Effectiveness of Non-invasive Ventilation in Treating Infants Aged 1 to 12 Months with Severe Bronchiolitis: A Systematic Review and Meta-analysis

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ABSTRACT

Objective. This study was done to determine the effectiveness of non-invasive ventilation (NIV) in treating infants aged 1 to 12 months with severe bronchiolitis based on a systematic review of literature and meta-analysis of quantitative results.

Methods. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for identification, screening, and identification of eligible studies. Five databases (PubMed, Herdin, Cochrane Library, Google Scholar, and Science Direct) were searched for relevant studies involving the use of NIV among children with severe bronchiolitis. Included studies were assessed for quality and risk of bias.

Results. There were 9 included eligible studies. The length of hospital stay and duration of respiratory support were significantly lower with the use of NIV compared with IMV (invasive mechanical ventilation) based on pooled standard mean difference (SMD) estimates; however, there was high statistical heterogeneity in the included studies. This can be attributed to differences in the mode of intervention used among studies, patient-specific factors, and viral virulence. Significant improvements in heart rate, oxygen saturation, and tCO_2 were seen in the included studies. One study showed statistically significant differences in changes in respiratory rate and improvement in respiratory status based on two bronchiolitis severity scores among infants placed on NIV.

Conclusion. Fair to good-quality evidence from included studies reveals that there is a significant reduction in length of hospital stay, duration of respiratory support, and improvements in respiratory parameters among infants who received NIV for severe bronchiolitis. Larger, well-designed clinical trials on the use of NIV among resource-limited settings wherein it may offer valuable clinical utility, are recommended for future study.

Keywords: non-invasive ventilation, bronchiolitis, infants, respiratory support, CPAP, BiPAP, NCPAP

INTRODUCTION

The most common cause of lower respiratory tract infection among infants is bronchiolitis.[1,2] This condition is commonly caused by a respiratory syncytial virus (RSV).[3] The pathophysiology involves airway inflammation, edema, necrosis of epithelial cells, increased mucus production, and hypoxemia.[4] This disease causes significant morbidity and mortality among infants.[5]

Severe bronchiolitis is the most common reason for the hospitalization of pediatric patients and may pose significant costs.[4,6-7] Furthermore, bronchiolitis leads to approximately 199,000 deaths every year in children under 5 years, with most cases occurring in developing countries.[8,9] According to the Philippine Department of Health, in 2010, bronchiolitis was the third leading cause of morbidity.[10] A study by

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Uenoet. al. showed that severe illness for RSV-related lower respiratory tract infections may be found in 25% of cases.[11]

Clinical features suggestive of severe bronchiolitis include poor feeding, tachypnea, severe chest retractions, presence of alar flaring, desaturation at room air, and lethargy; these may lead to acute respiratory failure.[11] Treatment options for bronchiolitis are few.[12] For more severe cases, invasive mechanical ventilation (IMV) has been widely used through an artificial airway.[2] In resource-limited settings, there is an increasing need to develop safe and effective alternatives to invasive mechanical ventilation. However, presently, there are limited studies that support the use of these respiratory interventions.[2]

Non-invasive ventilation (NIV) refers to the application of inspiratory and expiratory pressure levels to improve minute ventilation by enhancing carbon dioxide elimination in patients with respiratory failure without an artificial airway.[13] Recent studies have shown that NIV can be a beneficial alternative respiratory support for children with acute respiratory failure.[14,15] Theoretically, the use of NIV in respiratory failure facilitates the recruitment of non-ventilated alveoli to improve the ventilation-perfusion ratio and enhancing gas exchange.[15] Studies conducted by McNamara et al., showed improvement with the use of continuous positive airway pressure as a treatment in RSV bronchiolitis.[16] Moreover, studies conducted by Campio and Larrar showed a success rate of 75 to 83% with the use of NIV in bronchiolitis.[17,18] NIV may be administered via nasal continuous positive airway pressure (NCPAP) which uses a tight-fitting nasal mask held by head straps.[15] Meanwhile, bilevel positive airway pressure (BiPAP) is another mode of NIV, wherein a higher level of inspiratory positive airway pressure is administered.[15]

Approximately 1-3% of infected children may develop feeding difficulties, apnea, or are unable to maintain adequate oxygenation consistent with severe disease, which requires hospitalization.[8,19-20] Infants presenting with clinical signs of exhaustion, markers of acute respiratory failure defined as the partial pressure of oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) of less than 300 mmHg, or signs of apnea, may require the need for assisted ventilation through mechanical ventilation.[21,22] However, the use of invasive mechanical ventilation led to potential complications such as ventilator-associated pneumonia and subsequently, prolonged hospitalizations.[23]

Recognizing the potential complications, considerable costs, and longer hospitalization days among patients with severe bronchiolitis on mechanical ventilation, studies to explore the potential benefit of non-invasive modes of ventilation for infants with severe bronchiolitis are needed.

