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Shaam Bruet

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

BRUET Shaam

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High Flow Nasal Cannula (HFNC) versus Continuous Positive Airway Pressure (CPAP) for primary respiratory support in preterm infants: a meta-analysis

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1. Introduction

Suite à une étude récemment menée par Manley *et al.*¹, la question concernant l'efficacité de l'oxygénothérapie à lunette haut débit (OLHD) comparée à la ventilation en pression positive continue (CPAP) pour la prise en charge initiale du syndrome de détresse respiratoire du nouveau-né prématuré refait surface. L'efficacité et la tolérance de l'OLHD ont bien été démontrées en relais post extubation^{2,3}. Mais les données concernant l'OLHD pour la prise en charge initiale sont insuffisantes et discordantes. Une revue rapide de 6 études contrôlées randomisées⁴ avait conclu à un risque plus élevé d'échec de traitement par OLHD comparé à la CPAP en primo-thérapie du syndrome de détresse respiratoire du nouveau-né prématuré. Deux autres méta-analyses ont été publiées en 2019^{5,6}, ayant toutes les deux conclues à une équivalence d'efficacité entre les deux méthodes de ventilation. Plusieurs études ont été publiées depuis^{1,7-10}, augmentant la population totale de 34,2%, dont l'étude de Manley *et al.*¹, qui montre un risque accru d'échec de traitement dans le groupe OLHD. Les auteurs de ces deux revues avaient conclu à un manque de données pour pouvoir statuer dans ce contexte.

En outre, ces méta-analyses ne comportaient pas d'étude des paramètres cliniques pouvant influencer les résultats. Une indication débattue de l'OLHD est celle d'un seuil d'âge gestationnel¹¹. Certaines études ont suggéré que l'OLHD serait moins à risque d'échec chez des populations de plus de 30 semaines d'aménorrhée à la naissance¹¹. D'autres facteurs d'influences potentielles seraient la fraction d'oxygène inspirée (FiO₂) à l'initiation du traitement¹¹, l'utilisation de surfactant¹², le type de CPAP utilisé, les débits d'OLHD^{13,14}, et le poids de naissance¹¹.

Nous avons mené une revue avec méta-analyse d'études contrôlées randomisées pour évaluer l'efficacité et la tolérance de l'OLHD comparée à la CPAP pour la prise en charge initiale du syndrome de détresse respiratoire du nouveau-né prématuré, ainsi qu'une analyse en sous-

groupe par âge gestationnel et des méta-régressions de ces analyses à la recherche de facteurs d'influence.

2. Article

2.1 Title page

High Flow Nasal Cannula (HFNC) versus Continuous Positive Airway Pressure (CPAP) for primary respiratory support in preterm infants: a systematic review and meta-analysis

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Keywords: HFNC, CPAP, primary respiratory support, preterm, meta-analysis

2.2 Abstract

Background: While the safety and equivalence of High Flow Nasal Cannula (HFNC) compared to continuous positive airway pressure (CPAP) for respiratory support for preterm infants has been well demonstrated post extubation, evidence for primary respiratory support is lacking. We aimed to conduct a systematic review and meta-analysis of randomized controlled trials that assessed the clinical effectiveness and safety of HFNC compared to CPAP as primary respiratory support for early respiratory distress syndrome in preterm infants, as well as a gestational age subgroup analysis, and study the impact of clinical relevant parameters.

Methods: PubMed, Cochrane, EMBASE and CINHALL databases were searched for randomized controlled trials evaluating treatment failure as primary outcome. The last search was run on 31th August 2020. We calculated risk ratios in intention to treat analysis and random effects meta-analyses (DerSimonian and Laird approach) of risks were conducted. Heterogeneity was evaluated by examining forest plots and using formal tests for homogeneity based on the I-squared (I^2) statistic.

Results: We included 10 studies for a total of 1830 patients. Gestational age at birth ranged from 28 to 37 weeks. HFNC flow rates ranged from 2-5L/min to 5-8L/min. CPAP modes used were bubble CPAP, ventilator or a combination of both, with pressure ranging from 2 to 8 mmHg. Surfactant therapy was allowed in 7 studies. Meta-analysis demonstrated a risk of treatment failure multiplied by 1.42 using HFNC compared to CPAP (95CI 1.07 to 1.79, $I^2=25.4%$), without significant difference between gestational age subgroups. Metaregressions did not show any influence of gestational age and weight at birth, HFNC flow rate, type of CPAP generator, or use of surfactant.

Conclusions: We suggest that HFNC should not be used as primary respiratory support for preterm infants when CPAP would be available, regardless of gestational age at birth.

2.3 Introduction

Following a recently published study by Manley *et al.*¹, debate has once again been sparked on the clinical effectiveness and safety of High Flow Nasal Cannula (HFNC) compared to compared to continuous positive airway pressure (CPAP) as primary support for respiratory distress syndrome in preterm infants. While the safety and equivalence of HFNC has been well demonstrated as means of post extubation^{2,3}, evidence for primary support is lacking. A rapid systematic review was performed in 2018 reviewed 6 randomised controlled trials (RCT), and reported a significantly higher risk of treatment failure using HFNC compared to CPAP for primary respiratory support in preterm infants⁴. Two meta-analysis have been published since^{5,6}. They both showed equivalence in efficacy between the two methods of non-invasive ventilation. More RCT have been published since^{1,7-10}, increasing the population size by 34.2% and one of which showing opposite results i.e. an increase in treatment failure with HFNC compared to CPAP¹. Lack of data has led authors of both reviews to conclude that further trials were necessary to better clarify the efficacy of HFNC therapy in this clinical scenario.

Moreover, previous meta-analyses also lacked analyses of influencing parameters. One of the main clinically debated indication between HFNC and CPAP is gestational age at birth¹¹. Some data suggested that HFNC treatment was less likely to fail above 30 weeks of gestational age¹¹. Other influencing factors could be FiO₂ at initiation of treatment¹¹, the use of surfactant¹², types of CPAP (bubble or ventilator) and flow rates of HFNC^{13,14}, or weight at birth¹¹.

We reviewed RCTs that assessed the risk of treatment failure of HFNC compared to CPAP as primary respiratory support for early respiratory distress syndrome in preterm infants. Furthermore we conducted a subgroup analysis by gestational age at birth and meta-regressions to search for clinical relevant parameters.

2.4 Methods

Literature search

RCTs comparing HFNC vs CPAP as primary respiratory support in preterm infants (<37 weeks gestational age) with early respiratory distress syndrome (within 24h of life) were included. Studies were identified by searching electronic databases, scanning reference lists of articles and consultation with experts in the field. PubMed, Cochrane, EMBASE and CINAHL databases were searched. Additional studies were identified by checking the references of located, relevant papers. The last search was run on 31th of august 2020. Search algorithms for all four databases can be found in supplementary files ([Appendix 1](#)). Eligibility assessment for potentially includible studies was performed independently in an unblinded standardized manner by two authors (SB and VN), as well as data extraction. When necessary, disagreements were solved with a third author (MB). We sought clarification or additional data for the potentially includable studies, by contacting authors. Contacted authors, reasons for contact, responses from authors and inclusion or not are detailed in supplementary files ([Appendix 2](#)).

Data extraction

The primary outcome analysed was treatment failure (as defined by the trial authors). Secondary outcomes included rate of intubation, surfactant therapy, air leak syndrome, bronchopulmonary dysplasia, nasal trauma, necrotizing enterocolitis, retinopathy of prematurity, intraventricular haemorrhage and patent ductus aortus.

Risk of bias within studies

We assessed risk of bias using two independent scales: the Cochrane Risk of Bias tool (RoB2), version 2¹⁵ and Scottish Intercollegiate Guidelines Network (S.I.G.N) randomised Controlled trials checklist¹⁶. Risk of bias was assessed independently by two authors (SB and VN), with disagreements solved through discussion with a third author (FD). We prespecified that studies categorized in the “high risk of bias” group using the RoB2 tool would be excluded from analysis.

