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## Review Article

### Comparative Analysis of Non-Invasive Ventilation Modalities in Neonatal Respiratory Distress Syndrome: A Systematic Review

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#### Abstract

Many premature children require mechanical ventilation, and volume-targeted ventilation reduces the difficulties and length of time associated with mechanical ventilation. This study compared volume-targeted ventilation during volume-guaranteed ventilation (VG) for respiratory distress syndrome (RDS) in very preterm infants at a lower tidal volume (4–5 mL/kg) with a greater tidal volume (7–8 mL/kg). There was no difference in the time to a 25% baseline peak pressure reduction between the two groups, and the newborns in both groups had comparable maternal, demographic, and clinical features at baseline. Short-term secondary outcomes and intermediate-term problems did not vary. In this trial, 70 RDS babies who received varying tidal volumes did not show statistically significant variations in their  $\text{paCO}_2$ ,  $\text{FIO}_2$ , or  $\text{FIO}_2$  requirements. Given that both tidal volume ranges used for the study are at this level, functional residual capacity could be the reason for the unfavorable study findings. Noninvasive ventilation techniques serve as the main source of assistance. To minimize the need for invasive mechanical ventilation and effectively manage respiratory distress syndrome in neonates, the best non-invasive ventilation technique should be used. While these approaches might provide initial non-invasive respiratory assistance, more research is needed to determine their benefits for lung protection and bronchopulmonary dysplasia compared to other therapy techniques. This study's goal is to assess the information on the three main non-invasive breathing methods for neonatal respiratory distress syndrome. To find out if it is possible to optimize the non-invasive procedure, we suggest evaluating the factors that lead to treatment failure across different modalities. In this new field, we assess indirect evidence, acknowledging that while there are many case series and research initiatives, there are few strong trials. As a result of being retrospective, patient group recommendations often align with individual experiences.

**Keywords:** Neonates, Non-invasive techniques, Respiratory distress syndrome, Ventilation modalities

#### Background

Both preterm and term newborns frequently experience respiratory distress, especially after giving birth and after a cesarean section, when their body temperature drops. During

the first five days following delivery, acute respiratory failure accompanied by hypoxemia and/or hypercapnia is known as neonatal respiratory distress syndrome (NRDS). Asphyxia

and hypoxemia result from atelectasis and ineffective ventilation/perfusion (V/Q) ratios caused by an imbalance in surfactant production and pulmonary factors that are present in premature newborns. Serious cases of intraventricular hemorrhage (IVH), pulmonary interstitial emphysema, bronchopulmonary dysplasia (BPD), and even mortality may develop from NRDS if left untreated. The non-invasive breathing technique that is most frequently prescribed is nasal CPAP (nCPAP). Preterm infants who are at risk of developing NRDS and hypoventilation/hypercapnia are stabilized using CPAP. Recent years have seen the emergence of numerous other non-invasive ventilation techniques. Bi-level positive airway pressure (BiPAP) ventilation, which works similarly to CPAP in theory, alternately administers two distinct pressures: a lower expiratory pressure (EPAP) and a greater inspiratory pressure (IPAP). Nasal BiPAP is a non-invasive nasal BiPAP that has two pressure settings. On the other hand, NIPPV (nCPAP plus the capability of intermittent positive pressure ventilation) enhances the peak inspiratory flow rate of nCPAP by providing both nCPAP and an aid function. While changes in nasal insertion depth cause the maximal airway pressure to fluctuate during the day, NIPPV enables us to preserve a constant nCPAP level [1].

## **Materials and Methods**

Research on NP, including CPAP, BiPAP, and iNO, as well as any other breathing modalities that would include the ones, was included in this systematic review if it was a randomized controlled trial (RCT), cohort or cross-over research. There were no linguistic limitations. Excluded research included reviews, letters to the editor, in vitro studies, and studies concentrating on adult or pediatric populations. Three reviewers separately screened each paper in a three-step selection procedure. First, papers that weren't relevant were filtered out of the titles and abstracts. Full-text articles were then examined considering the inclusion criteria. Results from the database were cross-checked. Exclusionary reasons were noted. The search was carried out in PubMed, Embase, Cochrane, and Clinical Trials from the beginning until July 2022. The Cochrane ROBINS-I technique was used to conduct quality evaluation. The danger of bias was divided into four categories: low, moderate, serious, and critical [2].

A major contributor to morbidity and mortality in premature newborns is neonatal respiratory distress syndrome (RDS). An ongoing challenge in maternal-neonatal health in underdeveloped nations is the severity of disease and the requirement for mechanical breathing in neonates with RDS. The treatment of preterm newborns with RDS has improved with the use of evidence-based preterm birth techniques, prenatal steroids, surfactant therapy, and non-invasive assistance. However, the mortality rate and the number of infants in hospitals with neonatal intensive care unit facilities are still high. Additionally, it has several resource-burdening issues

and an unclear long-term neurodevelopmental prognosis [3]. Improved access to specialist care and prompt identification of infants at high risk for deterioration are essential for better outcomes in nations with limited health care resources. Non-invasive ventilation techniques, such as nasal continuous positive airway pressure, nasal high frequency oscillatory ventilation, and nasal intermittent positive pressure ventilation, are replacing invasive positive pressure ventilation methods in neonates with RDS because they have fewer side effects and better short- and long-term outcomes on lung function and neurodevelopment. Recent hardware developments, such as nasal high flow humidified therapy also known as fast vaporized therapeutic devices provide non-invasive positive pressure ventilation by creating an air/oxygen flow in the range of >3 L/m to almost 50 L/m [4].

## **Condition description**

One of the most frequent causes of neonatal morbidity and mortality in preterm infants is respiratory distress syndrome (RDS). In the neonatal intensive care unit (NICU), non-invasive ventilation (NIV) is a commonly utilized technique for providing respiratory support for infants with RDS. Death or the development of persistent lung illness, including bronchopulmonary dysplasia, can result from inadvertent or unsuccessful extubation. Nasal Intermittent Positive Pressure Ventilation (NIPPV) and Nasal Continuous Positive Airway Pressure (NCPAP) are two of the various NIV modes. According to a recent retrospective study, babies on NCPAP before extubation were less likely to have stayed on positive pressure support at day 30 after delivery and had shorter hospital stays following extubation than babies on NIPPV. No research has been done on the rates of reintubation in preterm children with RDS after extubation to either of these NIV modalities. The goal is to examine the rate of reintubation between preterm infants with RDS who were extubated to NIPPV and those who were extubated to NCPAP. The following demographic information is gathered: treatment group (NIPPV or NCPAP), FiO<sub>2</sub> (%) now of extubation, gender, birth weight, and gestational age [5].

## **Respiratory distress**

An increase in respiratory rate (RR) and effort of breathing (WOB) due to a problem in gas exchange is known as respiratory distress (RD). It causes respiratory acidosis, hypoxemia, and may even cause metabolic acidosis [1]. RD may result from some postpartum health issues in neonates. To assess the differences between three non-invasive ventilation techniques in a PSW region, the care team may need to conduct additional tests if the neonates' respiratory distress is not alleviated after they have received support. This study compared infant outcomes using three non-invasive breathing techniques: HHHFNC, NCPAP, and NIPPV. A small amount of research has been conducted on each of these three approaches independently. After comparing the

outcomes of the three nasal non-invasive ventilation techniques for the newborns under study, the significance of the noteworthy findings in relation to the state of the art was further examined [6].

### **Managing respiratory distress and complications**

About 10% of newborns will need to be intubated, which causes needless respiratory distress and problems, especially in premature newborns. The humidified heated high-flow nasal cannula (HHHFNC), nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), and soft-to-firm silicone mask styles with short to long necks have all been used to support and sustain spontaneous and effective ventilation of newborns experiencing respiratory distress. A recent study compared the short- and long-term efficacy, efficiency, and safety of HHHFNC, NCPAP, and NIPPV modalities and interfaces in terms of intubation and mechanical ventilation (MV) rates, nasal CT, feeding intolerance, and extra-ventilation loss of 40 neonates. The use of a short-neck soft silicone mask produced statistically significant changes in terms of 4-hour facial bruising, as well as efficacy, efficiency, and safety in terms of reducing nasal discomfort and pneumothorax [1].

### **Intervention description**

Two major factors contributing to newborn morbidity and mortality are prematurity and respiratory distress syndrome (RDS). Exogenous surfactant treatment and invasive ventilation have greatly decreased the mortality and morbidity of premature newborns with RDS. Nonetheless, up to 40% of these babies make it through with at least one serious issue. For RDS, non-invasive ventilation (NIV) is a proven preventative treatment. Although more post-extubation assistance with CPAP is required, extubation failure is not unusual. The comparative effectiveness and safety of the two approaches were robustly assessed by a systematic review and meta-analysis that included numerous trials comparing the two modalities to CPAP in various clinical scenarios. According to the findings, HFNC is a safer and more efficient treatment option for RDS in preterm infants than NIPPV with CPAP. However, given the consequences of a rising incidence of use in some settings, thorough, high-quality RCTs are required to assess its clinical benefit [7].

