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Eficacy and Safety of Restricted Fluid Therapy in Transient Tachypnea of the Newborn: A Randomized Controlled Study

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Study Protocol:

This prospective randomized study was conducted in a tertiary neonatal intensive care unit (NICU) between October 2021 and July 2023. The study was approved by Institutional Clinical Trials Ethics Committee (approval number: 2018/76). Neonates born at our hospital with a gestational age of ≥34$^{0}/_{7}$ weeks who were diagnosed with TTN were included in the study. TTN was diagnosed based on the presence of respiratory distress symptoms beginning within the first hours after birth, together with at least one of the following chest radiographic findings: symmetrical perihilar congestion, increased perihilar vascular markings, widened interlobar fissures, or air trapping, and after exclusion of other causes of respiratory distress, including respiratory distress syndrome, meconium aspiration syndrome, congenital pneumonia, congenital heart disease, polycythemia, and surgical conditions (6)

Infants with severe congenital anomalies, those who required intubation in the delivery room or upon admission to the NICU, infants born through meconium-stained amniotic fluid, perinatally asphyxiated infants, infants with suspected sepsis based on risk factors or clinical findings, and infants diagnosed with TTN who did not require NIV were not included from the study. In addition, infants initially included with the diagnosis of TTN who were diagnosed with congenital pneumonia and/or sepsis in the follow-up or who received surfactant therapy or who were evaluated as “complicated TTN” after developing pneumothorax, pneumomediastinum or persistent pulmonary hypertension were excluded from the study. The parents of all participating infants provided written informed consent. This study was reported in accordance with the CONSORT guidelines for randomized controlled trials.

Clinical and demographic characteristics of the patients were recorded. The degree of respiratory distress was evaluated using the Silverman–Anderson score prior to NIPPV, and clinical status was assessed using the SNAP-PE II score.

Randomization and follow-up

Infants with TTN requiring NIPPV were randomized within the first two hours of life to either the RF group or the standard fluid (SF) group using the sealed opaque envelope method. To ensure homogeneous distribution of infants with similar gestational ages between the groups, infants born at **$34^{0}/_{7}$–$36^{6}/_{7}$ weeks** and those born at **≥37 weeks of gestation** were randomized separately using a stratified randomization approach.

The total fluid volume administered on the first day was initiated at **50 mL/kg/day** in the RF group and **70 mL/kg/day** in the SF group for infants with a gestational age of **$34^{0}/_{7}$–$36^{6}/_{7}$ weeks**, whereas it was initiated at **40 mL/kg/day** in the RF group and **60 mL/kg/day** in the SF group for infants with a gestational age of **≥37 weeks**. During the subsequent days, the total fluid volume administered per kilogram was either increased by 10–20 mL/kg/day or maintained, depending on whether physiological weight loss occurred and on serum sodium levels. All infants received intravenous fluids containing **10% dextrose and 0.25% NaCl** during the first 24 hours. At 24 hours of postnatal age, **15 mmol/L of KCl** was added to the intravenous fluids if serum potassium and creatinine levels were within normal ranges and urine output was adequate. Blood glucose monitoring was performed at least every **6 hours**. The dextrose concentration of intravenous fluids was increased in infants whose blood glucose levels approached the lower limit **(50–60 mg/dL).** Blood glucose levels below **50 mg/dL** were considered hypoglycemia. Daily body weight, urine output, and fluid intake were recorded. Serum electrolyte levels, blood urea nitrogen (BUN), creatinine, calcium levels, and urine specific gravity were measured at **24 and 72 hours of postnatal age** and on **day 5.** In addition, the duration of NIPPV, time to first enteral feeding, time to full enteral feeding, and day of discharge were recorded. Primary outcomes included duration of NIPPV and the day of discharge. Secondary outcomes included changes in weight, urine output, biochemical parameters, and adverse events.

Non-invasive ventilation and weaning

Non-invasive ventilation was administered to all infants NIPPV mode (non-synchronised) and using short binasal prongs (Hudson® prong) as the nasal interface. Initial NIPPV settings were identical in both groups and were set as follows: positive end-expiratory pressure (PEEP) of **6 cmH_2O,** peak inspiratory pressure (PIP) of **20 cmH_2O,** inspiratory time of **0.4 seconds,** and a respiratory rate of **20–30 breaths per minute**. NIPPV was delivered using a neonatal ventilator (SLE; Specialised Laboratory Equipment, South Croydon, UK).

Weaning was initiated in infants whose respiratory distress regressed. Initially, PEEP was reduced to **4–5 cmH_2O**, followed by discontinuation of NIPPV through gradual reduction of the respiratory rate.

Statistics

Continuous variables are presented as mean ± standard deviation or median (and minimum–maximum) and categorical variables are presented as number and percentage. Categorical variables were compared using the chi-square test (2-tailed). Continuous variables were compared with Student's *t*-test or Mann-Whitney U test depending on data distribution. A p value <0.05 was considered as statistically significant. Statistical analyses were performed using **SPSS version 17.0** (SPSS Inc., Chicago, IL, USA).