Statistical Considerations

We extracted categorical data for each intervention group and calculated risk ratios (RR) on an intention to treat basis and 95% confidence intervals (95CI) of treatment failure for HFNC compared to CPAP. Random effects meta-analysis (DerSimonian and Laird approach) of risks were conducted using Stata software (v16, StataCorp, College Station, US)¹⁷⁻¹⁹. P values less than 0.05 were considered statistically significant. For the overall meta-analysis, when an individual study gave both results by subgroups and for the main population, we used the preterm subgroups for the overall meta-analysis, and then computed sensitivity analyses using data from the main population rather than those from subgroups. We also performed a subgroup analysis by gestational age at birth for the primary outcome. Heterogeneity in the study results was evaluated by examining forest plots, and using formal tests for homogeneity based on the I-squared (I^2) statistic. Funnel plots of these meta-analyses were used to search for potential publication bias (Egger Test)²⁰. When possible (sufficient sample size), meta-regressions were proposed to study the relationship between the risk of treatment failure and clinically relevant parameters such as gestational age and weight at birth, HFNC flow rate, type of CPAP generator, and use of surfactant.

2.5 Results

A total of 1555 titles and abstracts were screened, 61 publications were selected for full text review, and finally 10 studies were included : 8 on full text review only^{1,7,8,21-25}, and 2 after additional information given by authors^{9,10} (Figure 1).

Risk of bias within studies

The RoB2 tool showed a “low” risk of bias for one study¹ and “some concerns” for the other 9 studies (Figure 2). Concerning “randomization process”, 80% of articles scored low risk of bias and 20% “some concerns”. All studies used random allocation sequence. Concerning “Deviations from intended interventions”, 40% scored low risk and 60% some concerns. Blinding for patients and carers of assigned intervention was not attempted in any of the studies. Concerning “Missing outcome data”, 90% scored low risk and 10% some concerns. All studies used an “intention-to-treat” analysis except two studies^{10,25} where per protocol analysis was used. Concerning “measurement of the outcome”, 100% scored low risk. Concerning “selection of the reported result”, 40% scored low risk and 60% scored some concerns. Additional information on risk of bias assessment can be found in supplementary files (Appendix 3).

Population

Sample size: 1830 patients were included, 902 in the HFNC group and 926 in the CPAP group. Population size ranged from 40⁹ to 564²². Specific population characteristics are available for all studies, except two^{1,21}.

Gestational age at birth ranged from 30.0±1.9⁹ to 33.1±1.9²³ weeks for the HFNC group and 27.9±1.8⁹ to 33.0±2.1²³ weeks for the CPAP group.

Sex: HFNC group included 410 male patients (52.97%) and CPAP group included 425 male patients (53.73%, total 53.35%).

Birth weight ranged from 1231±235g⁹ to 1968±581g²³ for HFNC group, and 1153±226g⁷ to 1996±374g²⁵ for CPAP group.

Other parameters: Caesarean section birth (ranging from 25.0⁹ to 98.1%⁸ in the HFNC group and from 55.0⁹ to 96.3%⁸ in the CPAP group), and antenatal steroids treatment (ranging from 35.0⁹ to 88.9%¹⁰ in the HFNC group, and from 40.0⁹ to 83.0%¹⁰ in the CPAP group) were available in seven studies. Apgar scores was expressed as median in 7 studies^{7,8,10,22–25} and as mean in one study⁹, and were mostly between 8 and 9.

Setting, study design, inclusion and exclusion criteria

Setting: Studies took place in nine different countries over four continents. Four studies were multicentric^{1,12,21,24}, the six others single center studies.

Study designs: All 10 studies included in the review were **RCTs** published in English from 2013 to 2019 (Table 1).

Inclusion criteria: All studies included preterm infants with respiratory distress syndrome requiring non-invasive respiratory support within the first 24 hours from birth. Two studies also included term infants^{1,21} and post-extubation²¹ subgroups, that were not included in our meta-analyses.

Exclusion criteria, for all studies, were the need for intubation for mechanical ventilation at time of inclusion (except one study¹⁰ that did not explicitly state this exclusion criteria) and known major congenital abnormality. Three studies explicitly excluded patients having received surfactant therapy^{1,8,12,25}. All other seven studies allowed surfactant therapy if needed, by the intubation-surfactant-extubation technique (INSURE) only and extubated to primary support mode. One study only included pre-inclusion surfactant therapy²¹. In three

studies^{7,10,23} INSURE method was explicitly applied without any period of mechanical ventilation before extubation. In three studies^{8,9,24}, it is unclear whether a period of mechanical ventilation before extubation was accepted or not.

Characteristics of intervention

All studies compared HFNC to CPAP except one that compared HFNC to CPAP + non-invasive positive pressure ventilation (NIPPV)²³. **HFNC flow rates** ranged from a minimum flow of 2-5L/min to a maximum flow of 5-8 L/min (except one study⁷ ranging from 2.5L/min minimum to 3L/min maximum). **CPAP devices** were bubble CPAP exclusively in 3 studies^{1,7,24}, infant flow or ventilator exclusively in 5 studies^{8-10,23,25} and both in one²¹, with a range of pressures from 2 to 8 mmHg.

Outcomes

All ten studies had treatment failure as **primary outcome**, whether in the first 72 hours of life^{1,9,10,12,21} or without delay criteria^{7,8,23-25}, and needing intubation and mechanical ventilation^{9,10,21} or not^{1,7,8,12,23-25}. Definition of treatment failure varied slightly between studies, but all were defined by one or more of the following: respiratory acidosis (pH <7.2-7.25 and PCO₂>60-70 mmHg) (except one study²¹ that did not include a pH value), repeated apnoea and/or hypoxia despite fraction of inspired oxygen of 0.4-0.6 or higher. Three studies^{8,21,24} included objective clinical signs: worsening of work of breathing, and two studies^{1,12} included a subjective criteria: “urgent need for intubation at the clinicians’ discretion”.

Secondary outcome were *intubation rates*^{7-10,22-25} (ranging from 6.8²⁴ to 38.9%¹⁰ in the HFNC group and 7.7¹² to 37.7%¹⁰ in the CPAP group), *nasal trauma*^{9,10,12,24} (HFNC: 0.0⁹ to 9.3%¹⁰; CPAP: 5.0⁹ to 24.5%¹⁰), *surfactant therapy first dose*^{7,8,10,22-25} (HFNC: 14.3¹² to

74.3%⁷; CPAP: 10.5¹² to 59.5%⁷), *air leak syndrome/pneumothorax*^{7-10,22-25} (HFNC: 0.0²⁴ to 12.9%¹⁰; CPAP: 0.0^{9,25} to 13.5%⁷), *bronchopulmonary dysplasia* (including oxygen at 36 weeks)^{8-10,22-25} (HFNC: 0.0²⁵ to 20.0%⁹; CPAP: 0.0^{12,24,25} to 20.0%⁹), *intraventricular hemorrhage*^{7-10,22-25} (HFNC: 0.0^{24,25} to 16.7%¹⁰; CPAP: 0.0²⁵ to 13.5%⁷), *patent ductus aortus*^{7-10,22-25} (HFNC: 3.9¹² to 28.6%⁷; CPAP: 0.0⁹ to 21.6%⁷), *necrotizing enterocolitis*^{8,9,22-25} (HFNC: 0.0²⁵ to 20.0%⁹; CPAP: 0.0^{12,24,25} to 20.0%⁹) and *retinopathy of prematurity*^{8,9,22-24} (HFNC: 0.0¹² to 4.5%²⁴; CPAP: 0.0²³ to 10.0%⁹). Secondary outcomes were not available for the two studies that included subgroups^{1,21}.