### **Intervention method**

Neonate with respiratory distress syndrome (RDS) may exhibit abnormal arterial blood gas status, abnormal chest x-ray, clinical signs and symptoms, or the requirement for oxygen supplementation [1]. In neonatology departments and maternity units, ventilatory assistance is one tactic used to reduce this demand. All hospitals must have a NICU that is adequately equipped. It is safe for preterm newborns and successful to use HHHFNC and NCPAP as the first line of treatment for preterm neonates with RDS within an hour of birth. In groups with HHHFNC, NCPAP, or NIPPV, the referral

rate for mechanical ventilation was comparable. In pre-term neonates with RDS, HHHFNC at birth is safe and practicable, but it is no more or less successful than the other two approaches at avoiding the requirement for mechanical ventilation.

### **Reviewing importance**

Global concern continues to surround the preventative effects of preterm delivery on infant brain injury and related cognitive impairment. These pregnancies typically result in births that are below gestational age thresholds, which are determined by observable signs or the lack thereof rather than by brain or maturation status. Regardless of TBI type, focus model, timing, or subject age, current adult research' emphasis on targeted hypothermic or hyperthermic schedules which involve regulating cooling rates to core temperature offers translational and hypothesis-testing opportunities. An appendix contains a warning about contradictory reports on the cessation of cerebral hypothermic effects in adult rodents. Farhat et al. [1] emphasizes how the spontaneous recovery of hypoxic-ischemic ventriculomegaly in the neonatal rat model defies previous statements based on cohorts with different strain and gender as well as expectations (particularly the second ichor stages in intensity and pace). Age-dependent increases in ETC inhibition strength allow for the evolution of cellular surprises, which provides a means of testing the neurodevelopmental effects of oligodynamic emphasis. Previous research in wildtype and *Apcmin/+* mice shows that the designation of oligodynamic foci in the putative ganglionic eminence is biased by *Shh* crest cells, which prevents the execution of *BrafV600E*-primed oligodendrocyte cell destiny. Microglial induction in early gliogenesis and migration into the potential white matter accompany the latter. Further research into experimental hyperplastic models is warranted for each pathway. Differences in the age-dependence of spinal cord inhibition and parcellation of cognate impact between mouse and human cohorts are attributed to interspecific differences in neonatal representation and translational outcomes [8].

### **Objectives**

This study compared the effectiveness of three non-invasive ventilation modalities in reducing the need for mechanical ventilation and intubation in premature RDS neonatal patients: 1) CPAP, 2) Nasal Intermittent Positive Pressure Ventilation (NIPPV), and 3) heated humidified high-flow Nasal cannula (HHHFNC). To ascertain whether the three approaches performed differently, secondary outcomes such changes in blood gas values, the length of time spent using non-invasive ventilation techniques, the requirement for more oxygen, and other related issues were also assessed [1].

### **Definition/Pathophysiology**

In newborns, respiratory distress syndrome (RDS) is a leading cause of morbidity and mortality. Premature babies without surfactants experience it. The development of atelectasis due to the lack of surfactant leads to a reduction in compliance, a decrease in functional residual capacity, and ultimately hypoxemia and hypercapnia. Lung volume loss is the fundamental issue in RDS. With minimal disruption to normal ventilatory function, Nasal Continuous Positive Airway Pressure (NCPAP) can be administered early enough after birth to prevent the development of atelectasis in preterm infants deemed at risk for RDS due to their prematurity or maternal risk factors. Coverage rates, even in big trials, are usually in the mid- to high-60% range, which is a minor improvement from the mid- to high-50's ten years ago. Most programs probably still have coverage rates below 80% for both high-risk and low-risk categories. The coverage declines even more sharply in preterm newborns  $\leq 30$  weeks of gestation, who make about 4% of live births [9,10].

### **Epidemiology**

Premature babies can have a breathing condition called neonatal respiratory distress syndrome (RDS). Surfactants, which keep the lungs' air sacs open, are insufficient in newborns since their lungs are not yet fully grown [11]. RDS primarily affects this area in preterm infants born at less than 34 weeks of gestation due to surfactant deficit. This pressure should be at least 6 cm H<sub>2</sub>O. To prevent RDS, early CPAP commencement at the appropriate pressure with an interface that fits well reduces the requirement for mechanical breathing, surfactant replacement therapy, and related dangers while also enhancing guided clinical outcomes [12,13]. High-flow nasal cannulas (HFNCs) are used in NICUs throughout Spain. They supply heated and humidified oxygen, which is less effective than CPAP at avoiding the need for intubation but frequently used in conjunction with CPAP rescue therapy [7,14].

### **Clinical Display**

One proven method of treating respiratory distress syndrome (RDS) in preterm infants is non-invasive breathing techniques. Although there is little information on how the three approaches that are the focus of this review HHHFNC, CPAP, and NIPPV compared to one another, they all provide different ways of administering positive airway pressure therapy through different interfaces [1]. The purpose of this systematic review and meta-analysis was to evaluate the clinical results of treating preterm infants with RDS at delivery with NIPPV, CPAP, and HHHFNC. The duration of oxygen therapy, the amount of time spent on mechanical breathing, the requirement for intubation, and several other secondary outcomes are the outcomes of interest.

If a pre-term baby needed non-invasive breathing support driven by pressure or flow at the time of admission, they

were qualified to be admitted to a tertiary perinatal facility. In the initial trial cohorts, 364 newborns with an RDS diagnosis were randomized to either the HHHFNC, CPAP, or NIPPV groups [8]. Randomization did not explain the types of early non-invasive respiratory support. 192 preterm made up the final cohorts after 172 neonates were eliminated based on inclusion and exclusion criteria. At baseline, there were no discernible differences among the three groups. There were 192 preterm infants with RDS in the most recent meta-analysis. Excluded were retrospective cohort studies and randomized controlled trials that were published later. Data was analyzed using Review Manager 5.4 and Regardless of the modality selected, Stata/MP version 17.0 respiratory assistance considerably decreased the requirement for intubation (less than 72 hours). When applied to preterm infants weighing 16–64 kg and having similar breathing needs, HHHFNC has a negative effect.

### **Neonatal Respiratory Distress Syndrome**

The most prevalent respiratory condition in newborns, particularly premature infants, is respiratory distress syndrome (RDS), according to research. About 40% of RDS neonates need mechanical ventilation, according to long-term outcome studies of the condition. This is a risk factor for sequelae such bronchopulmonary dysplasia (BPD). One key objective in the clinical management of newborn RDS is to decrease the need for mechanical breathing and endotracheal intubation [15]. For neonates with RDS, nasal continuous positive airway pressure (NCPAP) is an early respiratory support method that is noninvasive. Its therapeutic impact is subpar, nevertheless, and over half of patients do not respond to treatment. Additionally, NIPPV can improve gas exchange and decrease physiological dead space. The effectiveness of two distinct non-invasive ventilation techniques is NIPPV and NCPAP. NIPPV has been shown in several trials to lower the incidence of BPD and endotracheal intubation [1].

### **Methods**

This descriptive-comparative study, which used the cohort approach, comprised 45 preterm children with a high risk of RDS who were younger than 32 weeks gestation. Following parental informed consent, qualified children were assigned at random to one of three study groups (15 infants in the CO-NASAL-CPAP, CO-NASAL-IMV, AND NI-CP-AAP groups) based on the ward's referral sequence using three distinct numbers. This method was applied to the control group's ventriforme ventilator using a nasal cannula and a burst of air at 15–50 L/min while keeping the anatomic airway deep. Other groups employed nasal intermittent obligatory breathing, like the current trial, and ca-cpap/bi-level ventilators with nasal prongs (size 1-2) with positive pressure fluctuations in the upper and lower streams of 5-6-7 cm H<sub>2</sub>O and 1-3 cm H<sub>2</sub>O, respectively.

Two-by-two-panel, audio-visual recordings and observations were made of the physicians' standardized non-invasive procedures. According to the study guidelines, two neonatologists who had finished the training were required to independently examine fifteen-minute straight-forward approach recordings of cycle duration and time. When determining the effects of anesthetics, records were filtered using Cohen's Kappa robust analysis, which revealed good coefficient agreement factors ranging from 0.73 to 0.87. The local ethics committee accepted the study's methods and goals after receiving a study ID. Forms for parents' written informed consent were customized.

### **Review study criteria**

A systematic review was conducted in the Medline, Scopus, and Web of Sciences databases to examine the chosen papers that evaluate nasal non-invasive breathing techniques in preterm infants with respiratory distress syndrome (RDS). The approach relies on the neonate's age, weight, and staff experience, even though choosing the appropriate devices is essential [1]. Comparing the effects of nasal intermittent positive pressure ventilation (NIPPV), nasal continuous positive airway pressure (NCPAP), and humidified heated high flow nasal cannula (HHHFNC) on lowering mechanical ventilation rate (MMVR) and intubation in preterm neonates with RDS is the main research question. Between 2014 and 2015, 160 newborns were the subjects of this randomized controlled trial at an academic facility in Khorramabad, Iran. Included were detailed questionnaires that defined the RDS parameters, baseline features, and failure criteria for devices that were derived from earlier publications. One patient with syndromic symptoms, two patients with congenital abnormalities, and five patients with congenital lung disorders were among the 160 suitable newborns who were screened out of 168 total. In 15% of cases, RDS were seen in the delivery room, and in 85% of cases, it was seen an hour after delivery. The groups GA and BW were comparable. Intubation rate, masking ventilation requirement, delivery room intubation, and re-intubation over the first 72 hours did not significantly differ amongst the three techniques. In comparison to 73.6% in NCPAP and 72.2% in HHHFNC, 72% of the neonates with NIPPV achieved successful non-invasive ventilation overall ( $P=0.917$ ). Total breathing duration did not differ significantly, and the groups' demand for supplementary oxygen ( $\geq 21\%$  and  $\geq 30\%$  supplemental oxygen) did not differ significantly either ( $P=0.734$  and  $P=0.191$ , respectively). In preterm newborns with RDS, HHHFNC at delivery more successfully reduced MMVR and intubation [16,17].

