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Original Article

Clinical course in infants diagnosed with transient tachypnea of newborn: A clinical trial assessing the role of conservative versus conventional management

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Abstract

Background: Transient tachypnea of the newborn (TTN) is a respiratory disorder secondary to inadequate or delayed clearance of lung fluids. Early symptoms of the disease are indistinguishable from neonatal respiratory distress syndrome, pneumonia, and persistent pulmonary hypertension. Therefore, these newborns, in addition to receiving conservative management, receive antibiotics until blood cultures provide definite results. In this study, we assessed the clinical course of neonates diagnosed with TTN who received conventional versus conservative management.

Methods: One hundred and thirty neonates diagnosed as having TTN were randomly enrolled in two study groups. While patients belonging to one group received conservative management, those from the other group were treated with conventional medical therapy.

Results: Mean duration of hospitalization was 7 ± 0.2 in the conventional and 5 ± 1.5 in the conservative group. Duration of antibiotic therapy was 6.7 ± 2.47 days in the conventional group.

Conclusion: Newborns diagnosed with TTN without prenatal risk factors and a negative C reactive protein test do not need to be administered antibiotics and hospitalized until confirmatory blood culture results are obtained.

Keywords: Antibiotics; Hospitalization; Transient tachypnea of newborn

1. Introduction

Transient tachypnea of the newborn (TTN) is a respiratory disorder secondary to inadequate or delayed clearance of lung fluids. It is usually observed in full- or late-preterm infants[1] showing an incidence of 5.7 per 1000 births.[2] It is more often seen in male infants born via cesarean section without starting the process of labor, or born to a mother with diabetes or asthma with a history of perinatal asphyxia.[3,4] Clinical findings noted in these neonates are tachypnea, expiratory grunting, nasal flaring, and intercostal retraction at or shortly after birth. These symptoms usually subside 48−72 h after birth even though they could last up to 5 days.[1] Early symptoms of this disease are often indistinguishable from neonatal respiratory distress syndrome, pneumonia, and persistent pulmonary hypertension. Therefore, these newborns in addition to receiving conservative management, receive antibiotics until there is clarity regarding blood culture results.[5] Cesarean section is a known risk factor for the development of TTN.[6] Prevalence of cesarean deliveries has increased in recent years.[7,8] The integrated monitoring evaluation system has reported the rate of cesarean sections in Iran to be 40%.[9] Thus, large numbers of neonatal intensive care unit (NICU) beds are expected to be occupied by such patients. Although 97.5% of bacteria are easily isolated within 72 h of

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incubation, most laboratories continue incubation for 5 days.[10] Based on this policy, despite an improvement in their breathing difficulty, these newborns remain in the hospital until blood culture results are available. In addition to the occupied beds in NICUs, continued use of antibiotics can lead to the spread of antibiotic resistance and development of adverse effects associated with unwarranted use. In this study, duration of hospitalization, need for nasal continuous positive airway pressure (NCPAP) and mechanical ventilation in neonates admitted with a diagnosis of TTN using conventional treatment (including fluid intake, oxygen therapy, and prescription of antibiotics) were compared to hospitalized infants who received conservative treatment (including fluid intake and oxygen therapy without antibiotic use).

2. Methods

This clinical trial was conducted at the NICU of Imam Khomeini Hospital of Ahvaz, Iran. The registration code for the trial is IRCT2015102314215N2. Sample size was calculated based on 80% power and 95% confidence intervals.[5] Thus, based on a random numbers table, 65 patients were enrolled in each group.

This study was not blinded. Newborns with diagnosis of TTN with gestational age 34−0.7 to 41−6.7 were enrolled in the study based on the following inclusion criteria in accordance with the Rawlings and Smith criteria[11]: 1) Incidence of tachypnea (respiratory rate > 60/min) within 6 h of birth. 2) Standing on tachypnea for at least 12 h. 3) A chest X-ray demonstrating at least one of the following findings—enlarged central pulmonary arteries, thickened interlobar fissures caused by fluid retention, bilateral hilar congestion, air-filled lungs (flattening of the diaphragmatic apex), or an increased anteroposterior diameter of the chest or both. 4) No history of meconium aspiration. 5) History of fetal distress. 6) Maternal fever. 7) Premature rupture of membranes lasting >18 h.

Exclusion criteria were: neonatal respiratory distress syndrome (based on radiography and clinical course), hypoglycemia (blood glucose < 50 mg/dL), hypocalcemia (calcium level <7 mg/dL), polycythemia (hematocrit > 60%), anemia (venous hemoglobin saturation <13.5 g%, leukopenia <5000/mm^3, leukocytes > 20,000/mm^3),[12] absolute neutrophil count < 1750/mm^3, immature:total neutrophil ratio ≥ 0.2,[13] platelet count < 150,000/mm^3, positive blood culture accompanying clinical signs, need for mechanical ventilation, positive C reactive protein (CRP), and hyperbilirubinemia requiring phototherapy. An informed consent form was obtained from all families.