Meta-analysis

Overall meta-analysis including the 10 retrieved studies demonstrated a risk of treatment failure multiplied by 1.42 using HFNC compared to CPAP (95CI 1.07 to 1.79, $I^2 = 25.4\%$) (Figure 3). Subgroup analysis on the seven studies^{1,8,9,9,12,23,24} with subgroups by gestational age at birth did not show a significant difference in the risk of treatment failure between ≤ 32 weeks (RR 1.36, 95CI 0.84 to 1.89, $I^2 = 0.0\%$) and 31-37 weeks (RR 1.54, 95CI 0.89 to 2.18, $I^2 = 21.3\%$) subgroups (Figure 4). No study included a subgroup analysis by fraction of inspired oxygen at randomization or by surfactant therapy received or not. Furthermore, for the overall meta-analysis, sensitivity analyses with main populations instead of preterm subgroups for two studies^{1,21} demonstrated the same results.

Meta-regressions and secondary outcomes

Analysis of clinically relevant parameters did not show any association between treatment failure and gestational age and weight at birth, HFNC flow rate, type of CPAP generator, and use of surfactant (Appendix 4).

Secondary outcome meta-analysis showed lower rate of nasal injuries using HFNC compared to CPAP (RR=0.45, CI 0.27 to 0.63, $I^2 = 0.0\%$). There were no significant differences in the rates of other secondary outcomes: intubation, surfactant therapy, air leak syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, patent ductus aortus, necrotizing enterocolitis, and retinopathy of prematurity ([Appendix 5](#)). Heterogeneity was not significant for all meta-analyses ($P>0.05$). All studies were evenly distributed around the base of the funnel plot ([Appendix 6](#)).

2.6 Discussion

The main findings were an increased risk of treatment failure of 42% with HFNC compared to CPAP (RR = 1.42, 95CI 1.07 to 1.79, $I^2=25.4\%$). Subgroup analysis by gestational age at birth did not show a significant difference in efficacy between groups. Meta-regressions did not show any influence of relevant clinical parameters.

HFNC in preterm infants

Our findings, showing an increased risk of treatment failure with HFNC compared to CPAP, are in stark contrast with prior literature. Two recently published meta-analysis^{5,6} have both shown equivalence in efficacy between the two methods of non-invasive ventilation. But the former⁵ defined “the need for intubation” as primary outcome. This outcome’s clinical relevance is questionable, as it has been shown that a rescue therapy by alternate non-invasive ventilation was efficient in a majority of failed primary treatment cases, without the need for intubation and mechanical ventilation¹². The latter⁶ is lacking a major study in its review that was published at the time²² and included a duplicate article of a same study^{23,26}, revealing flaws in its study design. Our meta-analysis included five RCTs not included in previous reviews^{1,7-10}, increasing the total population by a third (34.2%). We have excluded six studies

included in previous reviews: Nair *et al.*²⁷ and Iranpour *et al.*²⁸ were published only in abstract form and no additional data was obtained through author contact. Chen *et al.*²⁹ (included in review by Hong *et al.*⁶) was published in Chinese and no English version was obtained through author contact. Zheng *et al.*³⁰ (included in review by Hong *et al.*⁶) and Hedge *et al.*³¹ (included in review by Hong *et al.*⁶ and Fleeman *et al.*⁵) were not randomized trials and Ciuffini *et al.*²⁶ (included in review by Hong *et al.*⁶) reported intermediate results from study by Lavizzari *et al.*²³. Furthermore, only RCTs without high risk of bias assessed through the RoB2 tool were included. This strict methodology ensures strength of findings but may have introduced selective reporting bias. A visual assessment of the funnel plot did not show any asymmetry arising from publication bias.

An influence of gestational age?

In a secondary, non-randomized analysis of data from a randomized trial¹¹, HFNC treatment was less likely to fail in the subgroup with a gestational age ≥ 30 weeks and an early FiO₂ < 0.30 . The authors argued that, taking into account the advantages of HFNC, such as simplicity, comfort, and ease of use, it would be valuable to identify those patients likely to be treated successfully with HFNC, while ensuring those at greatest risk for treatment failure are treated early with CPAP. In our meta-analysis, there was no significant difference in treatment failure depending on gestational age, going against suggestions by a review group that preterm infants under 30 weeks of gestational age at birth would be more at risk of treatment failure than those over 30 weeks³². We also tried to conduct a subgroup analyses for very preterm infants (≤ 28 weeks) without highlighting differences but evidence is too weak with a very limited sample size (only two studies with ≤ 28 weeks subgroups^{8,9}).

Impact of clinical relevant parameters

The physiological aspects of HFNC include improved gas exchange through dead space washout¹³, a small amount of positive airway pressure^{13,14}, augmentation of spontaneous tidal volumes¹⁴ and stabilization or reduction in work of breathing¹⁴. Compared to CPAP, during HFNC, the distending pressure for a certain flow rate is not known, highly variable and unpredictable¹⁴. As such, it has been hypothesized that surfactant therapy may be an important confounding factor in evaluating HFNC to CPAP. In a previous study including only patients having not received surfactant therapy¹², authors found a higher rate of treatment failure with HFNC compared to CPAP in their study and suggested a reduced effectiveness of HFNC in infants with surfactant-deficient lungs. Unfortunately, no studies included surfactant therapy subgroups and we were not able to demonstrate this hypothesis. Meta-regression analysis also did not determine surfactant therapy as an influencing factor of treatment failure. Further RCT's are warranted to determine the implication of surfactant therapy in treatment failure.

Other outcomes

Secondary outcomes did not differ between groups except for a significant lower rate of nasal injuries using HFNC (RR=0.45, 95% CI 0.27 to 0.63). However, all secondary outcomes must be interpreted with caution as six studies^{7,10,12,12,21,24} permitted an alternate non-invasive ventilation as rescue therapy in the case of HFNC failure, entailing a high risk of bias linked to deviation of intended intervention for secondary outcomes. Nonetheless, literature does find a statistically higher risk ratio of nasal trauma using CPAP compared to HFNC^{5,6}. Close clinical surveillance of the nares is advised using CPAP, and nasal trauma could constitute a valid indication for HFNC as primary respiratory support. No differences were found between HFNC and CPAP for other adverse outcomes in accordance with previous meta-analysis³³^{5,6}, showing equivalence in short and medium term safety between the two methods of

ventilation. Long term respiratory and neurological development could be relevant factors to measure clinical effectiveness of HFNC compared to CPAP, and further RCT's with longer follow up's are required in this regard.

Limitations

Our meta-analysis may suffer from several limitations. Meta-analyses inherit the limitations of the individual studies of which they are composed: varying quality of studies and multiple variations in study protocols and evaluation. The inclusion criteria were similar, but not identical. The lack of a standardized assessment of treatment failure in included studies may have introduced a measure of bias. Our study included only ten studies, which may appear low. However, the analyses of the funnel plots revealed a homogenous distribution and therefore no major publication bias, probably because all studies shared a high quality randomised controlled design. Studies lacked blinding assessment, and despite the impossibility to blind HFNC and CPAP, this may have introduced bias. Moreover, patients from 9 countries were included (Iran ^{7,10}, Turkey ^{8,9}, Italie ¹⁴, Australia ^{1,12}, India ²⁴, Norway ¹², South Korea ²⁵, USA and China ²¹) over 4 continents and as such our results present high generalizability. These results have the potential for important health and financial impact as recent reports from New Zealand/Australia³³, Japan³⁴ and England³⁵ highlight the increasing use of HFNC in the NICU. Although interesting, the lack of very preterm infants precluded further analyses for extreme gestational ages. Another limitation to our study is the lack of long term follow up.

2.7 Conclusions

Based on our findings, we suggest that HFNC should not be used as primary respiratory support for preterm infants when CPAP would be available, regardless of gestational age at

birth. If HFNC is used as primary therapy we suggest that close clinical surveillance should be used to detect early signs of treatment failure, as switching to CPAP as means of rescue therapy has shown to be useful in preventing intubation. Future studies are needed to clarify the effect of surfactant on efficacy of HFNC, study long-term follow up as well as targeting extremely premature populations.