OBJECTIVES

Our study was done to determine the effectiveness of non-invasive ventilation in treating infants aged 1 to 12 months with severe bronchiolitis based on a systematic review of literature and meta-analysis of quantitative results.

Specifically, this paper aims:

1. To determine the effectiveness of non-invasive ventilation in preventing acute respiratory failure secondary to bronchiolitis based on the following outcomes and variables: age, non-invasive ventilatory success, non-invasive ventilatory failure, development of secondary pneumonia, mortality and intubation rate, improvement in clinical parameters (heart rate, respiratory rate), and oxygenation parameters (i.e., peripheral oxygen saturation, transcutaneous CO_2 [tCO_2],
2. To determine the effectiveness of non-invasive ventilation in decreasing the length of hospital stay and duration of ventilatory support among infants with severe bronchiolitis; and,
3. To determine the safety and complications of non-invasive ventilation in severe bronchiolitis.

METHODOLOGY

Study Selection

This systematic review and meta-analysis involved randomized controlled trials, retrospective studies, and prospective observational studies on children aged 1-12 months with severe bronchiolitis and given non-invasive ventilation. We analyzed researches specifically evaluating the following modes of NIV: CPAP (continuous positive airway pressure), biPAP (bilevel positive airway pressure), and nasal NIPPV (non-invasive positive pressure ventilation). Among studies included, invasive ventilation or standard therapy using supplemental oxygen was used as a comparison to non-invasive ventilatory support.

Outcomes

The following outcomes were assessed to determine the effectiveness of NIV in infants with severe bronchiolitis:

1. Length of hospital stay(mean ±SD)
2. Duration on ventilation support (mean ±SD)
3. Non-invasive ventilation success (odds ratio)
4. Non-invasive ventilation failure (odds ratio)
5. Intubation rate (odds ratio)
6. Development of secondary pneumonia (n/hazard ratio)
7. Mortality(n)
8. Pediatric Risk Mortality (PRISM) scoring[24]

Study Screening

Studies were independently selected. There were no restrictions as to the study location and language of publication. Included studies were conducted from 2000 to 2020. Irrelevant studies which do not address the PICO (population, intervention, control or exposures, and outcomes) of our study were excluded based on the first screening of titles and abstracts. Eligibility criteria were used to evaluate the remaining full text of the articles. Disagreement in

eligibility for inclusion was resolved by discussion between the two authors until consensus was reached.

Study Selection, Information Sources, and Search Strategy

We adhered to the PRISMA (P*referred Reporting Items for* S*ystematic Reviews and* M*eta-*A*nalyses)* flow for identification, screening, and identification of eligible and included studies.[25]

Two investigators searched online electronic databases such as PubMed, Herdin, Cochrane Library, Google Scholar, and Science Direct for related publications. The literature search was conducted from October 13 to November 3, 2020. There were no language restrictions. The search strategy combined Medical Subject Heading (MeSH) terms and free-text terms, including "severe bronchiolitis" and "non-invasive mechanical ventilation" or "NIPPV" or "nasal continuous positive airway ventilation" or "NCPAP" or "biPAP" or "bilevel airway pressure". A hand search was also done to look for unpublished studies (i.e, resident-in-training or fellow-in-training research papers or student theses). To avoid missing any related studies, reference lists of possible studies were checked as well. We included the following study designs: randomized controlled trials, retrospective studies, cohort studies, and prospective observational studies. Case reports, case series, and commentaries/editorials were not included in this systematic review and meta-analysis. Screening and determination of eligibility were done independently by two reviewers. In case of disagreements, it was discussed between the two reviewers until consensus was reached.

Data Collection Process

Data were extracted by two authors independently. Information on the first author, publication year, study design, study setting, number of participants, age range(mean±SD), and mode of non-invasive ventilation. The following data were extracted from the included studies; age, length of hospital stay, duration of ventilatory support (mean±SD), non-invasive ventilatory success (odds ratio), non-invasive ventilatory success (odds ratio), intubation rate (odds ratio), development of secondary pneumonia(n/hazard ratio), mortality (n), non-invasive ventilatory failure rate using PRISM scoring.

Quality Assessment and Risk of Bias Tools used in assessing individual Studies

Study quality of non-randomized controlled trials was assessed using NIH quality assessment form.[26] The Cochrane Collaboration tool,[27] and Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I)[28] for assessing the risk of bias were utilized for randomized controlled trials and non-randomized controlled trials, respectively.