Neonates enrolled in the study were divided into two groups based on a random numbers table. We administered 60 mL/kg of dextrose 10% on the first day with increments of 20 mL/kg/d up to a total dose of 100 mL/kg on the third day to neonates belonging to the intervention group that received conventional treatment. Sodium chloride (3 mEq/kg) and potassium chloride (2 mEq/kg) were added to the solution from the second day onward. Additionally, these infants were administered ampicillin and gentamicin. Infants belonging to the group that received conservative therapy received fluids and electrolytes at levels mentioned above; however, antibiotics were not administered to these patients. We evaluated a complete blood count (CBC), blood culture, blood glucose and calcium, a chest X-ray, and CRP (within 8 h after birth and 24 h later), and serum bilirubin (if needed) in all infants. Infants were placed under the hood, and the inspired oxygen concentration was adjusted using an air-oxygen blender. NCPAP was initiated for those with an oxygen requirement of >50%.[14] Mechanical ventilation was initiated if the newborn demonstrated respiratory failure (partial pressure of oxygen < 50 mmHg or oxygen saturation < 85%, partial pressure of carbon dioxide > 50 mmHg) even with inspired oxygen of 50% and positive end-expiratory pressure of 7 cm water.[15] Antibiotic use was discontinued based on negative blood culture results. Patients were examined 2 days after discharge.

Maternal records were extracted from maternal record files. The two groups were compared in terms of duration of hospitalization, clinical course, need for NCPAP, and mechanical ventilation. This study with code AJUMS.REC.1394.370 has been recorded in the Ethics Committee of Ahwaz University of Medical Sciences.

2.1. Statistical analysis

The independent *t*-test was used to compare quantitative variables between the two groups, the chi-squared test was used for qualitative variables showing a normal distribution, and non-parametric Mann Whitney *U* test was used for variables showing a non-normal distribution. Data were analyzed using SPSS 22 software.

3. Results

Of the 135 infants enrolled in the study, three patients belonging to the conservative therapy group and two belonging to the conventional therapy group were excluded from the study due to hyperbilirubinemia requiring phototherapy (Fig. 1).

We found that 91.5% of the studied infants had been delivered via a Cesarean section. There was no significant difference between the two study groups in terms of gender ($p = 0.85$), gestational age ($p = 1$), weight (0.2), and delivery route (0.5).

CRP was reported to be negative 8 and 24 h after birth in all infants studied. The duration for which NCPAP was administered did not significantly differ between the groups ($p = 0.2$). Based on non-normal distribution of the hospital stay variable, the median was used (Table 1). Mean duration of hospitalization was significantly different between the two groups ($p = 0.0001$) (Fig. 2).

In the conventional management group, mean duration of obtaining blood culture results and antibiotic administration was 6.7 days. We observed that three infants belonging to the group receiving antibiotics showed blood cultures positive for *methicillin resistant coagulase-negative Staphylococcus* while two infants belonging to the conservative management group

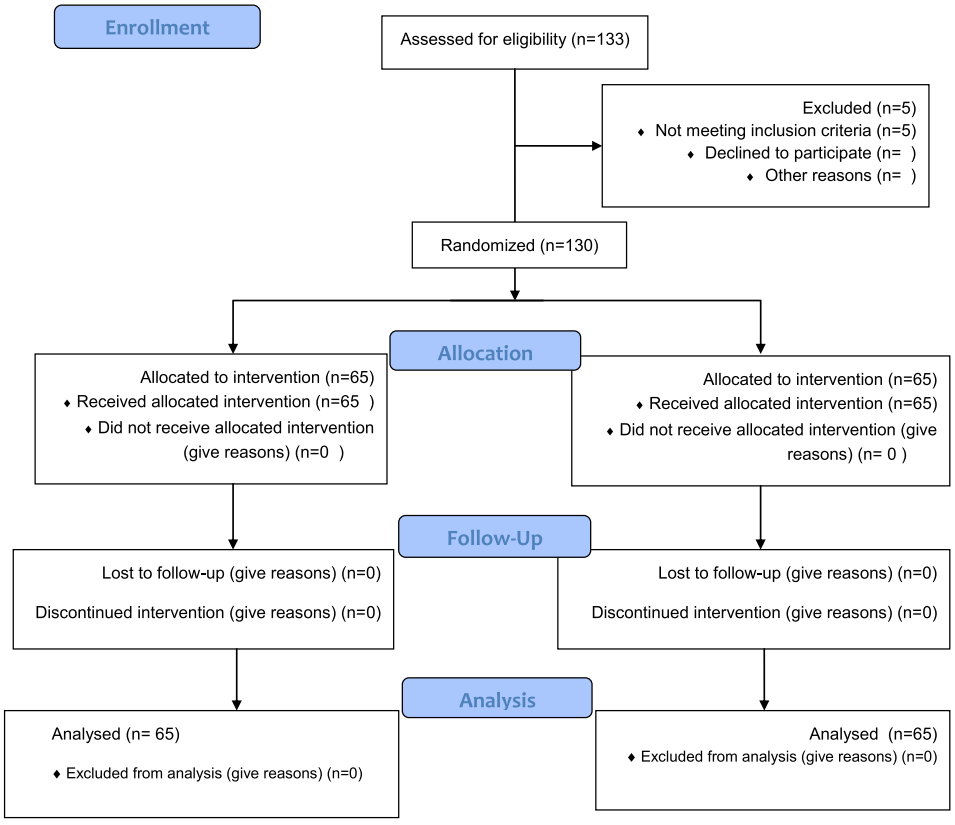

Fig. 1. Participant CONSORT flow diagram: approach to neonates with transient tachypnea of newborn with conventional or conservative treatment.