2.8 References

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38. Babaei H. Comparison of the effects of High flow nasal cannula versus nasal continuous positive Air way pressure in treatment of respiratory distress syndrome in premature newborns. WHO clinical trials register website. 2019. doi:10.1002/central/CN-01800409 <http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2015100814333N41>. Published online.
39. Kusuda S. A Randomized Controlled Trial to Compare High-Flow Nasal Cannula with Nasal CPAP after Extubation in Preterm infants. WHO clinical trials register website. 2019. doi:10.1002/central/CN-01824454. <http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000013906>.
40. Wang Z, Xiang JW, Gao WW, et al. [Comparison of clinical efficacy of two noninvasive respiratory support therapies for respiratory distress syndrome in very low birth weight preterm infants]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2018;20(8):603-607.

Table 1: summary of included studies

Source	Gestational age	Methods evaluated	HFNC low rate	CPAP method	Primary outcome	Surfactant	Subgroup analysis
Armanian 2019	<37 GA	NIPPV vs. CPAP vs. HFNC	2.5 - 3 L/min	Bubble	Failure and duration of NIV	If needed	no
Cetinkaya 2018	<32 GA	NIPPV vs. CPAP vs. HFNC	max 8 L/min	Infant flow	Failure of NIV and intubation within 72h	If needed	GA
Demirel 2019	<32 GA	HFNC vs. CPAP	6 - 8 L/min	Ventilator	Failure of NIV	If needed	GA
Farhat 2018	28-34 GA	NIPPV vs. CPAP vs. HFNC	2 - 5 L/min	Ventilator	Failure of NIV and intubation within 72h	If needed	no
Lavizzari 2016	29-37 GA	HFNC vs. CPAP/NIPPV	2 - 6 L/min	Infant flow	Failure of NIV	If needed	GA
Manley 2019	>31 GA	HFNC vs. CPAP	5 - 8 L/min	Bubble	Failure of NIV within 72h	no	GA
Murki 2018	28-37 GA	HFNC vs. CPAP	3 - 7 L/min	Bubble	Failure of NIV	If needed	GA
Roberts 2016	28-37 GA	HFNC vs. CPAP	4 - 8 L/min	Bubble, ventilator or infant flow	Failure of NIV within 72h	no	GA
Shin 2017	30-35 GA	HFNC vs. CPAP	3 - 7 L/min	Infant flow or ventilator	Failure of NIV	no	no
Yoder 2013	>28 GA	HFNC vs. CPAP	2 - 8 L/min	Bubble, ventilator or infant flow	Failure of NIV and intubation within 72h	If needed	GA

GA : gestational age, HFNC : high flow nasal canula, CPAP : continuous positive airway pressure, NIPPV: non invasive positive pressure ventilation, NIV: non invasive ventilation

Figure legends

Figure 1. Study selection flow diagram

Figure 2. Risk of bias within studies (RoB2)

Figure 3. Meta-analysis on Relative Risk of treatment failure using HFNC versus CPAP for primary support in preterm infants

Figure 4. Meta-analysis on Relative Risk of treatment failure using HFNC versus CPAP for primary support in preterm infants, sub-group analysis by gestational age at birth

Appendix

Appendix 1. Details for the search strategy used within each database

Appendix 2. Contacted authors

Appendix 3. Risk of bias assessment using the RoB2

Appendix 4. Meta-regressions analysis results for meta-analysis of relative risk of treatment failure using HFNC compared to CPAP in primary respiratory support for preterm infants.

Appendix 5. Meta-analysis on secondary outcomes using HFNC versus CPAP for primary support in preterm infants.

Appendix 6. Funnel plot for meta-analysis of relative risk of treatment failure using HFNC compared to CPAP in primary respiratory support for preterm infants.

Figure 1 : study selection flow diagram

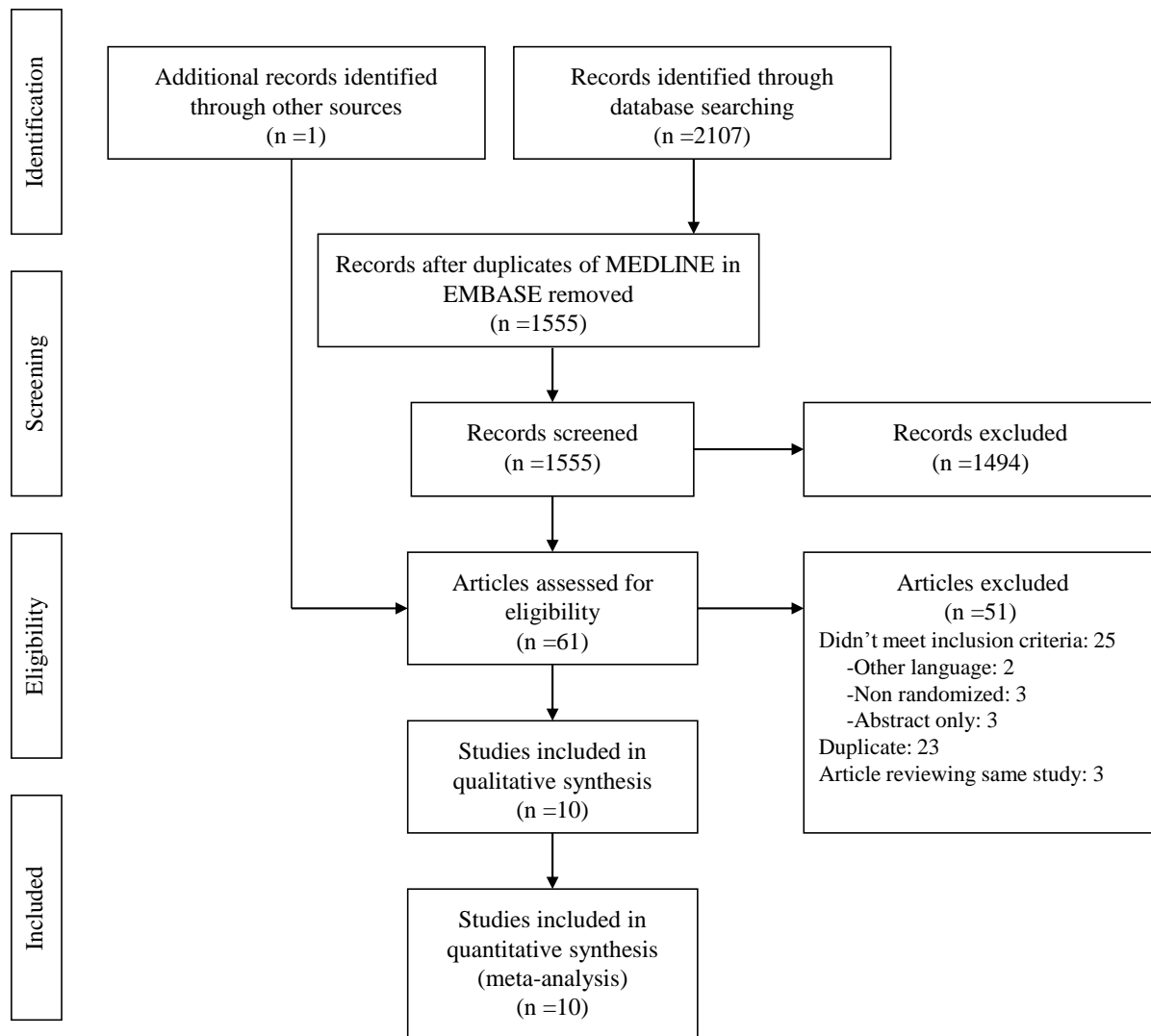


Figure 2: Risk of bias within studies (RoB2).

Study ID	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Armanian 2019	1	?	+	+	+	?	!
Cetinkaya 2018	1	+	+	+	+	?	!
Demirel 2019	1	+	+	+	+	?	!
Farhat 2018	1	?	?	?	+	+	!
Lavizzari 2016	1	+	?	+	+	+	!
Manley 2019	1	+	+	+	+	+	+
Murki 2018	1	+	?	+	+	?	!
Roberts 2016	1	+	?	+	+	+	!
Shin 2017	1	+	?	+	+	?	!
Yoder 2013	1	+	?	+	+	?	!

+ Low risk
? Some concerns
- High risk

Figure 3. Meta-analysis on Relative Risk of treatment failure using HFNC versus CPAP for primary support in preterm infants.

