Original Research

Transient tachypnea of the newborn: Is empiric antimicrobial therapy needed?

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Abstract

BACKGROUND: Transient tachypnea of the newborn (TTN) is a self-limited increase in the work of breathing in near- and full-term infants; it is attributed to a delay in the clearance of alveolar fluids. Prophylactic antibiotics are usually administered until blood cultures are reported negative for 48 hours.

OBJECTIVES: To prospectively compare outcomes of infants presented with classic TTN who were treated with or denied from intravenous antibiotics.

METHODS: A prospective cohort study was conducted on all infants admitted with classic TTN. Pre-set diagnostic criteria for classic TTN were applied in order to exclude other cases presenting with respiratory distress. Infants with classic TTN were stratified into two groups based on whether they received or did not receive antibiotics. The decision to administer antibiotics solely depended upon the style of the covering physician at the time of admission to the NICU. The following investigations were obtained from infants of both groups: blood culture, C-reactive protein, complete blood count, blood gas profile and chest X-ray.

RESULTS: A total of 15146 full-term infants were delivered during the study period; of them 923 were admitted to the NICU. Classic TTN was diagnosed in 168 infants; of them 106 (63%) received and 62 (37%) did not receive antibiotics. Two infants in the treated group and an infant in the non-treated group had microbiologically confirmed bacteremia. Infants in the treatment group stayed longer in the hospital (72 ± 6 vs. 48 ± 3 hrs). No recorded cases required readmission in either group.

CONCLUSIONS: With the application of strict criteria for classic TTN and the close observation in the NICU, the empiric use of antibiotics may be avoidable. Randomized controlled trials are needed to confirm the feasibility and safety of such approach.

Keywords: Transient tachypnea of newborn, microbiology, antibiotics, blood culture

1. Background

Transient tachypnea of the newborn (TTN) is the most common respiratory disorder among newborns [1]. It is a clinical condition associated with respiratory distress due to delayed evacuation of the lung fluids, which naturally occurs before, during and immediately
after delivery. It was first described in 1966 as a major cause of respiratory distress in term and near-term infants [2]. In 1981, Haliday and McClure described two different clinical entities of TTN: classical and severe [3]. The incidence of the condition varies widely among centers. In a review of 29,669 deliveries from 1992 to 1999 from a single center in the United States, TTN occurred in more infants after elective cesarean than after vaginal delivery (3.1 versus 1.1 percent) [4]. In another British review of 33,289 term deliveries (37 to 42 weeks), the incidence of TTN was 5.7 per 1000 births [5].

In a German study that analyzed data from perinatal regional registries of almost 240,000 full-term deliveries from 2001 to 2005, the incidence of TTN was 5.9 cases per 1000 singleton births [6]. Elective cesarean section was the most significant risk factor associated with TTN compared against vaginal deliveries in data from the national German perinatal registry (42 percent versus 9 percent). Other risk factors associated with TTN included small for gestational age (16 percent versus 10 percent), large for gestational age (14 percent versus 11 percent), and male gender (60 versus 51 percent). Maternal diabetes and asthma are also well-recognized risk factors [6].

At Hamad Medical Corporation (HMC) Women’s Hospital, the overall incidence of classic TTN is approximately 1.0 percent (10 cases per 1000 singleton live birth). The rate of cesarean section was 21% in 2010. In the same year, total number of live-born deliveries was 16550, and the total number of full-term newborn infants admitted to the NICU was 945. The overall rate of positive blood culture among newborn ≥2500 grams admitted to the NICU was 3.3 percent, whilst the incidence of early neonatal sepsis among full-term infants is approximately 3.2 percent.