Outcomes and Summary Measures

After inputting data gathered from relevant eligible studies, statistical analysis and forest plot figures of pooled outcomes were generated using Review Manager software (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).[29] Continuous outcome data were analyzed as mean differences (MDs). The standardized mean differences (SMD) were used to assess the association between non-invasive mechanical ventilation and the risk of respiratory failure. A random-effects model was used to calculate the pooled SMD. Dichotomous outcomes were analyzed by calculating the odds ratio (OR). Assessment of safety and harm based on the following parameters: age, length of hospital stay, duration of ventilatory support (mean±SD), non-invasive ventilatory success (odds ratio), non-invasive ventilatory success (odds ratio), intubation rate (odds ratio), development of secondary pneumonia, mortality (n/hazard ratio)) and non-invasive ventilatory failure rate using PRISM scoring.

Synthesis of Study Results

Results of quantitative variables were expressed in mean with standard deviation and or percentage values. Categorical values were compared using the Mantel-Haenszel test. A p-value of 0.05 was considered statistically significant.

Additional Analyses

The I^2 statistic was used to quantify the degree of heterogeneity. An I^2 > 30% will indicate high heterogeneity. Subgroup analysis was done to determine the probability of a positive subgroup analysis (treatment subgroup interaction).

Ethical Considerations

The research proposal was submitted to the ManilaMed Ethics Research Committee (MMERC) before the commencement of this study. It was granted exemption from ethical review as there are no human participants involved and the study entailed a systematic review and meta-analysis of researches (MMERC No. 2020-17).

RESULTS

Literature search and selection

A total of 237 studies were identified from an initial exhaustive search of online electronic databases and other sources. After removing duplicates, 51 studies remained for the first screening (title and abstract screening). A total of 41 studies were subsequently retrieved for full-text review. Of the 41 studies, 9 met the eligibility criteria and were included in the qualitative synthesis. Unrelated studies that did not address the population, intervention, comparison, and outcome (PICO) questions of our review, utilized high flow nasal cannula (HFNC), compared different modes of NIV from each other (i.e,CPAP vs BiPAP), those that

included neonates as well as non-severe bronchiolitis (moderate or mild cases of bronchiolitis) were excluded.

Our final screening revealed that 9 eligible papers underwent qualitative analysis (a total of 9 studies).[30-38] Only 7 studies were included for quantitative analysis consisting of 6 retrospective studies and 1 randomized controlled trial. Figure 1 shows the PRISMA flow chart[25] to illustrate the study selection process.

Study Characteristics

The characteristics of 9 included studies[30-38] are presented in Table 1. There were 6 retrospective studies[30,32,35-38], 2 prospective observational studies[31,34] and 1 randomized controlled trial.[33] All studies were published before October 2020, and study locations were Netherlands,[30] France,[30] Australia,[32-35,37] India,[33] Norway,[34] United Kingdom,[36] New Zealand[37] and the United States.[38] All of the included studies were in the English language. The number of participants varied across studies and ranged from 12 to 285 patients. In the included studies,[30-38] a total of 1283 patients were observed to be commenced on non-invasive ventilation. The modes of non-invasive ventilation used were nasal CPAP and biPAP. The rest of the characteristics of the included studies are shown in Table 1.

Quality Assessment and Risks of Bias of Included studies

The quality assessment was made based on the guide questions of the NIH Collaboration Tool,[26] while the risk of bias for non-randomized and randomized controlled trials was assessed by utilizing the Cochrane Collaboration tool[27] and ROBINS-I.[28] The included studies have addressed appropriate source population, measurement methods, study design, and statistical method.

The 8 included studies which were non-RCTs[30-32,34-38] were assessed to have fair to good quality based on the NIH Collaboration Tool for quality. Using the ROBINS-I tool, on the assessment of the risk of bias, the included non-RCTs[30-32,34-38] were evaluated to have a low risk of bias in the following domains: bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, and selection of reported results and measurements of outcomes. On the other hand, the only RCT, the study by Lal and colleagues[33] was assessed

Table 1. Summary of Included Studies

Author, Year of Publication	Type of Study	Study Setting (Location and Year)	Participants (number of patients)	Age Range (Mean)
Borckink, 2014[30]	Retrospective cohort analysis	Groningen, Netherlands and Paris, France (January 2009 to February 2010)	139 (NCPAP = 89, IMV = 46)	NCAP = 46.5±34.8 days IMV = 56.5±143 days
Cambonie, 2008[31]	Prospective study	Montpellier, France (November 2004 to March 2006)	12	NCAP = 46±6 days
Fleming, 2011[32]	Retrospective analysis	Victoria, Australia (January 2003 to July 2007)	192	Mean = 54 days
Lal, 2016[33]	Randomized controlled trial	Delhi, India (November 2014 to March 2016)	CPAP = 32 Standard care = 35	bCPAP = 4 months Standard care = 4.7 months
Oymar, 2014[34]	Prospective, observational (single center)	Stavanger, Norway (May 2008 to April 2012)	CPAP at ward = 33 CPAP at ICU = 13	CPAP at ward = 34 weeks CPAP at ICU = 37 weeks
Ganu, 2012[35]	Retrospective analysis (single center)	Westmead, Australia (January 2000 to December 2009)	CPAP = 285 IMV = 285	Not specified
Lazner, 2012[36]	Retrospective analysis (single center)	Sheffield, United Kingdom (January 2001 to February 2007)	CPAP = 61 IMV = 6	CPAP responders = 27-40 weeks CPAP non-responders = 28-40 weeks
Oakley, 2017[37]	Retrospecive analysis (multi-center)	Australia and New Zealand (2009 to 2011)	204	Non ICU patients = 195.6±84.5 days ICU patients = 176.9±84.7 days
Soshnick, 2019[38]	Retrospective cohort (single center)	Connecticut, USA (2 time periods: 2010-2012 and 2015-2019)	2010-2012: NCPAP = 97; BiPAP = 4 2015-2016: NCPAP = 52; BiPAP = 4	Not specified