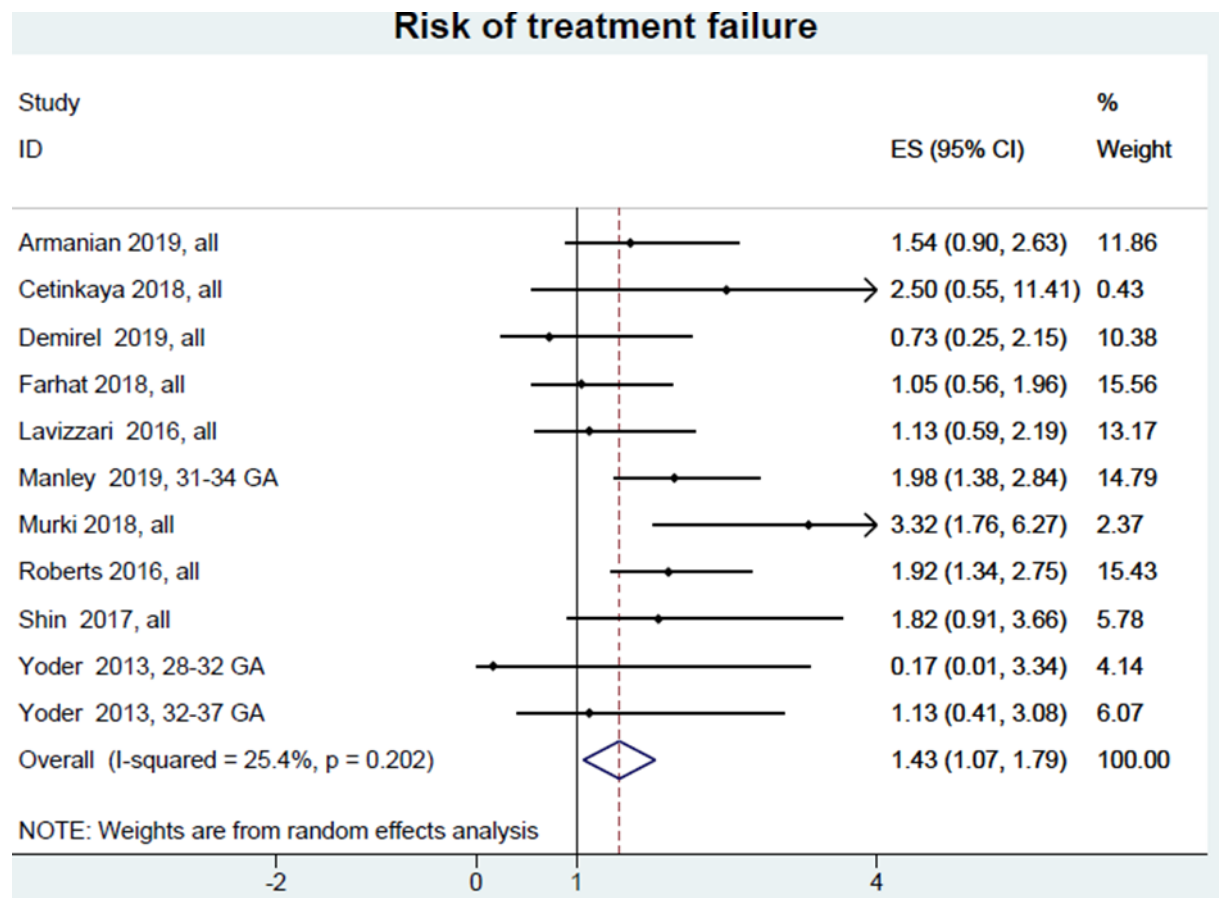
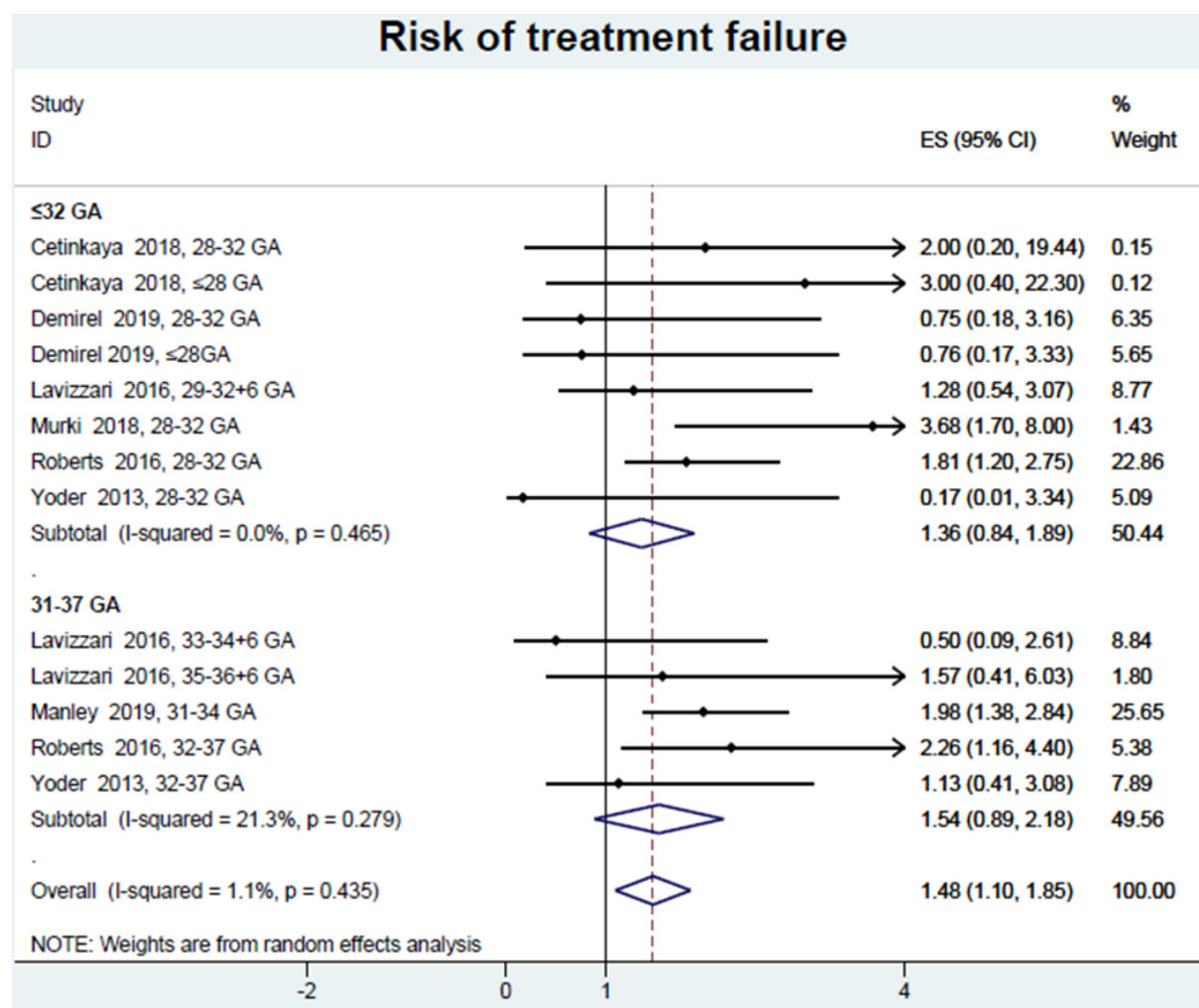


Figure 4: Meta-analysis on Relative Risk of treatment failure using HFNC versus CPAP for primary support in preterm infants, sub-group analysis by gestational age at birth.



