 (15)	0.495
Use of ART (IVF)	2 (2)	2 (1)	0.518
Respiratory support			
Low flow O_2	21 (21)	110 (57)	< 0.0001
nCPAP	80 (79)	80 (42)	< 0.0001
WBC, /mm^3	14940 ± 6035	14500 ± 5048	0.511
CRP[a], mg/dl	2.99 ±8.7	0.82 ±1.2	< 0.001
IL-6[b], IU/ml	56 ± 71	23 ± 23	< 0.0001
Hospital stay, days	7.8 ±3.6	5.5 ±3.1	< 0.0001

Values are means ± SD or n (%), unless otherwise indicated.IQR = interquartile range; ART = artificial reproductive technique; IVF = in vitro fertilization; NCPAP = nasal continuous positive airway pressure.

a: Values > 5 mg/dl is abnormal; b: Values > 50 IU/ml is abnormal.

Only 1/3 of the patients were treated with antibiotics during the hospitalization period. There was no significant difference in gender, GA, birth weight, parity, multiple gestation, or maternal disease between the treated and untreated groups (p=0.054-0.805).

APGAR scores at 1 min and 5 min did not significantly differed between treated and untreated infants (p>0.05 and p>0.1 respectively).

There was a statistically significant difference in laboratuary parameters including C-reactive protein (CRP) and interleukin-6 (IL-6) levels (2.99 ± 8.74 mg/dl vs 0.82 ± 1.19 mg/dl; p<0.001 and 56.5 ± 71IU/L vs 23.4 ± 23IU/L; p=0.0001 respectively), while white blood cell (WBC) did not significantly differ between the groups (p=0.51).

There was a statistically significant difference in length of hospital stay between the treated and untreated groups (7.7 ± 3.6 vs 5.5 ± 3.1 days; p<0.0001).

There was no significant difference in the mode of delivery between the groups (cesarean section vs. spontan vaginal delivery, 81% vs 73%; p=0.125). A greater degree of noninvasive respiratory support was used in the care of the treated infants when compared to untreated infants (p < 0.001), while the untreated group had a greater degree of low flow O2 (p<0.0001). In the untreated group, indications for preterm delivery were; abnormality in fetal well-being, multiple gestation, plasental abruptio, umblical cord prolapsus, preterm labor, maternal health problems such as preeclempsia, plasental insertion abnormalities, and elective delivery.

Of the 101 newborns treated with antibiotics, 26(25.7%) preterm labor, 14 (13.9%) PROM, 9(9.9%) PPROM, 5(5%) had maternal urinary tract infection, and 5 (5%) intrapartum antibiotic treatment in maternal obstetric history.

2 newborns out of 101 treated patients had blood culture proven sepsis, one

with Escherichia coli and the other with Klebsiella pneumoniae.

Of the 101 infants treated with antibiotics 26 (25.7%) developed a complication including 7 with pneumonia, 5 with early-onset sepsis, 4 with late-onset sepsis, 9 with pulmonary air leak and 1 with sellulitis. Sellulitis was associated with the intravenous access and treated with vancomycin and amicasin. In 190 untreated infants, 2 (1%) infants had a complication, one having late-onset sepsis and one with pulmonary air leak.One patient was placed on antibiotics for urinary tract infection prophylaxis based on an ultrasound finding of hydronephrosis. According to this findings, statistically the two groups differed significant on developing complications(Table 2).

Table 2. Infectious outcomes and pulmonary air leak complications among neonates with TTN

Variables	Received antibiotics (n=101)	Did not receive Antibiotics (n=190)	p value
Death	0	0	1
Positive culture result	2	0	0.01
Early-onset sepsis	5	0	< 0.001
Late-onset sepsis	4	1	< 0.001
Other[a]	1	0	
Pulmonary air leak			
Right pneumothorax	2	0	< 0.001
Left pneumothorax	6	0	< 0.001
Pneumomediastinum	1	1	1

Values are n (%). a: Sellulitis on the intravenous line access.

In the treatment group, 9 infants having an air leak; 2 had right pneumothorax, 6 had left pnemothorax and 1 had pneumomediastinum. On the other hand, only 1(0.5%) infant had pneumomediastium which was spontaneously resolved. According to this finding, there was a statistically significant difference between treated and untreated newborns on development of pulmonary air leak (p=0.001).

We identified a rate of coexisting culture-proven early-onset infection of 0.6% and codiagnosis of culture-positive or -negative infection of 3% in our population of 291 patients with TTN. All patients in the treatment group were treated with antibiotics based on risk factors or supporting laboratuary findings and clinical course individually.