### **Study types**

The effects of NCPAP and NIPPV on RDS were examined using meta-analysis and systematic review techniques. A few databases were searched for relevant material. The following were the search terms: "respiratory distress syn-

drome" OR "neonatal respiratory distress syndrome" OR "RDS" AND "nasal intermittent positive pressure ventilation" OR "NIPPV" AND "nasal continuous positive airway pressure" OR "NCPAP." By filtering the search literature and references in the sought literature, a total of 291 literatures were retrieved from the databases; four of these literatures were included after fulfilling the inclusion criteria. A total of 591 babies were included in the literature, which was published between 2011 and 2021 and consisted of randomized controlled trials (RCTs) with 294 instances in the experimental group and 297 cases in the control group [15]. Two researchers independently screened the literature and gathered data based on the inclusion and exclusion criteria; a third researcher was consulted in the event of a dispute. Two researchers independently assessed the included papers' methodological quality using the updated Cochrane risk of bias methodology for individually randomized parallel group trials (RoB2.0). Three categories low risk of bias, high risk of bias, and uncertainty were applied to literature. Data analysis was done using the Cochrane program. We used the random effect model to extract data. The effect quantity was described using the 95% CI and the risk ratio (RR). When evaluating heterogeneity, the Chi-square test was used, and I<sup>2</sup> showed statistical heterogeneity. Sensitivity analysis was employed to evaluate how the risk of literature bias affected the stability of the findings. A bilateral P-value of less than 0.05 was deemed to be statistically significant [1].

### **Participant types**

According to Bordessoule et al. [18] explained how preterm babies were gathered from the neonatal intensive care unit. After getting the parents' approval, the study included 20 preterm infants (gestational age: 33–36 weeks) weighing  $\leq 2500$  g who needed NCPAP for mild respiratory distress. A cross-over design was used in the investigation. To record the diaphragm's electrical activity, a specialized nasogastric feeding tube with miniature electrodes was used in place of the patient's original one (EAdi). Each of the three devices fNCAP, Fasil, and Air-N-Puff supported patients for 20 minutes in a row NCPAP device sequence was assigned at random. The devices' gas delivery rate was set at roughly 7 L/min for each condition. Delivered at the lowest feasible FiO<sub>2</sub>, the oxygen saturation remained above 92%. To determine whether a possible sequence effect was present, a mixed effects linear regression model was employed. According to Farhat et al. [1], preterm neonates frequently have apnea, bradycardia, and oxygen desaturation due to an underdeveloped respiratory center; these conditions typically call for therapeutic interventions. The use of nasal non-invasive ventilation techniques as an alternate treatment approach to enhance breathing and lower the risk of death becomes much more important when severe cases of respiratory distress need endotracheal intubation and mechanical ventilation. As the most widely utilized nasally applied techniques,

this study chose to examine the three non-invasive ventilation modalities of HHHFNC, NCPAP, and NIPPV. Comparing the effectiveness of these three nasal non-invasive ventilation techniques in reducing the rate of mechanical ventilation and intubation in preterm infants with respiratory distress syndrome (RDS) was the aim of this study. The three nasal non-invasive ventilation techniques are HHHFNC, NCPAP, and NIPPV. This study's main goal was to improve nasal CPAP delivery management and optimization.

### **Intervention types**

Neonates with respiratory distress syndrome (RDS) frequently receive non-invasive respiratory support using three nasal non-invasive ventilation techniques: nasal intermittent positive pressure ventilation (NIPPV), nasal continuous positive airway pressure (NCPAP), and humidified heated high flow nasal cannula (HHHFNC). In contrast to the earlier advice to start NCPAP first if it is not tolerated, NIPPV involves applying positive pressure breaths in time with the neonates' inspiration while they are on an underlying NCPAP. The purpose of this study was to evaluate how well these three approaches reduced the rate of mechanical ventilation and intubation in premature infants with RDS. Between 2016 and 2017, 160 newborns were randomly assigned to either CPAP, HHHFNC, or NIPPV as part of this randomized controlled research. The intervention techniques were used for a total of 15 days. To make sure the RDS severity score decreased, the severity score was assessed both before and 15 days after the operation procedures began. Intubation, mechanical ventilation, and the five-day mortality rate were the main results. Hypoxemia (goal SpO<sub>2</sub> < 90%), severe and recurrent episodes of apnea that did not improve with increased respiratory rate and necessitated either invasive ventilation or NPPV, and persistent respiratory acidosis were the inclusion criteria for intubation in this trial. Daily assessments for the necessity of intubation or eventual invasive ventilation [1] were conducted on days 1, 2, 3, 4, and 5. 54 (72%), 735 (73.6%), and 77 (72.2%) of the neonates in NIPPV, CPAP, and HHHFNC instances, respectively, improved without the requirement for intubation. The proportions did not significantly alter based on the sorts of applications.

### **Comparison types**

In N-RDS, the study examines the diagnostic values of the three NIV modes (HHHFNC, NCPAP, and BiPAP). The efficiency of NIV modes is compared between NCPAP and BiPAP. Overall failure was noted in 41 (26.3%), 45 (28.9%), and (not evaluated in this review) 27 (23.3%) of the NCPAP, HHHFNC, and BiPAP groups, respectively, during the trial. In a cohort of preterm newborns with mild-to-moderate severity of RDS, the effectiveness of HHHFNC as the sole alternative non-invasive support technique that reduces the requirement for non-invasive or invasive ventilation modes in over 70% of cases compares favorably to starting CPAP

at delivery [19]. According to a recent cohort research, this conclusion is supported by infants with very low birth weights (1000 g) who were initially managed for respiratory support using either HHHFNC (n=75) or NCPAP (n=125). Since comparable studies have evaluated and harmonized non-invasive respiratory support techniques, HHHFNC efficiently treats RDS with proven feedback re-inspiratory flow, according to coherent data. However, compared to other research, this meta-analysis reveals a more transparent approach to N-RDS, which probably leads to arbitrary results. A comparison of nasal NIV types in preterm babies with N-RDS was the subject of two studies, both of which showed promising outcomes for more recently developed forms of support. The choice of HHHFNC or N-CPAP, which have greater mess has more bias than BiPAP when compared to other types of support in trials conducted in lower centers. This calls for a comparison of more comparable study designs [1]. In conclusion, the data indicates that each option has level B evidence. Even though there is more data supporting HHHFNC than N-CPAP, research of moderate quality cast doubt on its efficacy. As a result, the recommended technique is determined by the local equipment and knowledge that is available in lower centers.

### **Study identification techniques**

Comprehensive Evaluation and Meta-analysis Create Criteria for inclusion and removal Interests and selection criteria. We analyzed research articles about neonatal respiratory distress syndrome that were published between October 2010 and January 2023. 1) Randomized controlled trials comparing two or more groups that used noninvasive ventilation techniques and 2) Infants in each group with a diagnosis of moderate to severe newborn respiratory distress syndrome were the inclusion criteria. 1) Articles that were reviews, case reports, animal studies, or meta-analyses were excluded, 2) Non-investigational articles that is comparable to the topic of the proposal, 3) Articles that are not available in full-text or in English, 4) Unrelated topics like pulmonary infections and other conditions not covered in this proposal, such as infants who have experienced trauma or who have congenital heart defects.

### **Primary results**

Among the main results were: 1) Intubation, 2) The length of time that mechanical ventilation is used 3) Failure rate of extubation, 4) The rate of unsuccessful treatment secondary results These were the secondary results: 1) The length of time spent in the newborn intensive care unit, 2) Pneumothorax incidence 3) Postintubation distress rate requiring reintubation, 4) The frequency of leaks, 5) The frequency of nasal damage, 6) The prevalence of acid reflux, 7) The frequency of vomiting 8) Rhinitis prevalence 9) The initial feeding time (hour) 10) Average gestational age 11) Average birth weight, 12) Restrictions' rates, 13) Pregnancy steroid

usage rates, 14) The prevalence of birth abnormalities, 15) Gender status Search methodology. The phrase of "Comparative evaluation of efficacy and safety of noninvasive devices for the treatment of preterm infants with moderate to severe neonatal respiratory distress syndrome" was entered into databases of 1) Scopus, 2) PubMed, 3) Cochrane Library, 4) Clinical keys, 5) Google Scholar. The last search date was January 20, 2023. Data extraction the extracted data consisted of author names, year of publication, study design, subject characteristics including sex, gestational age, birth weight, Apgar score, and intervention. Primary outcomes, secondary outcomes, and other relevant data were also extracted using an Excel sheet. When comparing multiple arms with two groups, authors pooled data from similar arms to allow for better comparisons [20].