Appendix

Appendix 1. Details for the search strategy used within each database

Pubmed

"high flow"[TW] OR "high-flow" [TW] OR HFNC[TW] OR ("high frequency"[Title] AND nasal[Title]) OR "nasal cannula"[TW] OR "nasal cannulas"[TW] OR "nasal prong"[TW] OR "nasal prongs"[TW]

AND

"continuous positive airway pressure"[MH] OR "continuous positive airway pressure"[TW] OR CPAP[TW] OR nCPAP[TW] OR "continuous distending pressure"[TW] OR "distending pressure"[TW] OR "continuous positive transpulmonary pressure"[TW] OR "continuous transpulmonary pressure"[TW] OR "positive pressure"[TW] OR "positive expiratory pressure"[TW] OR "positive end expiratory pressure"[TW] OR "Positive-Pressure respiration"[MH] OR "positive pressure respirations"[TW] OR "non-invasive positive-pressure ventilation"[TW] OR "positive end-expiratory pressures"[TW] OR "positive pressure ventilation"[TW] OR "positive end-expiratory pressure"[TW] OR "Positive Pressure respiration"[TW] OR "positive pressure ventilations"[TW] OR "positive-pressure non-invasive ventilation"[TW] OR "positive pressure non invasive ventilation"[TW] OR "positive end expiratory pressure"[TW]

AND

newborn*[TW] OR "infant"[MH] OR infant*[TW] OR baby[TW] OR "low birth weight"[TW] OR VLBW[TW] OR LBW[TW] OR neonat*[TW] OR perinatal[TW] OR preterm[TW] OR Intensive Care Units, Neonatal[Mesh] OR "premature infants"[TW] OR "infants, premature"[TW] OR "infant, premature"[TW] OR "premature infant"[TW]

Cochrane

"high flow" OR HFNC ("high frequency" AND nasal) OR "nasal cannula" OR "nasal cannulas" OR "nasal prong" OR "nasal prongs"

AND

"continuous positive airway pressure" OR CPAP OR nCPAP OR "airway pressure release ventilation" OR "continuous distending pressure" OR "distending pressure" OR "continuous positive transpulmonary pressure" OR "continuous transpulmonary pressure" OR "positive pressure" OR "positive expiratory pressure" OR "positive end expiratory pressure" OR "positive pressure respirations" OR "non-invasive positive-pressure ventilation" OR "positive end-expiratory pressures" OR "positive pressure ventilation" OR "positive end-expiratory pressure" OR "Positive Pressure respiration" OR "positive pressure ventilations" OR "positive-pressure non-invasive ventilation" OR "positive pressure non invasive ventilation" OR "positive end expiratory pressure"

AND

(newborn* OR infant* OR baby OR "low birth weight" OR VLBW OR LBW OR neonat* OR perinatal OR preterm OR "premature infants" OR "infants, premature" OR "infant, premature" OR "premature infant")

Embase

('high flow nasal cannula'/exp OR 'high flow nasal cannula oxygen therapy'/exp OR 'high flow nasal cannula therapy'/exp OR 'high flow nasal oxygen therapy'/exp OR 'high flow nasal oxygen'/exp OR 'high flow nasal cannula oxygen'/exp OR 'high flow nasal therapy'/exp OR 'nasal prong'/exp OR ('high frequency':ti,ab,kw AND nasal:ti,ab,kw) OR 'high flow':ti,ab,kw OR 'high-flow':ti,ab,kw OR hfnc:ti,ab,kw OR 'nasal cannula':ti,ab,kw OR 'nasal cannulas':ti,ab,kw OR 'nasal prong':ti,ab,kw OR 'nasal prongs':ti,ab,kw)

AND

('positive end expiratory pressure'/exp OR 'cpap device'/exp OR 'continuous positive airway pressure':ti,ab,kw OR cpap:ti,ab,kw OR ncpap:ti,ab,kw OR 'continuous distending pressure':ti,ab,kw OR 'distending pressure':ti,ab,kw OR 'continuous positive transpulmonary pressure':ti,ab,kw OR 'continuous transpulmonary pressure':ti,ab,kw OR 'positive pressure':ti,ab,kw OR 'positive expiratory pressure':ti,ab,kw OR 'positive-pressure respiration':ti,ab,kw OR 'positive pressure respirations':ti,ab,kw OR 'non-invasive positive-pressure ventilation':ti,ab,kw OR 'positive end-expiratory pressures':ti,ab,kw OR 'positive pressure ventilation':ti,ab,kw OR 'positive end-expiratory pressure':ti,ab,kw OR 'positive pressure respiration':ti,ab,kw OR 'positive pressure ventilations':ti,ab,kw OR 'positive-pressure non-invasive ventilation':ti,ab,kw OR 'positive pressure non invasive ventilation':ti,ab,kw OR 'positive end expiratory pressure':ti,ab,kw)

AND

('infant'/exp OR 'low birth weight'/exp OR 'perinatal period'/exp OR 'prematurity'/exp OR 'neonatal intensive care unit'/exp OR newborn*:ti,ab,kw OR infant*:ti,ab,kw OR baby:ti,ab,kw OR 'low birth weight':ti,ab,kw OR vlbw:ti,ab,kw OR lbw:ti,ab,kw OR neonat*:ti,ab,kw OR perinatal:ti,ab,kw OR preterm:ti,ab,kw OR 'premature infants':ti,ab,kw OR 'infants, premature':ti,ab,kw OR 'infant, premature':ti,ab,kw OR 'premature infant':ti,ab,kw)

CINAHL

TI "high flow" OR AB "high flow" OR TI "high-flow" OR AB "high-flow" OR TI HFNC OR AB HFNC OR TI (("high frequency" AND nasal)) OR AB (("high frequency" AND nasal)) OR TI "nasal cannula" OR AB "nasal cannula" OR TI "nasal cannulas" OR AB "nasal cannulas" OR TI "nasal prong" OR AB "nasal prong" OR TI "nasal prongs" OR AB "nasal prongs"

AND

TI "continuous positive airway pressure" OR AB "continuous positive airway pressure" OR TI CPAP OR AB CPAP OR TI nCPAP OR AB nCPAP OR TI "continuous distending pressure" OR AB "continuous distending pressure" OR TI "distending pressure" OR AB "distending pressure" OR TI "continuous positive transpulmonary pressure" OR AB "continuous positive transpulmonary pressure" OR TI "continuous transpulmonary pressure"

OR AB "continuous transpulmonary pressure" OR TI "positive pressure" OR AB "positive pressure" OR TI "positive expiratory pressure" OR AB "positive expiratory pressure" OR TI "positive end expiratory pressure" OR AB "positive end expiratory pressure" OR TI "Positive-Pressure respiration" OR AB "Positive-Pressure respiration" OR TI "positive pressure respirations" OR AB "positive pressure respirations" OR TI "non-invasive positive-pressure ventilation" OR AB "non-invasive positive-pressure ventilation" OR TI "positive end-expiratory pressures" OR AB "positive end-expiratory pressures" OR TI "positive pressure ventilation" OR AB "positive pressure ventilation" OR TI "positive end-expiratory pressure" OR AB "positive end-expiratory pressure" OR TI "Positive Pressure respiration" OR AB "Positive Pressure respiration" OR TI "positive pressure ventilations" OR AB "positive pressure ventilations" OR TI "positive-pressure non-invasive ventilation" OR AB "positive-pressure non-invasive ventilation" OR TI "positive pressure non invasive ventilation" OR AB "positive pressure non invasive ventilation" OR TI "positive end expiratory pressure" OR AB "positive end expiratory pressure"

AND

TI newborn* OR AB newborn* OR TI infant* OR AB infant* OR TI baby OR AB baby OR TI "low birth weight" OR AB "low birth weight" OR TI VLBW OR AB VLBW OR TI LBW OR AB LBW OR

TI neonat* OR AB neonat* OR TI perinatal OR AB perinatal OR TI preterm OR AB preterm OR TI "Neonatal Intensive Care Units" OR AB "Neonatal Intensive Care Units" OR TI "premature infants" OR AB "premature infants" OR TI "infants, premature" OR AB "infants, premature" OR

TI "infant, premature" OR AB "infant, premature" OR TI "premature infant" OR AB "premature infant"

Appendix 2. Contacted authors

Five potentially eligible reports ([supplementary table 1](#)) were not retrievable through author contact by email. An additional study that met the criteria for inclusion was identified by checking the references of located, relevant papers³⁶. This study, although included in all prior reviews^{5,6,37}, was published only in abstract form and no additional information was obtained after contacting the authors, and was therefore excluded from the meta-analysis.