Abbreviations: NCPAP = nasal continuous positive airway pressure, biPAP = bilevel airway pressure, IMV = invasive mechanical ventilation, tCO_2 = transcutaneous CO_2, FiO_2= fraction of inspired oxygen

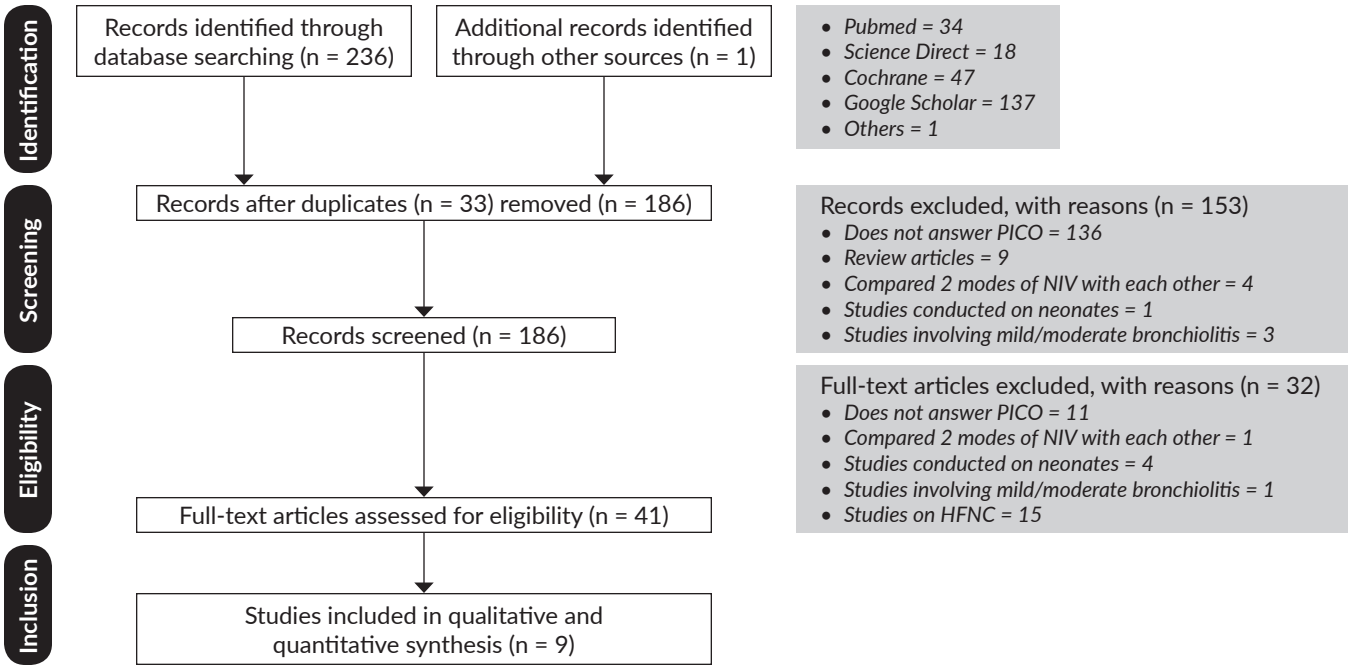

Figure 1. The PRISMA flow diagram.[25]