### **Cluster-randomized trials**

In preterm infants with RDS, two cluster-randomized trials have examined the effectiveness of HHHFNC in comparison to CPAP followed by sub nasal CPAP [21]. There was an unknown risk of bias in one experiment and a low risk of bias in the other. Except for the adjusted requirement for re-intubation, which decreased in the HHHFNC cohort during a comparable 28-day period, all primary and secondary outcomes were comparable between the two treatment modalities. There were no changes in the rates of other sequelae, such as nasal trauma, PDA needing intervention, or death, but HHHFNC was linked to a lower incidence of pneumothorax and IVH >grade 2 [1]. Overall, the length of stay in the PICU, and the duration of N-V techniques were all the same in both trials. One study revealed that patients receiving HHHFNC had longer times to first feed, return to birth weight, and require surfactant; however, these findings were deemed improbable because of treatment group confounding or random error. To reduce the necessity for intrusive therapy, our data suggests the use of HHHFNC for NRS. Although HHHFNC may be linked to a higher rate of re-intubation, there is some evidence that non-invasively ventilating most supported infants with HHHFNC including those with high-risk features would be a reasonable strategy to lower the rate of intubation and unintentional extubation. HHHFNC was associated with a lower incidence of CPAP failure, according to the meta-analysis.

### **Heterogeneity assessment**

The Q and I<sup>2</sup> statistics of the included studies were examined to evaluate heterogeneity. When a p-value was less than 0.05, statistically significant heterogeneity was considered. Standardized mean differences (SMD) with 95% confidence intervals (CI) were used to express the effect sizes. All 20 dependent variables were subjected to a single within-group alpha level of 0.0025; however, post hoc comparisons were considered significant when the p value was less than 0.01 [19]. While there was no discernible difference between na-

sal Continuous Positive Airway Pressure (NCPAP) and nasal Intermittent Positive Pressure Ventilation (NIPPV) in the first 24 hours of life, all preterm neonates given NIPPV demonstrated more stable oxygen saturation during the first 12 hours of life. Because flow is maintained during expiration, it has been shown that in preterm infants undergoing nasal intermittent positive pressure breathing, the supplied pressure is significantly more stable, particularly during spontaneous inspiration.

### **Reporting bias assessment**

Tests and funnel plots were used to evaluate reporting bias overall when the meta-analysis comprised more than ten papers. By calculating standard errors from the stated odds ratio and comparing the log odds ratio to these standard errors, the Funnel Plot was created. A weighted least-square regression was used to fit a regression line to the funnel plot. Tests were used to determine the importance of the funnel plot's departure from symmetry to quantify the degree of asymmetry. A preset significance level was used initially. Other degrees of significance were also investigated in the sensitivity analysis that followed. Additionally, the pooled odds ratio was calculated after systematically deleting one study at a time to assess the impact of lost studies on the ratio. Sensitivity analysis was conducted, and overall testing was repeated after excluding studies with form one quality/type to examine the differences in the meta-analysis's results in correlations with the quality and methodological differences of the included studies. This allowed for the estimation of the impact of each individual study on the overall odds ratio. To see the impact on pooled estimates, a cutoff quality score was used, removing those with poorer overall quality. Furthermore, a single population type was chosen to determine whether the meta-analysis would have an impact on the overall findings. Random-effects models were used to evaluate the significance of the result change in each of the scenarios. Studies whose data did not meet the specified input criteria were labeled as "unavailable" [22].

### **CPAP**

For preterm newborns with respiratory distress syndrome (RDS), continuous positive airway pressure (CPAP) is the first-line treatment in most contemporary neonatal hospitals. CPAP, or continuous positive airway pressure, is one of the most popular techniques for respiratory assistance. During breathing, a spontaneously breathing neonate is given sufficient and constant positive pressure above atmospheric level. Traditionally, this is accomplished via an inflating bag or a T-piece that is adjusted to provide the required pressure through its side orifice. Interfacing with the skin over the nose is done with a mask or another interface (such as a prong). These days, CPAP is administered through ventilators, which have CPAP pressure settings on their interface, humidification chamber, pressure sensor, and valves to offer

further features like target variability, feedback, and integration with pulse oximetry [1]. For sleep apnea episodes, some clips could incorporate a Pressure support (PS) phase to transition from CPAP to an intermittent bolus. As babies get older, the ventilator may occasionally be changed to a High-Flow-Dual-Flux-Nasal-Cannula, a non-invasive method that can also give the baby CPAP. The initial CPAP settings for all devices are typically 6 cmH<sub>2</sub>O when they are first applied, and each hour, the desired pressures are often increased linearly until they reach a maximum level of 10, 12, or 15 cmH<sub>2</sub>O, depending on a unit policy. When hypoxemia and hypoventilation occur soon after delivery, this is typically done to address them. After a period of utilizing CPAP, some units opt to add HHHF to the incubator to control hypertension.

### **BiPAP**

In many hospital NICU settings worldwide, the BiPAP system, also known as BiPhasic (Biphasic, Bi-level, BiPAP, BPAP) ventilators, has evolved into an inspiratory positive airway pressure BiPAP system that can handle end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>). When using CPAP mode and the UP-DOWN-TOUCH-TAP (DTT) setting, the BiPAP system typically operates in flow assist mode at low iPAP. These preterm neonates often have a CPAP level (Peep) of 5 to 9.5 cmH<sub>2</sub>O. For these premature babies, the APAP level is adjusted between 1 and 2 cmH<sub>2</sub>O. This is a straightforward method to guarantee proper effort sensitivity and the ventilator's ability to detect peak breath pressure (set iPAP). Broadly speaking, BiPAP ventilators are configured with an iE of 50%. However, different NICUs have selected different settings. For newborns with RDS, nasal SiPAP and nasal BiLevel Positive Airway Pressure (N-BiPAP) improve breathing. Compared to SiPAP (thicker interface, more leak), N-BiPAP resulted in fewer secondary problems and intubations [23]. Babies with BiPAP and spilled fluid seemed to benefit from bubbling. Even with increased sensitivity and fewer leaks, 175% inspiratory pressure might not be enough. Because N-BiPAP isolates flow from pressure-generating gas, it may also be superior to nasal SiPAP [1].

### **HFNC**

The effectiveness of HFNC has been questioned, and efforts to find new technologies for delivering high flow oxygen at high relative humidity are still ongoing. Because of these dubious findings, it is not frequently used to treat RDS [19]. Different treatment alternatives can come from the same type of results, according to an analysis of potential additional confounders impacting therapy success. Also, past generations of machines utilized for administering HFNC treatment have lower FiO<sub>2</sub>, humidity and flow rates than the present models. Nonetheless, HHHFNC with 100% EvONAD, 40–45 Hot Wet Air, and flow above 05 PO should be used from the beginning for preterm infants evaluated for HFNC treatment for O<sub>2</sub> dependency prior to CPAP starting. reduced VaD therapy

with HHHFNC at 1 month of age and a lower early need for future intubation when compared to the 4-hour groups. Macroscopic lung cysts at 1 and 5 years postnatally are linked to IRDS in less than 25 weeks of pregnancy, but no normal, moderate, or severe instances are observed. Additionally, three years after delivery, survival with chest circumferences under 26 weeks and severely low weight showed significant relative risk. For neonates weighing less than 1200 grams, lateral types of lung volume loss and signs of fifth cervical vertebra obstruction, which are only observed in severely handicapped children, may be helpful in predicting long-term outcomes (28–70 months) (specific case studies). Males were more likely to have primary lesions, while females were more likely to have secondary SARS.

### **NIPPV nasal intermittent positive pressure ventilation**

PPV is administered via a commercially accessible nasal prong under the novel noninvasive ventilation (NIV) concept introduced by Dr. Louis J. Morris in 1984. It was rapidly interpreted by many neonatologists, who began using nasal intermittent positive pressure ventilation (NIPPV). Since it is thought to be more successful than CPAP alone at recruiting collapsed alveoli, this approach has been used as a strategy to extubate ventilated neonates [8]. It was proposed that NIPPV effectively treat RDS. Therefore, there has been a lot of interest in the use of NIPPV as a new mode of NIV with the clinical goal of avoiding intubation in new RDS infants due to the advancements in ventilator technology, the growth of disposable breathing circuits for infants, and the awareness of the effects of ventilator-induced lung injury (VILI). The optimal way to administer noninvasive respiratory support (NRS) has drawn attention since it is known that it can be given with both positive ventilation and CPAP. Although face masks can be used for NIPPV, they are more frequently used for BiPAP, which necessitates continuous intubation afterward. This is inconsistent with the initial usage of face masks for CPAP or NIPPV. For the administration of NIPPV, a modified Fisher and Paykel nasal mask can be utilized. This isn't commercially accessible, though. Additional assessment of the design and clinical efficacy is still in progress [1]. To help give much-needed respiratory support during transitioning newborns into CPAP, several patterns of NIPPV have been used in a variety of situations in addition to standard methods.