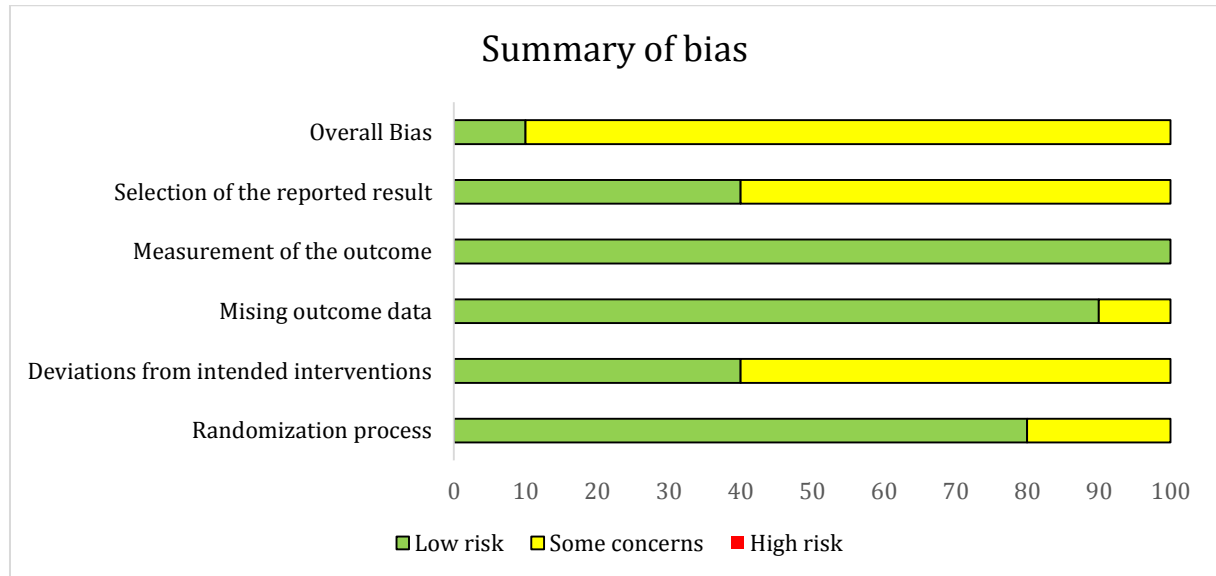
Studies	reasons for contact	response	Inclusion	reasons for exclusion
Akbarian 2018 (reference removed)	unpublished	response	no	no data obtained
Babaei 2015 ³⁸	unpublished	no response	no	post mechanical ventilation
Cetinkaya 2015 ⁹	unpublished	response	yes	–
Chen 2015 ²⁹	not english	No author contact information available	no	article in chinese
Farhat 2019 ¹⁰	missing data	response	yes	–
Iranpour 2012 ²⁸	abstract only	no response	no	abstract only
Kusuda 2019 ³⁹	unpublished	response	no	post mechanical ventilation
Nair 2005 ³⁶	abstract only	no author contact information available	no	abstract only
Wang 2018 ⁴⁰	not english	no response	no	article in chinese

Appendix 3. Risk of bias assessment using the RoB2

Randomisation process showed “low risk” of bias for all studies except two: “some concerns” for Armanian *et al.*⁷ for which baseline differences between intervention groups suggested a problem with the randomisation process (Mean gestational age in the neonates of the HHHFNC group was significantly higher than those of the other two groups (P = 0.02). Furthermore, the birth weight of neonates treated with HHHFNC was higher than those of the other two groups (P = 0.02) and Farhat *et al.*¹⁰ for which allocation sequence was not concealed but for which there was no baseline difference between intervention groups.

Concerning “deviations from intended interventions” risk of bias domain, “some concerns” were noted in 6 of ten studies: in the study by Lavizzari *et al.*²³, deviations from the intended intervention may have arisen because “The study was conducted in an nCPAP-oriented NICU”. This deviation was probably not likely to affect the outcome as “The use of HHHFNC was also non inferior to CPAP/BiPAP when applying a per-protocol analysis”. Protocol deviations were noted in Murki *et al.*²⁴ in 8 patients in each group. However protocol deviation was balanced between groups and per protocol analysis found similar results: “Excluding these 16 patients (per protocol analysis), the treatment failure was still significantly higher in the HFNC group”. Deviations to the intended intervention were noted in the study by Roberts *et al.*¹², “A total of 21 infants were excluded from this analysis because either they did not receive the assigned treatment (14 infants) or the assigned treatment was changed during the primary-outcome period without the protocol-specified criteria for treatment failure or nasal trauma having been met (7 infants)”. These deviations were not likely to affect the outcome: “Results were similar in an analysis of the 543 infants (264 in the high-flow group and 279 in the CPAP group) who were treated as specified by the protocol”. Deviations to the intended intervention were noted in the study by Yoder *et al.*²¹: “Given that more infants in the nCPAP group were switched to HHHFNC after the initial 72-hour study window, it is possible that HHHFNC may have been preferred by the bedside providers.”. These deviations were not likely to affect the outcome: “Crossover between HHHFNC and nCPAP was not permitted for the first 72 hours of study support”. All studies used an “intention-to-treat” analysis except Shin *et al.*²⁵ and Farhat *et al.*¹⁰ which used a per protocol analysis. In both these studies there was little potential for a substantial impact because very few patients were omitted in the analysis (one per group for Shin *et al.* and for Farhat *et al.*). Measurement of outcome bias was classified as “low risk” for all studies.