Males	Comparison/ Control	Mode of Non-Invasive Ventilation	Main Outcomes	Other Outcomes
NCAP = 47/89; IMV = 23/46	Invasive Mechanical Ventilation	NCPAP	• Duration of respiratory support	Length of PICU stay; Level and time course of SpO_2/FiO_2 ratio; Occurrence of secondary pneumonia
Not reported	None	NCPAP (6 cm H_2O via mask)	• Respiratory distress based on Modified Wood's clinical asthma score (m-WCAS)	Heart rate; O_2 saturation; tCO_2, mean arterial blood pressure
Not reported	Invasive Mechanical Ventilation, Supplemental oxygen, no respiratory support	NCPAP	• FiO_2 requirement	tCO_2, peripheral O_2 saturation
bCPAP = 26/32 Standard care = 28/35	Oxygen via face mask or hood	BCPAP	• Change in respiratory rate	Need for mechanical ventilation; Silverman-Anderson score; Modified Pediatric Society of New Zealand Severity Score
CPAP at ward = 17/33 CPAP at ICU = 10/13	None	CPAP	• Capillary pCO_2	Need for mechanical ventilation
Not specified	Invasive mechanical ventilation	Nasal or full face mask CPAP	• Intubation rate • Failure vs success of NIV	Length of hospital stay
CPAP responders = 31/55 CPAP non-responders = 4/6	CPAP responders vs CPAP non-responders vs IMV	Nasal prongs or Nasal mask CPAP (4-6 cm H_2O)	• Ventilation days • Peak FiO_2 • Duration of O_2 administration • Place of treatment • Total hospital days	Changes in O_2 saturation, respiratory rate, pH, pCO_2
Not specified	CPAP use on ICU vs non-ICU patients	CPAP	• Length of hospital stay	
Not specified	CPAP and biPAP use	Nasal CPAP and biPAP	• Intubation rate • Number of intubation days • Hospital length of stay • ICU length of stay	Rate of use of non-invasive devices

to have a low risk of bias based on the following parameters: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective reporting.

Outcome evaluation and Meta-Analysis

Length of Hospital Stay and Duration of Ventilatory Support

Two studies directly compared the length of hospital stay and duration of respiratory/ventilatory support among infants with severe bronchiolitis who were commenced on NIV versus invasive mechanical ventilation.[30,31] Results showed that length of hospital stay is significantly lower with the use of NIV compared with invasive ventilation controls, with a pooled SMD estimate of -1.06 (95%CI = -1.28, -0.84). However, there was high statistical heterogeneity between the two studies, I^2 = 99%. This can be due to variability in the type of intervention used i.e. CPAP vs IMV. Also, the use of NIV also decreases the duration of ventilatory support. Using pooled SMD estimate of -1.18(95%CI = -1.42, -0.95); similarly, statistical heterogeneity between studies was also noted to be high.

Non-invasive ventilatory success

Evidence supporting NIV success in the proportion of infants with severe bronchiolitis with impending respiratory failure was available. After pooling data of 6 studies,[32,34-38] Odds Ratio (OR) of NIV in severe bronchiolitis was 6.44 (95%CI 5.34, 7.76). The odds of NIV success were six times greater among those with NIV as shown in included studies in Figure 2. There was highly significant statistical heterogeneity across studies, I^2 = 97%. This can be attributed to variation in the types of intervention being compared.

To eliminate the effect of variation in the type of intervention being used among included studies, a subgroup analysis was done. NIV success among studies,[32,34,35] which utilized CPAP (Figure 3) as a treatment for severe bronchiolitis OR was 3.10 (95%CI 2.47, 3.88). There was highly significant statistical heterogeneity across studies, I^2 = 86%. This was due to the differences in patient-specific factors such as baseline apnea, refractory hypoxia, hypercarbia with acidosis, and poor general condition. In contrast, NIV success in studies utilizing NCPAP±/ BiPAP/ NIPPV,[36-38] (Figure 4) showed an OR of 86.54(95%CI 52.69, 142.12). There is no observed heterogeneity across the studies. Thus, it can be deduced that the use of NCPAP±/ BiPAP/NIPPV was 86 times greater in preventing acute respiratory failure in severe bronchiolitis.

Treatment failure of NIV and Escalation to Mechanical Ventilation

Non-invasive failure in infants with severe bronchiolitis was commonly seen due to interface intolerance.[36] In the study by Lal, among patients belonging to the CPAP group, 2/36 patients were escalated to mechanical ventilation compared to 1/36 patients in the standard care group (supplemental oxygen only; non-CPAP).[33]

On the other hand, Lazner reported that there was a 10% requirement of escalating to invasive ventilation once

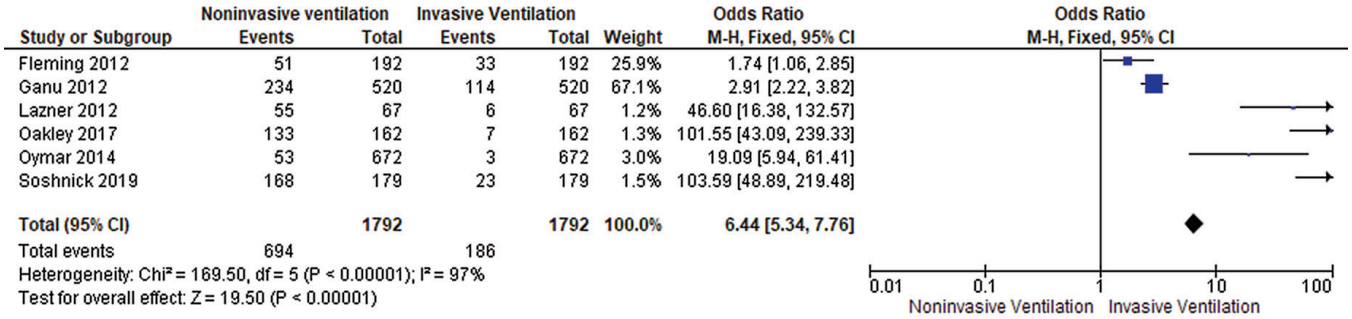

Figure 2. Forest plot of the proportion of NIV success.