Many infants who have TTN are treated with antibiotics for the first 24 to 48 hours until the blood culture is shown to be negative, as sepsis is considered an important differential diagnosis [2]. Prescribing intravenous antibiotics in the treatment course of TTN is gradually changing and is usually left to the clinical judgment of the treating physician. However, it has been traditionally recommended to treat based on a terror of hidden infection [7]. Nonetheless, in several review articles discussing the respiratory outcomes of late preterm and term infants, the use of intravenous antibiotics is seldom investigated in the literature. Recently, Costa et al. compared TTN against pneumonia in a small sample size retrospective study, the conclusion of which was that both are indistinguishable except in the history of perinatal infection [8]. Their argument was based on non-microbiological evidence. Considering the importance of increased bacterial resistance to antibiotics used inside the nursery, this study was carried out to justify the use of routine prophylactic intravenous antibiotics and whether it will protect the infants from suspected infection.

2. Objective

The aim of this prospective study was to assess the rate of positive blood cultures in the course of treatment of classic TTN and whether the empirical use of antibiotics is required during the management of classic TTN.

3. Methods

A non-randomized prospective cohort study was performed to follow up the course of infants aged 37 to 41 weeks’ gestation born over a ten-month period, March 2010 to December 2010, at Women’s Hospital and admitted to the NICU with an initial diagnosis of classic TTN after strict application of the clinical, laboratory and radiological characteristics of classic TTN. Women’s Hospital is the largest and main tertiary maternity hospital in the state of Qatar with an average 17000 deliveries per year.

3.1. Patient recruitment

Classic TTN was defined in the study according to the following inclusion criteria adopted from the literature [3, 7, 9–12] (Fig. 1). The following infants were excluded from the study: infants with an antenatal history suggestive of chorioamnionitis or maternal infection, significant congenital malformation, infants with a history of meconium at delivery who required intubation and endotracheal suctioning, a low enough Apgar score to require advanced resuscitation, chest X-ray finding suggestive of pneumonia or significant shadows, which is not consistent with the radiological features of TTN. Infants with required mechanical ventilation, and those who showed signs of early neonatal septicemia. All infants in the study received an initial blood gas, complete blood count, C-reactive protein (CRP), blood culture and chest X-ray.
at four hours of age if respiratory signs persisted. The decision to commence antibiotics was left up to the admitting physician, based merely on his own belief whether TTN cases need antibiotic treatment or not. The investigators did not attempt to interfere with the decision of the managing physician. Infants were stratified into two treatment groups; the first one received intravenous antibiotics (penicillin G and gentamicin) beside the supportive treatment and the second group received only supportive treatment. The study has been approved by the Institutional Review Board at HMC. Since the study included only data monitoring, parental consent was waived.

3.2. After discharge follow-up

Infants’ medical records were tracked through the electronic pediatric patient data registry, national pediatric emergency registry, inpatient pediatric admission registry, and microbiology registry to identify any readmissions within 30 days after discharge.

4. Results

There were 15146 live births between 37–41 weeks gestation during the study period and of these, 923 full-term infants were admitted to the NICU where 168 infants were admitted with the initial diagnosis of classic TTN. The overall rate of TTN was 1.1 percent or 11 cases per 1000 live birth. The number of cases that received antibiotics was 106 infants, whilst 62 infants did not (Fig. 2). The mean CRP was 9.6± 3 mg/dl in the antibiotic group versus 6.7 ± 4.4 in the no-antibiotic group. True blood cultures were positive in three infants, whilst three cultures grew more than two non-pathological organisms and were considered con-
Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Antibiotics (106 infants)</th>
<th>No antibiotics (64 infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial diagnosis as TTN</td>
<td>106</td>
<td>64</td>
</tr>
<tr>
<td>Diagnosis of TTN at time of discharge</td>
<td>104</td>
<td>82</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>37.7 ± 1.9</td>
<td>37.2 ± 2.1</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>2.9 ± 0.7</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>Females</td>
<td>61 (58%)</td>
<td>30 (47%)</td>
</tr>
<tr>
<td>Apgar score at 5th min</td>
<td>9.5 ± 0.8</td>
<td>9.8 ± 0.4</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>43 (40%)</td>
<td>46 (75%)</td>
</tr>
<tr>
<td>Maternal antibiotics (≥2 doses)</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Prolonged rupture of membrane (≥24 hrs)</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Infant of diabetic mother</td>
<td>10.1%</td>
<td>14.3%</td>
</tr>
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<td>Bronchial asthma in the family</td>
<td>0.9%</td>
<td>0.4%</td>
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<tr>
<td>Positive maternal cultures</td>
<td></td>
<td></td>
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<tr>
<td>High vaginal swabs</td>
<td>Candida (n=7)</td>
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</tr>
<tr>
<td>Urine</td>
<td>Candida (n=1)</td>
<td>0</td>
</tr>
<tr>
<td>WBC (1 × 10^6 liters)</td>
<td>13.5 ± 3.6</td>
<td>13.0 ± 6.6</td>
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<tr>
<td>Neutrophile count (1 × 10^6 liters)</td>
<td>7.2 ± 4.4</td>
<td>6.7 ± 4.4</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>9.3 ± 5.8</td>
<td>1.6 ± 5.1</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hospital stay (hrs)</td>
<td>72 ± 6</td>
<td>48 ± 3</td>
</tr>
<tr>
<td>Late neonatal sepsis (3–28 days after birth)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HVS = high vaginal swab of mixed bacterial growth; S. aur = Staphylococcus aureus, S. epi = Staphylococcus epidermidis, GBS = Group B streptococcus. *Values >10 mg/dl is abnormal; the greatest value was 11 in the antibiotics group and 8 in the noantibiotics.