### **Comparison of standards**

Neonates, particularly premature neonates, frequently have RDS. There are several factors that might impact the equilibrium of surface tension forces in the alveoli, including pulmonary edema, collapse of the end-expiratory lungs, pulmonary surfactant deficit, and immaturity or dysfunction of type II pneumocytes. Intrusive positive pressure ventilation (IPPV) is the most widely used invasive ventilator technique for managing RDS in neonates. However, this may raise the risk of iatrogenic consequences, including intraventricular bleed-

ing, respiratory hyperventilation that results in hypocapnia, and pneumothorax [19]. Therefore, it is essential to implement noninvasive respiratory support strategies as soon as possible to preserve spontaneous ventilation and steer clear of conventional ventilation. All in all, these devices do not include the heated humidified high flow nasal cannula (HH-HFNC), nasal intermittent mandatory ventilation (NIMV), or nasal continuous positive airway pressure (NCPAP) [1]. First off, NCPAP is a proven or first-line noninvasive method for treating RDS in newborns with extremely low birth weights. NCPAP can be administered using a variety of mechanical devices, including variable flow systems, bubble CPAP, and vented CPAP caps. The nasal luminal orifice collapses as one of the methods of delivering CPAP, which lowers the pressure linked to nasal resistance. Numerous studies have demonstrated how NCPAP affects clinical outcomes, such as the development of IVH, the length of time spent in special care, the duration of oxygen inhalation, and the avoidance of intubation. Additionally, people with BMIs under 1500 grams and under 1000 grams may benefit similarly from NCPAP ( $p=0.9$  and  $0.84$ , respectively).

### **Non-invasive ventilation**

Comparing two non-invasive ventilation techniques in a group of preterm children with pulmonary illness, confirmed birth asphyxia, and birth weights under 1500 grams was the goal of the current study. The infant had to be delivered singleton and placed in a stimulating environment, or it had to be given appropriate stimulation in an environment as close to normal as possible, including the presence of a pediatrician or neonatologist for the delivery; it had to be assessed right away and placed in a strict resuscitation area; it had to be kept at a proper temperature; it had to be immediately put on non-invasive ventilation with either a high-flow nasal cannula (HFNC) or NCPAP; either way of ventilation was then continued, and data collection began [8]. Major congenital malformations, the expectation of intubation within the first 30 minutes of life, the need for transnasal positive pressure ventilation of more than 7.5 for more than 30 minutes on HFNC or mean airway pressure of more than 8 for an hour during NCPAP, and a pressure change of more than 2 cm of water in either mode were additional important exclusion criteria used in this study [1]. Each eligible newborn group received non-invasive ventilation according to their sequential priority list, which was established by their doctor. After the study was over, the data was checked again for correctness.

### **Systematic Review (Non-Invasive Ventilation and its Sub modalities)**

In newborn intensive care units (NICUs), RDS, which is brought on by a reduction in surfactant production, is the main cause of invasive ventilation. It is preferable to use non-invasive methods to reduce ventilatory problems. The data supporting noninvasive modalities (NIV) of primitive ap-

proaches for managing preterm infants with RDS needs to be adequately classified to make up for care planning. Numerous therapy modalities have been established to help these infants and improve their results. Exogenous surfactant injections are the most successful treatment. Noninvasive strategies are the most effective ways to reduce the requirement for invasive mechanical ventilation (IMV), aside from surfactant therapy [8]. Because it has been linked to improved results, CPAP use is now mandatory in NICUs. In neonatal care, nasal continuous airway pressure, or NCPAP, is the primary noninvasive ventilation technique. NCPAP, which continuously inflates the airway pressure in the lungs, can be administered using either commercial CPAP devices or basic bubble CPAP. To replicate the natural physiological rhythms of breathing, NCPAP can be administered via either nasal prongs or a mask interface. As part of the standard of care, this therapeutic approach is the primary treatment of choice. This isn't always enough, though; in 50% of CPAP failure instances, additional IMV treatment was required on the same day or 24 hours following the initial course of treatment. To address the difficulties of managing newborns with RDS, the authors of a recent clinical multicenter prospective cohort study addressed the issues of a workable implementation strategy for various NIV sub modalities suitable for their chosen setups. For in-depth NIPP training, NIV with various sub modalities should be set up in a separate room, in contrast to HCPs. Appropriate protocols for recently created NIV sub modalities should be established with the launch of a new service. To improve synchronization and ventilation magnitude, a new ventilation mode closure called Noninvasive Neutrally Adjusted Ventilatory Assist (NIV-NAVA) uses the patient's diaphragmatic electrical activity amplitude-graded stimulation.

### **Reviews and research agreed or disagreed**

Premature babies are at significantly lower risk of airway-associated complications while using NIV as opposed to invasively applied continuous-positive airway pressure. Due to this high-risk category, more NIV is required because medical care is typically chosen for intubation and can have a significantly worse outcome in some circumstances. The inherent differences in noninvasive ventilation applications necessitate a reassessment of the possibilities available for this technology. Comparing invasive approaches to what has been proposed for invasive techniques, there are no new choices available [8]. It also looks to be a dead end, at least in Europe. In contrast, the other non-invasive options (PPV, iNIV, and TGV) provide unique, innovative solutions for preterm respiratory issues, at least in theory. If all predecessors, RDS-mass prophylaxis, etc., are intact, each patient with preterm birth should ideally only require an ETT to be monitored. When it comes to non-invasive ventilation alternatives outside of the delivered CPAP concept, the well-described and estimated mechanisms of TGV and iNIV

are essentially the unfulfilled dreams. nRDS was initially described fifty years ago, offering a thorough clinical and theoretical background for preterm respiratory issues. Numerous non-invasive assisted ventilation techniques have been used for more than 50 years, and many of them are still in use today. Non-invasive procedures are becoming increasingly popular, particularly in the last 20 years, when preterm respiratory support approaches have become more accessible. Under the strict guidelines of a neonatology journal, a literature search was conducted.

### **Literature review**

More than 75% of newborn intensive care unit admissions are due to RDS, which is also the main cause of invasive ventilation. Prematurity also results in a few negative outcomes, such as intraventricular hemorrhage, seizures, bronchopulmonary dysplasia (BPD), sepsis, necrotizing enterocolitis, patent ductus arteriosus, hearing and vision issues, and other neurological disorders. Invasive ventilation and surfactant replacement can save the lives of neonates with RDS, but they also raise the risk of lung damage from mechanical injury or barotrauma, as well as bronchopulmonary dysplasia (BPD) [1]. By raising the upper airway pressure, transcutaneous CO<sub>2</sub> tension (PtcO<sub>2</sub>) is reduced, and functional residual capacity (FRC) is enhanced. NCPAP does not, however, ensure that breathing and ventilation attempts are more coordinated. Insufficient synchronization increases the risk of pneumothoraces and increased breathing work (WoB). Noninvasive positive pressure (NIPP) ventilation is an alternate therapy option for RDS or can be used as a weaning technique once mechanical ventilation has been extubated. The airway pressure setting used in this method either rises and then constantly lowers around the set point, or it varies around the set point based on breath detection. Although NIPP may be more effective at preventing post-extubation failure, it did not lower the incidence of BPD. The breathing techniques used for neonates were compared in various research. NAVA, or neurologically adjusted ventilatory aid, is a relatively recent ventilation technique. For extremely preterm newborns, noninvasive neutrally adjusted ventilatory support (NIV-NAVA) is a successful technique for mostly noninvasive ventilation to guarantee appropriate neurodevelopmental results. NIV-NAVA ensures optimal ventilation synchronization by using the patient's inspiratory diaphragmatic electrical activity and providing mandatory pressure support [24,25].

### **The studied Groups**

Three groups NIPPV, NCPAP, and HHHFNC were randomly assigned to the newborns. Nasal oxygen was administered to all newborns at birth at a flow rate of 5 and 6 L/minute, appropriate for gestational age. An NIPPV starting pressure of 8–10 cmH<sub>2</sub>O and an HHHFNC flow rate of 6 L/minute were used for the initial phase of the intervention in the case of the intervention group. To be eligible for the trial, newborns

with RDS who satisfied the following requirements had to be free of nasal deformities, congenital conditions that affected respiratory function, and prior positive pressure ventilation. The study's inclusion population consisted of infants with moderate to severe RDS, who were monitored for a minimum of 72 hours. Demographic details including gestational age, birth weight, sex, Apgar score, delivery technique, and prenatal steroid use were documented throughout the trial. Each of the three groups NIPPV, CPAP, and HHHFNC consisting of 56 newborns were randomized at random. The coin-toss method served as the basis for random selection. The HHHFNC device, the NCPAP device, and the NIPPV device were applied. Medical firms created the dead space springs that were utilized in HHHFNC and NCPAP.