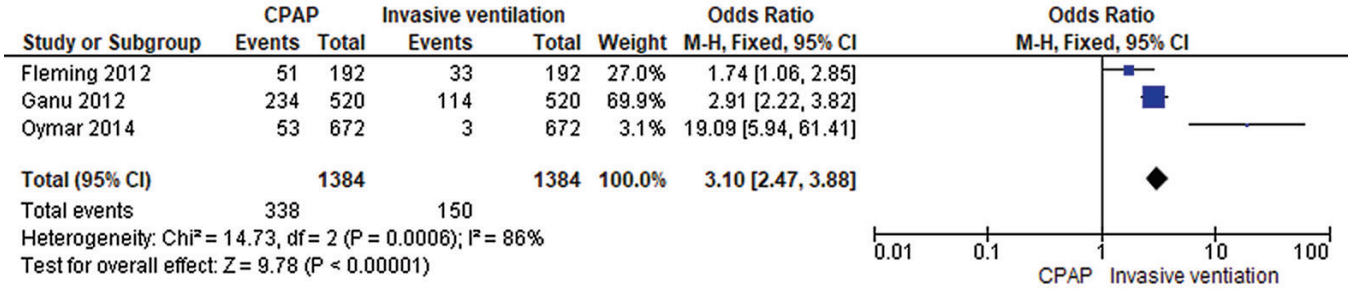

Figure 3. Forest plot of proportion of NIV success among patients placed on CPAP vs IMV.

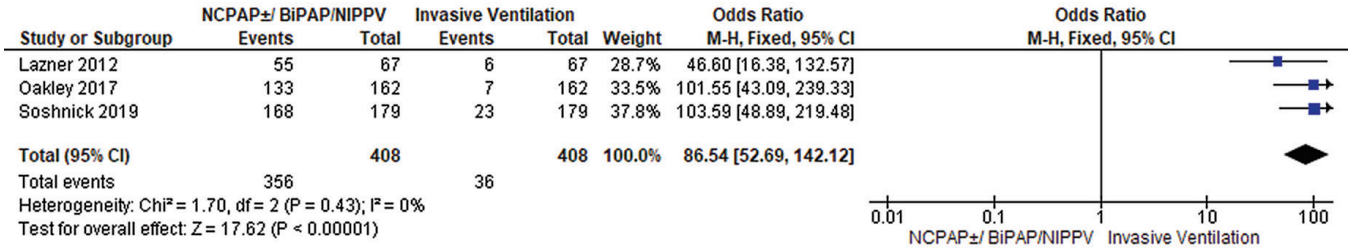

Figure 4. Forest plot of the proportion of NIV success among patients placed on NCPAP±/ BiPAP/NIPPV vs IMV.

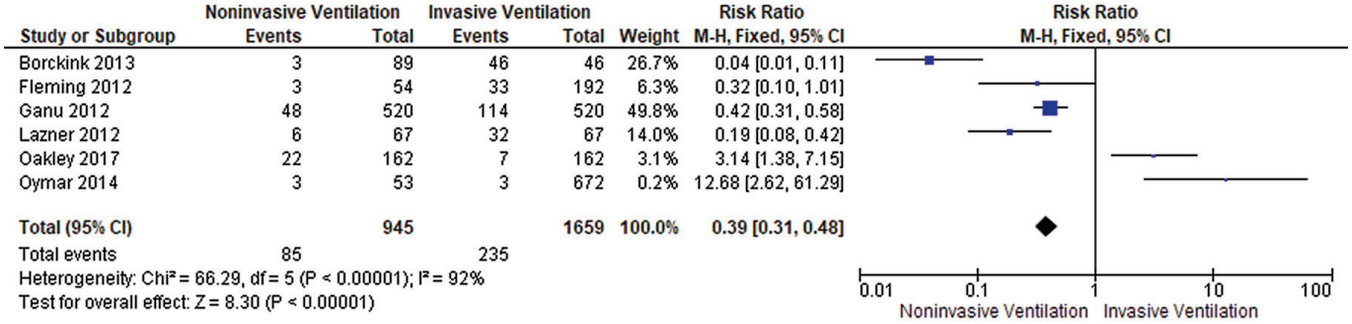

Figure 5. Forest plot of the proportion of NIV failure.