DISCUSSION

TTN, also known as wet lung is one of the most frequent causes os repiratory distress in tern and late preterm infants and delayed resorption of fetal lung fluid is thought to be underlying cause(5,6). The incidence is reported to be 14-18 per 1000 live births in the USA. Risk factors for TTN are prematurity, cesarean delivery without labor, small for gestational age, large for gestational age, male gender, infants of diabetic mothers, and maternal astma(7-12). Clinical signs of TTN are not spesific and can be presentation of other neonatal disorders such as pnemonia and sepsis which must be treated with antibiotics. So it is a clinical practice to initiate empiric antibiotics for suspected pneumonia in newborns presenting with respiratory distress(13-15). However this is not evidence-based and has a potential risk of emergence of resistant organisms, exposure to ototoxic and nephrotoxic drugs and alteration of the normal immune maturation developed and induced by intestinal microbiata(12). As a consequence of these factors, the patients in the study were given antimicrobial therapy according to perinatal risk factors and on the basis of abnormal laboratory tests such as elevated CRP and IL-6 levels. Of the 291 infants included in the study, 101 (34.7%) were given antibiotic treatment and 190 (65.3%) were followed with conservative treatment. In 2013, Weintraub et al. reported a percentage of 34% and 66% for the treated and untreated groups in their study including 745 infants. Although prescribing intravenous antibiotics in the treatment course of TTN changes from centre to centre it is possible to say that there is a tendency to give less antibiotics and for shorter durations of courses(12).

Weintraub et al. reported culture-proven early-onset infection of 0.4% and codiagnosis of culture-positive or culture negative infection of 1.1% in patients with TTN, while our finding was 0.6% for culture-proven early-onset infection and 3% for codiagnosis of culture-positive or culture negative infection(12).

Although the treatment group had a greater degree of low flow oxygen and noninvasive respiratory support in their care compared to untreated infants, we do not think that use of suplemental oxygen or noninvasive support is a marker or predictor of infection and complications. We speculate that not only perinatal risk factors but also abnormal laboratory tests such as CRP and IL-6 levels must be evaluated when iniating antibiotic treatment.

As we were not focused on the cut-off levels for CRP and IL-6, it is difficult to state the cut off values for initiation of antibiotics.

Weintraub et al. reported no difference in median length of hospital stay between the treated and untreated groups. Similarly, in 2015, Li et al reported no difference between the control and treated groups. In contrast to literature, in our study duration of hospital stay was longer in the treatment group compared to untreated group(12,16).

Pulmonary air leak, being discovered more frequently in the newborn period than at any other time of life is associated with signficant morbidity and mortality in newborns(17). In our study, 10 infants had an air leak; 2 had right pneumothorax, 6 had left pnemothorax and 1 had pneumomediastinum in the treatment group. On the other hand, only one infant had pneumomediastium which was spontaneously resolved in the untreated group. It is important to be aware of this potential complication and at the beginning the infant must be evaluated for pulmonary air leak as this can be the cause of respiratory distress rather than TTN and in the follow up of TTN patients it will be helpfull keeping in mind pulmonary air leaks so that the infant can be handled with good care.

This study has several limitations, first this is a single center study, as there is no recommended treatment guidelines, in different hospitals and localizations prescribing intravenous antibiotics is usually decided by the treating physician. Second, the total number of cases examined was not sufficient to generalize the conclusion. As the data was obtained from the medical records, incorrect or absent data may have failed to identify potential eligible subjects. Third, since we investigated the treatment outcomes that developed in the early period, we could not demonstrate long-term serious complications and outcomes. Although its limitations our study documents not only infectious complications but also pulmonary air leak complications which is not included in many studies on TTN.

The reasons considered to initiate antibiotics such as elevated infectious markers may cause not only longer hospital stay but also long hospital stay related possible complicatons such as nosocomial infections. Besides, with the results of our study it is not possible to make the distinction; we believe that these observations will inspire new clinical trials in the future and lead to clinicians question themselves while initiating antibiotics. In the light of our results we emphasize that most infants with TTN receive unnecessary antibiotics.

In our study we tried to make a risk factor based-approach to antibiotic use in late preterm and term neonates with TTN. A more judicious approach to the use of postnatal antibiotics in infants with TTN may be beneficial and warranted. To achieve this aim, larger and multi-center studies are needed to help characterize TTN infants for better management of TTN with or without antibiotics and prevention of long term antibiotic treatment related.

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Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Research Ethics committee at Zekai Tahir Burak Women's Health Training and Research Hospital, Faculty of Medicine, University of Health Sciences. Informed consent was obtained from all individual participants included in the study.

Authors' contribution: Erbu Yarci and Fuat Emre Canpolat performed this study. Erbu Yarci wrote the manuscript and was responsible for critical review and approval of the manuscript. Aslihan Kose Cetinkaya was responsible for the patients follow up. Fuat Emre Canpolat revised the intellectual content and performed the statistical analysis.

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