Table 1: Characteristics of patients included in the study (number of infants)

5. Discussion

Use of antibiotics in newborn infants alters the microflora of their gastrointestinal tract; that has been shown to associate with multiple health hazards [7, 14, 15]. In this prospective study we report that, even with vigilant efforts to exclude infections, significant pathological organisms were grown in three blood culture. The rate of infection in our cohort was consistent with previously reported figures [16, 17]. In the group who did not empiric treatment, there was a single case of Staphylococcus aureus bacteremia; that infant was not clinically compromised with the delay of antibiotic treatment until culture results were obtained. It can be possibly explained by the vigilant application of the criteria that could determine any hemodynamically compromised infant.

There are no pathognomonic features of neonatal sepsis [18–20], and the clinical presentation of neonatal sepsis can vary. In a study conducted in Kenya, difficult feeding, unexplained pallor, cyanosis and unconsciousness were strongly associated with severe sepsis, whereas rapid breathing, nasal flaring, grunting and lethargy were found to be associated with a moderate form of sepsis [21].

The positive rate of neonatal blood cultures has been found to range from 25 to 54 percent [6, 10–12]. Blood culture to isolate the offending pathogen remains the gold standard for the definitive diagnosis of septicemia [22, 23]. However, the results of a blood culture take hours to days, thus necessitating the initial empirical treatment of suspected cases. In Costa et al.’s study, the risk of perinatal infection was significantly more frequent in patients with pneumonia, and together with cesarean section, were the only differences between the TTN group and the pneumonia group. They concluded that antibiotics should initially be prescribed until cultures, biological markers of infection and clinical evolution definitely exclude the presence of infection [8].

This study is the first cohort study to challenge the usefulness of prescribing antibiotics as part of the treatment protocol of classic transient tachypnea of the newborn. In this study, the authors carefully applied...
the diagnostic criteria for classic TTN; all patients had a negative blood culture, except for three patients with significant pathogens. Among the two groups, there was no difference in white blood count, neutrophile count, or CRP, whilst those who were not prescribed antibiotics were discharged 24 hours earlier. All cases in both groups did well and ran uneventful clinical course. No recorded cases were readmitted to the pediatric service after discharge from the nursery. In the present study, we offer an alternative strategy for management of TTN that includes the application of strict criteria for classic TTN and close observation without empirical antibiotic treatment. Nevertheless, failure to apply such criteria or following up the infant inside the NICU will definitely dispute this approach. Indeed, this study is good enough to generate the hypothesis of conservative management in classic TTN. However, the study was not powered to prove safety of this approach; a large scale randomized trial is needed to examine this hypothesis.

Financial disclosure statement

All authors do not claim any financial interests related to this manuscript.

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