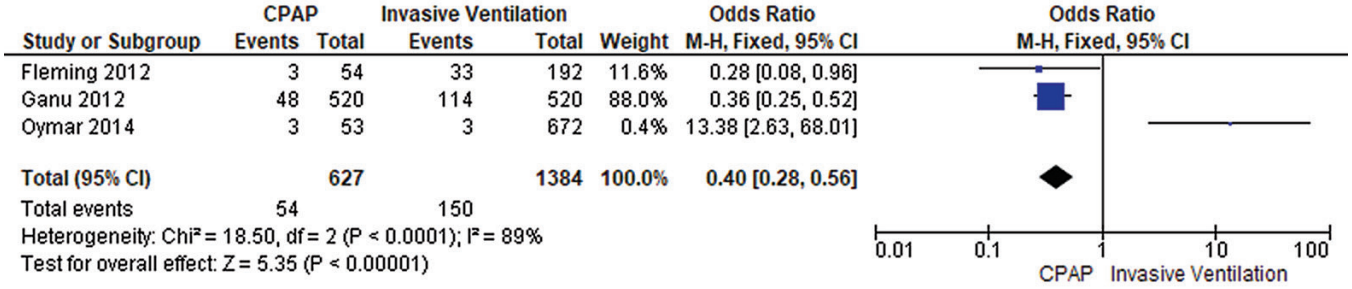

Figure 6. Forest plot of the proportion of NIV failure among CPAP vs IMV.

NIV had commenced.[36] In this study, the proportion of infants with severe bronchiolitis after pooling of data showed that OR of NIV Failure was 0.39 (95%CI 0.31, 0.48). The odds ratio of respiratory failure was lesser compared to invasive ventilation. There was highly significant statistical heterogeneity across studies, I^2 = 92% (Figure 5). This can be due to variation in treatment protocols and types of intervention among studies included.

NIV failure across studies,[32,34,35] which utilized CPAP as a treatment for severe bronchiolitis has an OR of 0.40 (95%CI 0.28, 0.58). In contrast, those that utilized NCPAP±/ BiPAP/NIPPV,[36-38] showed an OR of 0.26 (95%CI 0.17, 0.38).However, there was high significant statistical heterogeneity across studies in CPAP(Figure 6) which may be due to the differences in patient-specific factors and viral virulence.[34]

Changes in Clinical and Respiratory Parameters

The RCT study by Lal et. al revealed significant differences in changes in respiratory rate (decrease in tachypnea; p-value = 0.008) among patients placed in NCPAP (14/32) compared to those placed on standard care which involved supplemental oxygen via face mask (5/35). The respiratory status improvement as reflected on the Silverman-Anderson score and Modified Pediatric Society of New Zealand Severity Score for assessing bronchiolitis was also noted to be statistically significant among patients placed on CPAP.[33]

Furthermore, significant improvements in heart rate, respiratory rate, oxygen saturation, and tCO_2 were seen in the included studies. In terms of reduction in tachycardia, a study conducted by Lazner[36] showed improvement in heart rate with a mean difference of 2 beats per minute (±1.75-2SD). Also, reduction in respiratory rate there was 0.5 cycles per minute mean difference (±18-12.5 SD), while peripheral oxygen saturation improved with a mean difference of 1% (±1.75-2SD). Lastly, there was noted improvement in the tCO_2 mean difference of 0.6 (±2-6.5SD).[36]

Complications

Among the studies included, Lazner[36] reported that intolerance to face masks or prong is the most common complication leading to escalation to invasive ventilation. The development of secondary pneumonia was reported in 1 participant.[36] In addition, a study conducted by Borckick,[30] reported an increased probability of secondary pneumonia with increased ventilatory support at a given time with a hazard ratio of 1.336 (95%CI 0.749-2.384) with a p-value of 0.326.

PRISM (Pediatric Risk Mortality) and Mortality

Treatment failure with non-invasive ventilatory has been measured in some studies using PRISM (Pediatric Risk Mortality). In which, low values of PRISM correlate with success in NIV and high values with acute respiratory failure.[24] In the studies conducted by Bornick and Cambonie showed that PRISM scored showed mean of 5.1 to 8.6 (±1.2-2.8 SD).[30-31] These values predict a higher success rate with NIV use. Also, the mortality rate was only reported in the study conducted by Soshnick, which showed 1 out of 179 patients treated with NIV.[38]

Funnel Plot

Pooled results showed high heterogeneity and included studies were assessed to have true statistical heterogeneity based on asymmetric funnel plot, as shown in Figure 7. Hence, further studies with more standardized and less heterogeneous baseline values such as baseline apnea, level of hypoxemia, and participants' general condition may be recommended.