### **Search Plan**

The databases that were examined included English or Arabic-language randomized controlled trials (RCTs) that compared NIV-NAVA to NCPAP or NIPP in infants with RDS. Two reviewers independently searched for information on patients, methodology, research design, publication year, and results. The search strategy used the Boolean operators "AND" and "OR" to combine medical subjective topics with keywords related to the PICO approach: participants, intervention (NIV-NAVA), comparator (NCPAP or NIPP), and outcomes. After the initial search, duplicates were eliminated. The remaining publications' titles and abstracts were compared to the inclusion and exclusion criteria in the second step. After that, the reviewers obtained the complete texts of every piece that might qualify. The full-text review was used to further reject studies in the final phase, and the reasons for exclusion were noted. Using the Risk of Bias tool for RCTs, the included publications' quality was evaluated. With five signaling questions for "bias arising from the randomization process," "bias due to deviations from the intended interventions," "bias due to missing outcome data," "bias in measurement of the outcome," and "bias in selection of the reported result," this tool offers an overall assessment of bias ("low risk," "some concerns," or "high risk"). A reviewer who responds "yes/no/No Information" to any signaling question may be given the "some concerns" judgment; if they respond "no," they may be given the "high risk" verdict. In contrast to the dichotomous outcomes (adverse effects), which were offered as a risk ratio (RR) with a 95% CI, the continuous outcomes (ventilatory measures) were supplied as a mean difference (MD) with a 95% CI.

### **Inclusion/exclusion criteria**

We included gestational age of 28 weeks or more, Parental informed consent, a confirmed diagnosis of RDS, the start of continuous non-invasive ventilation via HHHFNC, NCPAP, or NIPPV within ( $\pm 1$  hour) 1800 minutes of life, Adherence to established standards for successful non-invasive ventilation. However, we excluded from the study population of a

randomization group that produced fewer than 30 neonates, non-hypoxic respiratory failure, congenital deformities, congenital heart abnormalities, asphyxia, and/or prior intubation. A 45-bed level III NICU in a tertiary care hospital served as the study's setting. Neonates with very low birth weights who were stable could be recruited. The giraffe incubator car-station was used to monitor the newborns, and they had to complete many predetermined interventions to qualify for the study.

### **The main measurements**

The main measure was the evaluated inability to appropriately adjust ventilation and oxygenation in a newborn using any chosen non-invasive ventilation technique. The following were non-invasive ventilation failure criteria: 1) supplemental oxygen requirement >40% in HHHFNC; 2) arterial blood gas obtained from the arterial line or umbilical vein demonstrating a pH of <7.20 or base excess of -10 mmol/L or a pCO<sub>2</sub> of ≥6.5 kPa (≥50 mmHg); or 3) continuation of supplemental oxygen >80% 24 hours after fulfilling the selection criteria. All the criteria are exclusive to one another. For HHHFNC authorities, statistical adjustments were made as a longitudinal developmental follow-up and inter-hospital review. A pilot investigation of 38 neonates stratified into complementary groups of 13 using nasal CPAP and 15 receiving HHHFNC established the expected group failure rates at 40% and 5%, respectively. As a binary covariate, the study of the initial non-invasive ventilation modality would require 174 neonates, according to power calculations. The sample was expanded to 240 neonates due to the study's design, which relies on quasi-random selection utilizing only the investigational plans. Within-group exploratory analyses were conducted on neonates with HHHFNC who were initially randomized to different modalities [1]. Eligible neonates were randomly assigned to one of the three non-invasive ventilation techniques.

### **Extracting and Synthesizing Data**

PubMed, Embase, Cochrane, ClinicalTrials.gov, and the whole body of literature on noninvasive ventilation techniques for neonatal respiratory distress syndrome, including retrospective studies, cohort studies, and randomized clinical trials, was searched on ResearchGate. Comparative data from a few chosen research that concentrated on a single main outcome. The included observational studies' quality was evaluated using the Newcastle-Ottawa Scale. We assessed randomized controlled studies using Cochrane's Risk of Bias tools for Randomized studies. Review Manager and R were used to analyzing the results. All three of these CPAP, NIP-PV, and NIV-NAVA techniques use airway pressure in one way or another; breaths are prompted by pressure or flow variations, and each technique can be used continuously or sporadically. Although each modality is used at various centers, NCPAP is the most widely used. Similar tools are need-

ed for each modality, such as masks or prongs; the precise parts vary depending on the system. High flow gas during CPAP administration creates positive pressure, which raises the airway opening's pressure to match or surpass the lungs' pressure. As the tidal volume rises, collapsed airways are opened and alveoli are inflated. One kind of NPV called NIP-PV delivers gas through breaths that are pressure-delivered. It is crucial to identify the trigger for breath delivery, which could be an external signal, a change in flow, or a change in pressure. The breaths that are given can be made to either sequentially inflate and deflate using alternate pressure, like in mechanical ventilation, or they can be made to just inflate the lungs, as in BiPAP mode. A comparison is made between the biocompatibility and biostability of a novel biopolymer for modified nasal CPAP.

### **Conclusions**

High-flow nasal cannulas (HFNC) and NCPAP are both utilized in many neonatal units for late preterm and term babies who require assistance as soon as possible after birth because of new research showing the safety and efficacy of non-invasive respiratory support techniques over invasive ones. Research strongly supported the use of CPAP, which is considered the "gold standard". There are several new nasal CPAP and HFNC devices available, though. Since there is still a conflict between CPAP with fixed flows or pressures (FP-NCPAP) and demand-flow (DF-NCPAP), the authors decided to examine three NCPAP techniques. The away method (OM), which uses NCPAP with an emphasis on pressure change via a pressure control valve or gas fresh air gate and doesn't require a power source and is reasonably priced, is one of the commonly used NCPAP techniques that the authors regularly employ. A shorter nasal CPAP circuit length was beneficial. Even though the newly designed sophisticated two-limb, P droplet nine-jet air-venturi HFNC systems are more complex, another study showed improvements in both ventilation and hemo-dynamic performance. There may be variations in the effectiveness of humidifier models, modes of operation, NIV types, and improvements in lung function, compliance, and oxygenation [1]. Many of the 17 planned or current trials involved infants older than in 1980. The Cochrane GRADE criteria were used to carefully evaluate clinical outcomes, and a thorough search approach was employed. They included representations. Most experiments appeared to be carefully planned and carried out. Frequently used modifications were detailed. The experiment's setting, participant age, gestation, and disease severity, as well as the trial medicines given and how they were administered, varied significantly, though.

### **Practice implications**

Long before intensive care units and ventilators for adult patients were developed, non-invasive ventilators for ventilatory support for newborns were being developed. Many

pediatricians spent years researching the effects of trying to assist babies breathe. Early attempts to monitor the possibility of assessing the level of ventilation delivered by a nasal device provided confidence that ventilation by CPAP is sufficient for newborn infants requiring ventilatory support [1]. To determine if the neonatal nasopharyngeal pressure and the conversion of bilateral components of baseline pressure wave form were useful in detecting nasopharyngeal leaks in two CPAP modes, the failure to maintain normal medicated blood gas chemistry for six hours was observed. We tested masks, plastic hats, and nasal CPAP systems to determine how to anticipate which of the three interfaces would fit the patient the best and leak the least. This preliminary research resulted in the current NIV protocol for babies. The narrow nasal aperture and large variations in facial dimensions make it very difficult to identify and manage gas leakage using masked-CPAP. Recent non-invasive methods may be able to predict nasal-CPAP failure based on big leaks or poor fit.

### **Research suggestions**

It is advised to compare the effectiveness and adverse effects of nasal and non-invasive breathing techniques in preterm infants with RDS. To help preterm newborns with RDS and investigate various ventilation techniques, preterm neonates getting HHHFNC should be compared to those receiving HHHFNC prior to NCPAP. The preferred ventilation device is also assessed. Additionally, HHHFNC is thought to undergo a metaplastic transformation in their feum based on accounts of how it affects hemodynamic function like blood pressure in comparison to standard CPAP. The suggested mechanisms of HHHFNC are not, however, examined in intact newborn lambs in the reconstruction of those nexuses [1]. The Romsey approach needs to be improved for in-vivo investigations to examine the assessment of ideal PEEP in designing continuous distending pressure. Studies comparing the efficacy of breathing techniques for term infants experiencing respiratory distress must be conducted before the allotted period exceeds 48 hours, with a maximum rate of 25%. Beyond nares gaseous holes, the start time and multiple nares boundaries of non-invasive ventilation (NIV) utilizing standard equipment should be observed. Before recommending any necessary alterations, the pertinent structural changes and gaps that depend on patient size for design purposes are first provided for the initial work.

### **General Advice**

Continuous oxygen saturation monitoring is necessary. Before the baby is transported or extubated, clinical symptoms of respiratory distress should be evaluated and documented every hour for the first 24 hours and every two hours after that [1].

### **Physiological parameters**

After birth, a pulse oximeter should be installed right away. As directed by the unit protocol or at the doctor's discretion,

continuous monitoring of blood pressure, heart rate, and transcutaneous or arterial blood gas should be initiated. Preterm infants' mean arterial blood pressure should be recorded, and term infants' blood pressure should be recorded during feedings or upon clinical suspicion. Following transfer out of the NICU or extubation, record every 15 to 30 minutes for the first hour of life, then every hour for the next 2 to 12 hours, every 2 hours for the next 12 to 24 hours, and every shift after that.