Table 1
Clinical course of participant patients with transient tachypnea of newborn with conventional or conservative treatment.

Variable	Conventional group	Conservative group	*p*
NCPAP, mean ± sd (h)	20.9 ± 18.4	16.7 ± 20.3	0.2
Oxyhood, mean ± sd (h)	39.6 ± 29.7	34.7 ± 23.3	0.3
Hospitalization			
Median (d)	7	5	Z = −4
Interquartile range (d)	5–8	4–6	–

showed a positive blood culture to the same organism. Workup for evaluation of sepsis was repeated in the group receiving antibiotics, although they did not show clinical signs of sepsis, and the antibiotic was changed to vancomycin until blood culture results were available. Blood culture was repeated for two cases belonging to the conservative management group who showed positive blood cultures in the absence of clinical symptoms. These patients were discharged with warning signs. Blood cultures were found to be negative during follow-up, and the infants did not demonstrate signs or symptoms of infection.

4. Discussion

Because infection features as one of the important differential diagnoses in cases of TTN, a majority of infants diagnosed with this disorder are treated with antibiotics until blood culture results become available.[16] Conventionally, blood cultures should normally be incubated for 5 days.[17] Using newer techniques to obtain blood cultures like the BACTEC blood culture system, the required time and accuracy to culture bacteria may be shortened.[18] However, these new methods are not available in many parts of the world, including our hospital, and blood samples are cultured using older conventional methods. While awaiting blood culture results, newborns diagnosed with TTN are unnecessarily exposed to nephrotoxic and ototoxic antibiotics, which continue to be administered until blood culture results can be obtained. Antibiotic use in infants causes alterations in gut microflora, which can predispose them to several risks.[19] Short-term use of antibiotics even for short periods and for exclude the possibility of infection can be associated with the risk of changes in microflora, an increase in microorganisms' resistant to antibiotics and highly emergence of resistant fungi in the NICUs.[19] Despite the use of newer diagnostic markers of infection, estimation of CRP continues to be very important in diagnosing early infections in newborns.[20] In our study, 91.5% of the studied infants had been delivered by a Cesarean section, which has been shown to be the most important risk factor for the development of TTN—ratio compared with vaginal delivery is 42% versus 9%.[21] Reportedly, the rate of cesarean sections performed in Iran is 40%.[22] The incidence of TTN has been reported as 5.9 per 1000 singleton births.[22] A high incidence of cesarean section deliveries is associated with an increase in the number of newborns with TTN. The number of beds occupied by these patients in the NICU is unknown in

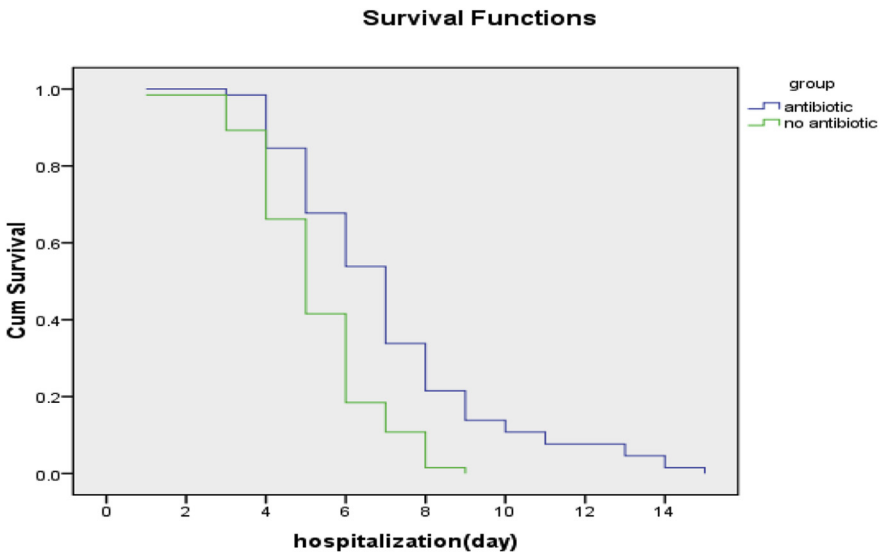

Fig. 2. Comparison of duration of hospitalization between two groups.

Iran. However, given the high incidence of cesarean section deliveries in Iran, these infants probably occupy a large number of NICU beds. Previous studies have also shown that empirical use of antibiotics may not be necessary in infants with TTN.[5,22] Prolonged hospitalization while awaiting blood culture results in patients in the NICU may be unwarranted and is associated with high bed occupancy rates and high economic costs.

In conclusion newborns diagnosed with TTN without any prenatal risk factors and demonstrating a negative CRP do not need to be administered antibiotics and hospitalized until confirmatory blood culture results are obtained.

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