DISCUSSION

This review yielded 9 eligible studies with a total of 1283 infants with severe bronchiolitis who received NIV via CPAP or BiPAP. Affected infants' age ranges from a mean of 46±6 days to 40 weeks. Assessment of relevant studies revealed that there is fair to good quality evidence that demonstrates that infants with severe bronchiolitis could be safely and effectively be supported by NIV. Included studies were assessed to have a low risk of bias. The length of hospital stay and duration of respiratory support is significantly lower with the use of NIV compared IMV based on pooled SMD estimates; however, there was high significant statistical heterogeneity in the included studies.[30-31] Significant improvements in heart rate, respiratory rate, oxygen saturation, and tCO_2 were seen in the included studies.[36] The only RCT included in this review showed statistically significant differences in changes in respiratory rate and improvement in respiratory status based on 2 bronchiolitis severity scores among children placed on NIV compared to standard therapy only.[33]

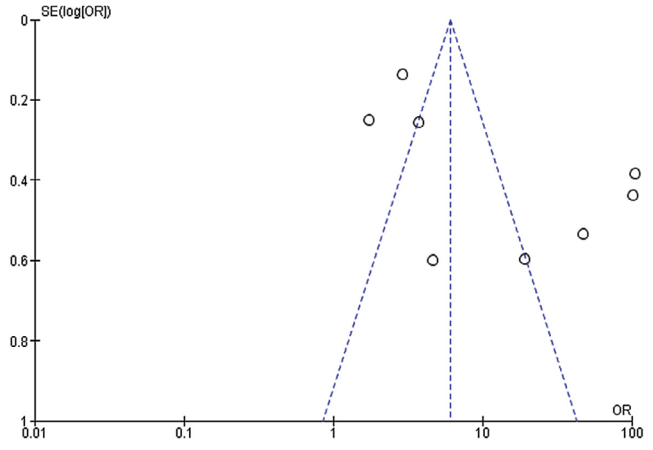

Figure 7. Funnel Plot: Noninvasive Mechanical Ventilation in Severe Bronchiolitis.

We observed that during the past two decades, there has been an increased use of NIV as part of the treatment of infant bronchiolitis in different areas around the world; the earliest study in the eligible papers was the one by Ganu et al., involved admitted patients in the year 2000 and was conducted in Australia.[35] Soshnick et al. also reported an increase in the use of NIV in a retrospective cohort study examining the use of NIV between two time periods (2010-2012 and 2015-2016).[38] Presently, there is no published literature on its use among children in our country. Aside from its use in the ICU setting, it may also be offered as a viable option for respiratory support among patients who are admitted at the wards, as studied in the paper by Oymar.[34]

Furthermore, NIV may potentially avoid risks and complications of invasive mechanical ventilation such as prolonged hospital stay, secondary bacterial infections, ventilator-associated lung injury, and oxygen toxicity secondary to exposure to high concentrations of inspired oxygen from IMV.[33]

Among patients with moderate severity of bronchiolitis, the study by Thia, et al. showed that young infants less than 1-year-old placed on CPAP showed statistically significant improvement in pCO_2 reduction.[39] CPAP was noted to be well-tolerated among patients.[39] Similarly, our results also showed statistically lower NIV failure rates [OR of NIV Failure was 0.39 (95%CI 0.31, 0.48)], although there was wide heterogeneity in the included studies.

In comparison with other studies, a meta-analysis by Liu[40] et al. showed that non-invasive positive pressure ventilation (NIPPV), another mode of NIV, in acute respiratory failure among adult patients showed that the use of NIV was associated with significantly reduced intubation rates.[40] However, it did not have significant differences in length of ICU or hospital stay.[40] This is in contrast with findings in our study, wherein we found significant reductions in the duration of hospital admission and length of respiratory support among studies that examined these parameters.

Similarly, studies conducted by Combret,[41] showed that NIV reduces respiratory distress, heart rate, respiratory rate, and respiratory effort with a $P<0.05$. This leads to better

cardiorespiratory function. However, while the results of the said study noted a reduction in pCO_2, the use of NIV was inconclusive in preventing endotracheal intubation. Several factors were noted to be predictive of NIV failure, particularly apnea, high pCO_2, young age, low weight, elevated heart rate, and high pediatric risk mortality score.[41]

CONCLUSIONS AND RECOMMENDATIONS

Fair to good-quality evidence from included studies in our systematic review and meta-analysis on bronchiolitis reveals that there is a significant reduction in length of hospital stay, duration of respiratory support, improvements in heart rate, respiratory rate, oxygen saturation, and tCO_2, among infants who received NIV. Larger, well-designed clinical trials in multi-center or single-center institutions, especially in resource-limited settings where NIV may offer potential benefit are recommended for future study. Other clinical variables such as intubation rate and mortality rate among children placed on NIV for severe bronchiolitis should also be included for further research.

Statement of Authorship

The final paper has been approved for submission by both authors.

Author Disclosure

Both authors declared no conflicts of interest in this study.

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