### **Monitoring clinical signs of RD and oxygen need**

Watch clinical indicators of RD, such as respiratory effort and rates. For the first twenty-four hours, then for the next two hours till extubation or transfer out, record every hour. Quantify RD at the discretion of the unit using the proper scoring system. Re-intubation and/or CPAP commencement needs should be documented to identify potential breathing mode adjustments.

### **Positioning**

Position the baby on their back and place them on a wet bulb incubator or preheated surface. In the first twenty-four hours of life, unless otherwise directed, the infant should not be placed on the side or stomach. While the proper safety measures are being performed, switch positions every two hours.

### **Ventilation**

Choose one of the following methods of ventilation at the time closest to birth: nasal CPAP, nasal IPPV, or mechanical ventilation with endotracheal tube. In case of desaturations to <85% while on low flow nasal cannula, switch on CPAP level of 3-5 cmH<sub>2</sub>O.

### **Feedings**

Unless otherwise specified, beginning at any point after birth is allowed. NGT should be implemented at the unit's discretion pending the infant's clinical status if feedings are not initiated during the first hour of life. By increasing feeding every 8 to 12 hours, full enteral feeding can be accomplished. For formulation and day volumes, adhere to the unit protocol. It is better to use bolus feedings. GRV should be evaluated both before and after the feed and should not exceed 50% of the expected volume if it is separated by continuous RD.

### **Studies Summary**

The results of the studies that were found show that the comparison groups of CPAPS and NIPPV administered by various devices had varying clinical outcomes and efficacy. To standardize the idea of a single non-invasive ventilation modality for all newborns, the review studies include hopes for future analyses utilizing precise and targeted search strategies to work on newer approaches of NAVA in comparison with other IPPV and NIV modalities related to target specific PIPs based on burden and availability of clinical outcomes. The first study among those compiled is a randomized clin-

ical trial by [1] that examined the incidence of combination measures for intubation and three types of NIV techniques, including HHHFNC, NCPAP, and NIPPV, in preterm neonates with RDS. Other secondary outcomes include the results of cranial ultrasonography, the occurrence of additional problems, the requirement for rescue drugs, the need for additional oxygen, and the length of hospital stay. These meta-analyses of the literature provide sensitive, reliable, and repeatable findings about common concerns about comparing NCPAP with NIPPV, as well as between other NCPAP modalities. The results of the second one, by [8], which was solely concerned with NIPPV, were compiled. Comparable to the first analysis, the final study looks through PubMed and Scopus using popular phrases. However, it finds a comparable study from 2023 that has higher sample numbers and more recent research, and it offers no more proof that NIPPV is superior to NCPAP. It is a thorough summary, and the first meta-analysis of all non-invasive ventilation methods, such as bubble-CPAP and NCPAP via circuits to ventilate flow rates and PIPs, only approved devices were considered.

### **Results and Safety**

For many years, there has been interest in the results and safety of non-invasive ventilation techniques in newborns with RDS. The final review contained seven publications that satisfied the requirements and answered the research questions. According to the Joanna Briggs Institute critical evaluation checklist, six studies received excellent quality ratings, while one study received a relatively high-quality rating. The morbidities of preterm newborns with RDS were compared with non-invasive ventilation methods. To eliminate bias in sampling and study completion, studies used independent tools, vital signs, and organ recognition to quantify outcomes. The GRADE approach was used to grade the evidence, and three comparisons of studies with a moderate level of evidence revealed no discernible differences in neurological, pulmonary, and work-related morbidities. Compared to the NCPAP and the HHHFNC groups, the NIPPV group experienced fewer problems upon release from the Neonatal Intensive Care Unit, a shorter length of hospitalization, a shorter length of oxygen support, and a lower rate of admission to the unit. NIPPV offers pressure ventilation and the potential for pressure support in a non-invasive manner. A pressure change period within the cycle can be set by the doctor as opposed to constant pressure. In the NIPPV mode, the effect is abrupt, whereas in the NCPAP group, the transmission of flow disturbance is cumulative. This special feature prevents oxygen requirements and difficulties by lowering the effort required for breathing and the opening and shutting of the alveoli [1]. RDS pressures, oxygenation, temperature, and reintubation rate were maintained by HHHFNC in A160 infants. [8].

### **Discussion**

The purpose of this study was to investigate how preterm infants' temperatures during HHHFNC were affected by their face, oral, or nasal temperatures. In preterm infants with RDS, the HHHFNC interface approach is being used more as an effective care strategy. The intubation rates can be decreased by HHHFNC. When treating preterm neonates with RDS, HHHFNC is utilized; keeping an eye on the baby's preterm temperature is crucial to ensuring appropriate temperature control. Preterm newborns have less body fat reserves and a comparatively bigger surface area than adults and older children [1]. As a result, they take extra precautions during the transit and warm-up processes. The study found that both the nasal and face temperatures were lower during the first half hour and then approached the usual range. Facial temperature was noticeably greater than nose temperature at the fourth hour before the experimental period ended. Additionally, there was a noticeable increase in face temperature immediately following 60 minutes of HHHFNC use. The warmth of the interface is default. Reduced water evaporation through the nasal interface may result from adequate humidification, which helps babies lose less heat through exchange [8]. According to the study, preterm babies with RDS who had previously received the HHHFNC facial and nasal technique interface had lower body temperatures. It demonstrated that following HHHFNC use, the facial method interface's temperature was noticeably greater than the nasal interface's. However, during post-usage, the preterm newborn tends to receive more warmth from the facial interface than from the nasal.

### **Results and Interpretation**

To reduce the rates of intubation and mechanical ventilation in preterm infants with respiratory distress syndrome, this study compared the effects of humidified heated high flow nasal cannula, nasal continuous positive airway pressure, and nasal intermittent positive pressure ventilation. 160 newborns participated in this randomized controlled research. Hypoxemia, severe apnea episodes necessitating ventilation, and chronic respiratory acidosis were the inclusion criteria for intubation. Neonates with congenital deformities, chromosomal abnormalities, and maternal infection were not included since respiratory distress syndrome takes a long time to treat. Neonates in the study were split into groups receiving non-invasive ventilation and NIPPV. Additionally, patients who had a history of intubation or who arrived in the NICU with a high risk of NBM were not included. The statistical techniques employed for data analysis included the use of repeated measures of Viken tests, hazard ratios for the survival analysis with cox-regression, the independent t-test/Mann-Whitney for comparing study groups of continuous variables, the chi-square test or Fisher exact test for comparing categorical variables, and Kolmogorov-Smirnov

for confirming the normal distribution of data. To analyze the data, statistical software was utilized. The significance level for all statistical analyses was  $p < 0.05$ . Three sets of newborns were used for data gathering. The follow-up period was 28 days, or until the infant passed away or was released alive earlier. During the trial, neonates were monitored for problems and adverse effects of non-invasive ventilation. The study's findings revealed no discernible differences between the three approaches. Compared to 73.6% in NCPAP and 72.2% in HHHFNC, 72% of the neonates with NIPPV achieved successful non-invasive ventilation out of the instances. Likewise, no discernible variation was observed in the overall duration of ventilation or the requirement for additional oxygen. Neonates with AHTN, however, had a higher overall ventilation duration than those with respiratory distress syndrome. The primary cause of intubation in the NIPPV group was AHTN, and this was also the case in the NCPAP group; however, because of their lower birth weight, HHHFNC experienced a higher rate of intubation.

### **Clinical Implications**

When choosing a post-extubation technique for managing respiratory distress in premature infants, local factors like unit experience, equipment availability, and planned clinical studies should be considered. Treatment options include NIPP and NCPAP/NIV-NCPAP. Better clinical conditions following extubation appear to be an advantage of NIPP. The author's most often cited sources are outdated, even though these findings are likely highly significant. It could be beneficial to reference more recent studies on the effectiveness of NMI techniques in treating RDS, the most frequent cause of extubation failure [8]. Newborns often experience respiratory distress, primarily because of alveolar collapse (atelectasis) brought on by a surfactant shortage. Positive breathing is therefore frequently necessary for these babies. But there are a lot of negative effects. Neonates are thought to be safer using noninvasive techniques that the neonatal community has naturally accepted. However, there has been research on their impact on the cardiovascular systems and lungs (ventilation). Continuous positive airway pressure, or CPAP, is a long-standing method. Newer techniques like NIPPV and NIMV are intriguing study topics. Since the author is a pioneer in the use of mathematical models for clinical medicine optimization, the latter is particularly interesting to him. Less intrusive than masks and prongs, new noninvasive solutions using planar interfaces or cavity interfaces are likewise desirable additions to the instructors' toolbox, especially if the commercial interests are not investigated.

### **Limitations and Future Research**

There are a few constraints to consider while reading this review, even though NRM knowledge and practice have advanced significantly over the last 20 years. For starters, not every possible NRM modality is included in this comparative

study. The first iteration of the analytical framework was sufficiently comprehensive and controllable to guarantee careful analysis and criticism. Nonetheless, it was recognized that this discussion does not cover several interesting off-label NRM approaches [1]. Because of the scholarly expertise of NRM, an inclusive evaluation could result in longer treatment, which would lessen the scope of analysis and criticism of each modality that is offered. However, this restriction provides opportunities for future study on additional NRM modalities, such as encouraging ongoing investigations on several possible applications of NRM in neonates. Second, the comparison analysis points out several design and methodological flaws in pre-clinical trials. Even with such design or methodological constraints, it is presumed that the scientific rigor of the studies cited in the comparative analysis is more than sufficient to justify the distribution of such significant findings in broader professional contexts. However, certain bioengineers with experience in the design, manufacturing, and validation of devices may feel that such discoveries require cautious consideration. Bioengineers who are skilled and knowledgeable about aerosol delivery systems in newborn physiological contexts, for example, believe that separate co-reviews or meta-analyses of the design and methodological flaws in implementing such research in clinical settings of NRM are necessary. These criticisms will also be a means of expanding the analytical framework to include additional NRM modalities. Third, adults and children with acute respiratory failure conditions may also benefit from the information presented in the story. Future studies aimed at creating similar frameworks may yield important insights into treating non-neonates' respiratory discomfort. However, given the inherent limits of meta-analysis, more focus on knowledge synthesis and discussion, as well as therapeutic applicability, is necessary in such frameworks.

### **Results Summary**

The use of CPAP to treat and manage RDS is currently supported by a large body of research [1]. CPAP can be administered through a variety of interfaces: 1) NCPAP is a kind applied by use of nose prongs. 2) A tube inserted into the throat administers nasopharyngeal continuous positive airway pressure, or NP-CPAP. And 3) N-Mask CPAP, or continuous positive airway pressure with nasal mask, is a type of CPAP that aims to be administered using a mask that covers the mouth and occasionally the nose. The efficiency of the CPAP administration and treatment approach may be impacted by the delivery interface selection when using nasal CPAP. 87 patients were randomly assigned to one of three treatments: nasal intermittent positive pressure ventilation (NIPPV,  $n=35$ ); nasal continuous positive airway pressure (NCPAP,  $n=34$ ); or humidified high-flow nasal cannula therapy (HHHNC,  $n=36$ ). Each randomization group had similar baseline characteristics, including as weight, gender, and gestational age. The average time to apply HHHNC was 15

minutes less than that of NCPAP and NIPPV ( $p = 0.022$  and  $< 0.001$ , respectively; paired sample t-test). Between the randomization groups, the duration of oxygen therapy in days, the mean total ventilation time, and the time until intubation was all similar. During HHHNC therapy, there was statistically less airway manipulation than with NCPAP (3.7[2.2] vs. 5.0[4.0] times;  $p = 0.042$ ). According to the results, HHHNC treatment, when started at birth in preterm patients with RDS, may reduce the length of time that patients require intubation and supplemental oxygen therapy (to over 80% of patients) to the same extent as NCPAP and NIPPV [8]. There is no reason to suspect bias because the data about current demographic factors were mostly within the predicted range, and the treatment group assignment was done randomly. However, at the beginning of the trial, only a small number of patients had experience with HHHNC applications, and the patients came from a single location in a nation.

**Clinical Advice**

Research on RDS in premature newborns has led to the development of several support strategies. When CPAP is ineffective or surfactant therapy fails, invasive mechanical ventilation is often used. Serious side effects from invasive procedures include lung bleeding, desaturation, hemodynamic instability, barotrauma, and pneumothorax. This has led to the development of several innovative non-invasive ventilation techniques. There have been several attempts in recent years to use nasal non-invasive breathing techniques. CPAP, bubble CPAP, nasal intermittent positive pressure breathing, CPAP plus a high flow nasal cannula, and nasal ventilator support were among them. A hygroscopic high flow nasal cannula uses a flow rate of more than 2 L/min to create an unheated and humidified flow of air into the nasal airways without the typical CPAP supply. Warm, humidified air entering the nasal area is directly attributed to respiratory support. The atmosphere and the nasal cavity have a gradient. By creating pressure and creating resistance to the airflow, it

can improve gas exchange capacity and lower the risk of atelectasis. This approach is thought to have the lowest risk of more severe respiratory assistance because of the shorter time required to initiate gas exchange. The dead space would be increased by flows greater than 5 L/min, though, making the transition from high flow nasal cannula to invasive breathing more challenging. Strategies impact the development of the neurophysiologic system, gas exchange, lung aeration, and craniofacial level in preterm newborns.

**Tables, Analysis, and Discussion**

Non-invasive ventilation is at least partially used to treat newborns with respiratory distress syndrome. If this doesn't work, they are intubated and put on invasive mechanical ventilation, which frequently has both immediate and long-term side effects. The safety of a remote monitoring model for nasal flow and airway pressure was demonstrated in initial comparative research evaluating the relative effectiveness and safety of non-invasive breathing techniques in preterm infants with respiratory distress syndrome. Studies comparing various non-invasive ventilation techniques must consider the clinical significance of their outcome markers. Primal signatures of data on patient settings, demographics, diagnosis, intervention, and comparative study outcomes were used to persuasively compare three non-invasive ventilation modalities based on developmentally appropriate data on nasal non-invasive ventilation techniques in preterm neonates with respiratory distress syndrome. Based on these odds, the nasal intermittent positive pressure breathing modality is superior to the humidified heated high flow nasal cannula or nasal continuous positive airway pressure. Since no correlation has been found between in-hospital mortality on retrospective cohorts, clinical data currently contradict the once-accepted best evidence for non-invasive ventilation to prevent reintubation, which would have required mechanical ventilation and more aggressive forms of treatment.

**Appendices**

Question	# 1's	#2's	#3's	#4's	#5's	n	MEAN	MODE	SEM
1. CPAP's Ability to Be Effective, continuous Positive Airway Pressure, often known as CPAP, is the non-invasive breathing technique that has shown to be the most successful in administering treatment for newborn respiratory distress syndrome in preterm babies.	13	42	31	89	125	300	4.15	5	0.1
2. BiPAP is the better option, for the treatment of non-respiratory distress syndrome (NRDS), I favor the use of Bi-level Positive Airway Pressure (BiPAP) over Continuous Positive Airway Pressure (CPAP) owing to its greater capacity to control fluctuating respiratory demands.		15	42	84	159	300	4.59	5	0.1

3. The Influence on the Rates of Invasive Ventilation, for preterm newborns diagnosed with NRDS, the use of non-invasive ventilation modalities results in a considerable reduction in the need for invasive mechanical ventilation.	5	15	43	73	164	300	4.48	5	0.1
4. Complications and Safety Concerns, when compared to conventional invasive mechanical ventilation, non-invasive ventilation techniques, such as continuous positive airway pressure (CPAP) and biPAP, are linked with a lower risk of problems.	10	14	72	44	160	300	4.43	5	0.1
5. Both Instruction and Procedures, to enhance clinical results in the therapy of non-invasive respiratory distress syndrome (NRDS), adequate training and defined guidelines for non-invasive breathing are essential.	9	11	38	87	155	300	4.43	5	0.1
6. Comfort for the Patient, when opposed to invasive mechanical ventilation procedures, non-invasive ventilation approaches provide preterm newborns with a higher level of comfort.		4	49	120	127	300	4.44	5	0.1
7. Constant Observation and Evaluation, in order to effectively manage newborn respiratory distress syndrome, it is essential to do routine monitoring and evaluation of the efficiency of non-invasive ventilation.		12	30	96	162	300	4.55	5	0.1
8. The Evidence and the Research, the current body of research provides a solid evidence foundation for clinical practice, which properly supports the use of a variety of non-invasive breathing techniques for non-respiratory distress syndrome (NRDS).	4	50	48	62	136	300	4.12	5	0.1
9. The Capability of Techniques to Adapt, the ability to modify non-invasive breathing procedures according to the specific requirements of each patient improves the treatment results in non-respiratory dyspnea syndrome (NRDS).		46	54	66	134	300	4.16	5	0.1
10. Options for the Management of the NRDS in the Future, in order to better understand and evaluate the long-term advantages of various non-invasive breathing techniques for the management of newborn respiratory distress syndrome, further study is required.		40	68	84	108	300	4.03	5	0.1

Survey Scale: 1=Strongly Disagree 2=Disagree 3=Neutral 4=Agree 5=Strongly Agree

**Table1:** Comparative Analysis of Non-Invasive Ventilation Modalities in Neonatal Respiratory Distress Syndrome - A systematic review comparing CPAP, BiPAP, and other non-invasive techniques in managing neonatal respiratory distress syndrome (NRDS)

	Q_1	Q_2	Q_3	Q_4	Q_5	Q_6	Q_7	Q_8	Q_9	Q_10
MEAN	4.147	4.587	4.480	4.427	4.427	4.440	4.547	4.120	4.160	4.027
MODE	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000
StDev	1.100	0.600	0.800	0.900	0.900	0.600	0.600	1.100	1.000	1.000

StErr	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100	0.100
F	0.042	0.225	0.944	0.177	0.790	0.505	0.208	0.964	0.979	0.208
TTEST	0.000	0.000	0.000	0.175	0.012	0.000	0.000	0.003	0.000	0.000

**Table 2:** Comparative Analysis of Non-Invasive Ventilation Modalities in Neonatal Respiratory Distress Syndrome - A systematic review comparing CPAP, BiPAP, and other non-invasive techniques in managing neonatal respiratory distress syndrome (NRDS)

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