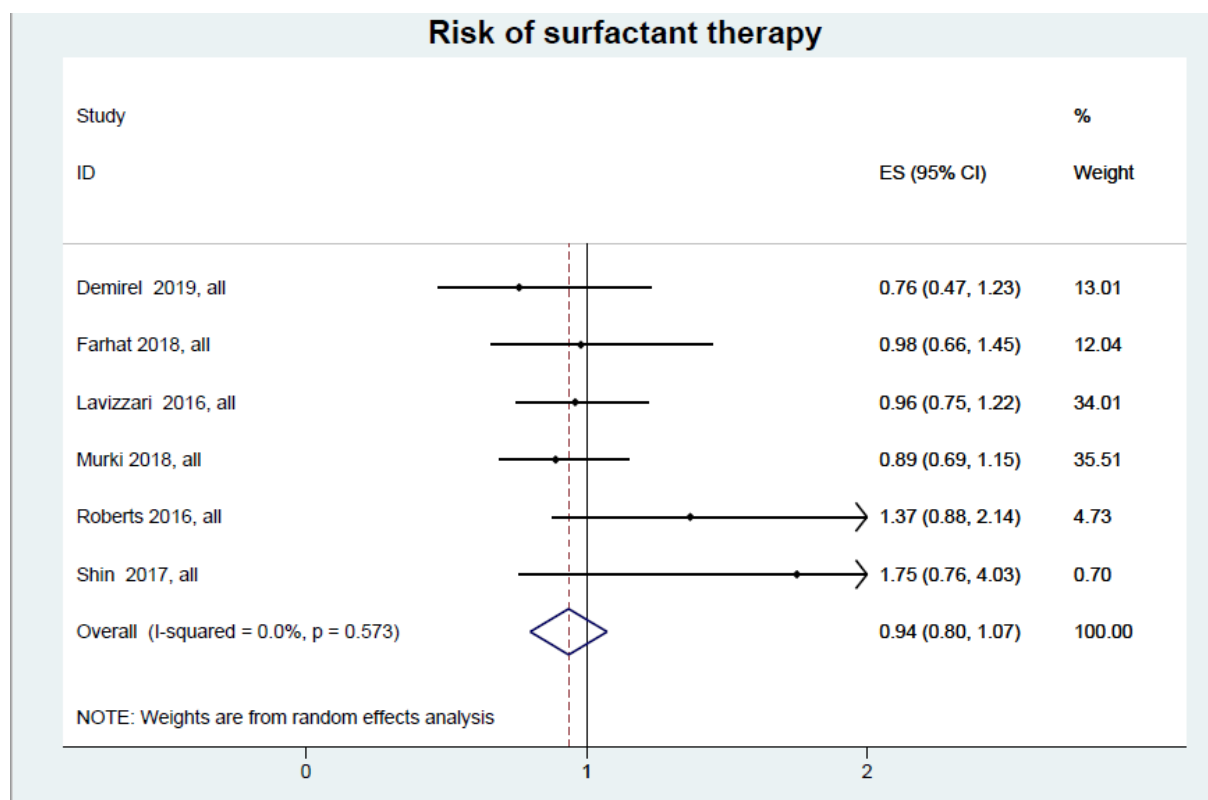
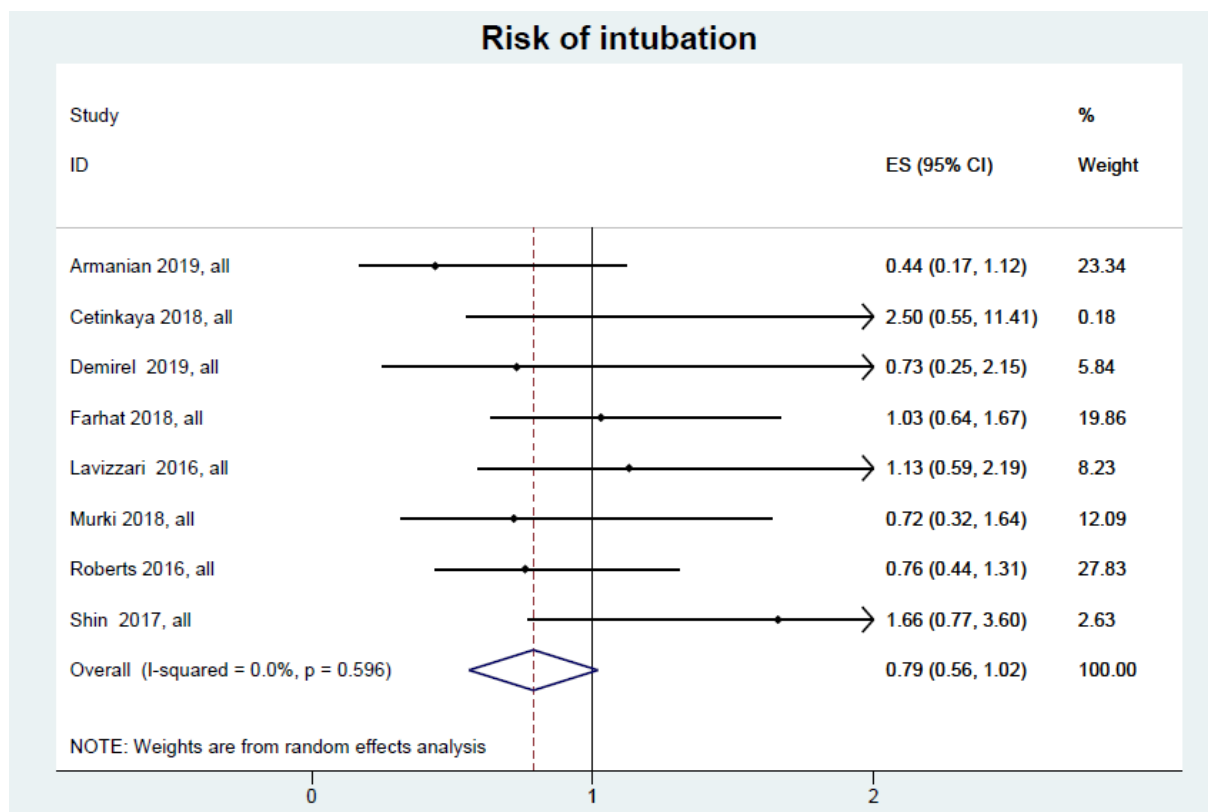
Selection of reported result was classified as “low” for four studies: Lavizzari *et al.*²³, Manley *et al.*¹, Roberts *et al.*¹² and Farhat *et al.*¹⁰ All seven other studies were classified as “some concerns”, either for lack of pre-specified analysis plan^{7-9,21,25} or primary outcome measurements were not specified in specified analysis plan²⁴, raising the potential for selective reporting of outcome. Results of risk of bias analysis can be found in [supplementary figure 1](#).



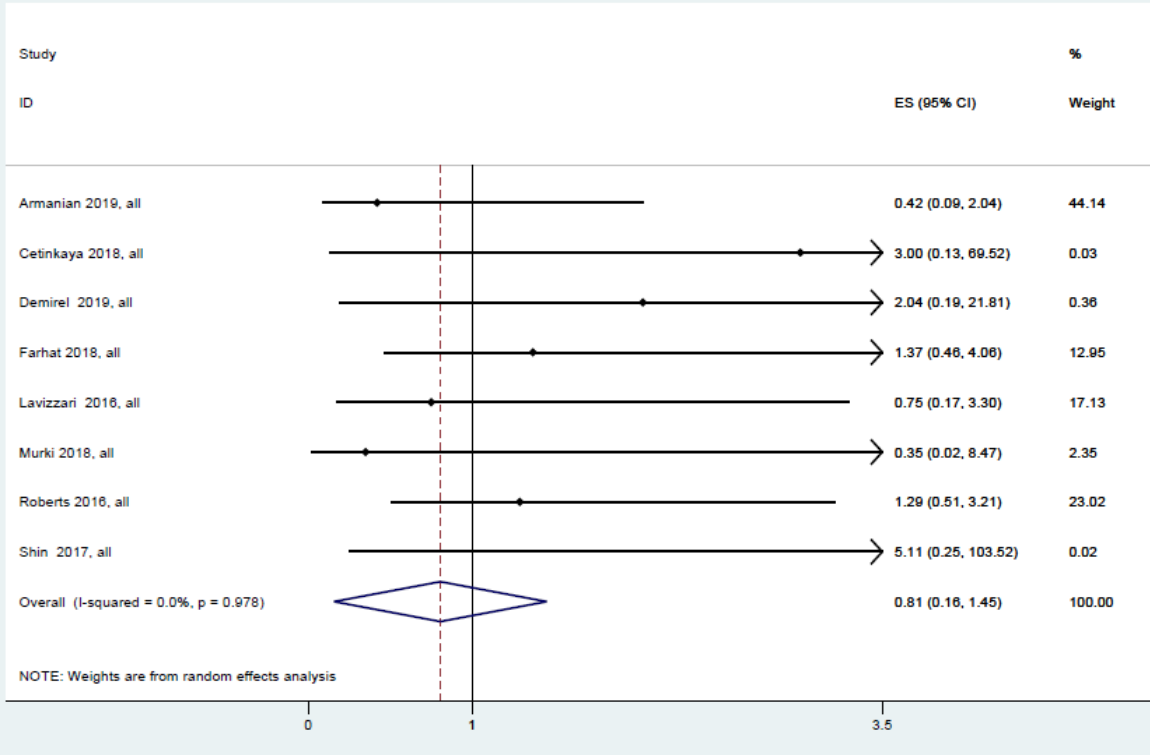
Appendix 4. Meta-regressions analysis results for meta-analysis of relative risk of treatment failure using HFNC compared to CPAP in primary respiratory support for preterm infants.

	n studies		Coefficient (95% CI)	p-value (%)
All			0,14 (-0,28 to 0,56)	0.162
HFNC flow rate	11		-0,48 (-1,41 to 0,44)	0.775
CPAP device	11		0,80 (-1,03 to 2,64)	0.214
surfactant therapy	11		0,53 (-0,84 to 1,92)	0.215
gestational age HFNC	8		-0,52 (-1,49 to 0,46)	0.073
gestational age CPAP	8		0,00 (-0,00 to 0,00)	0.006
birth weight HFNC	8		-0,14 (-1,42 to 1,13)	0.189
gestational age subgroups	13			

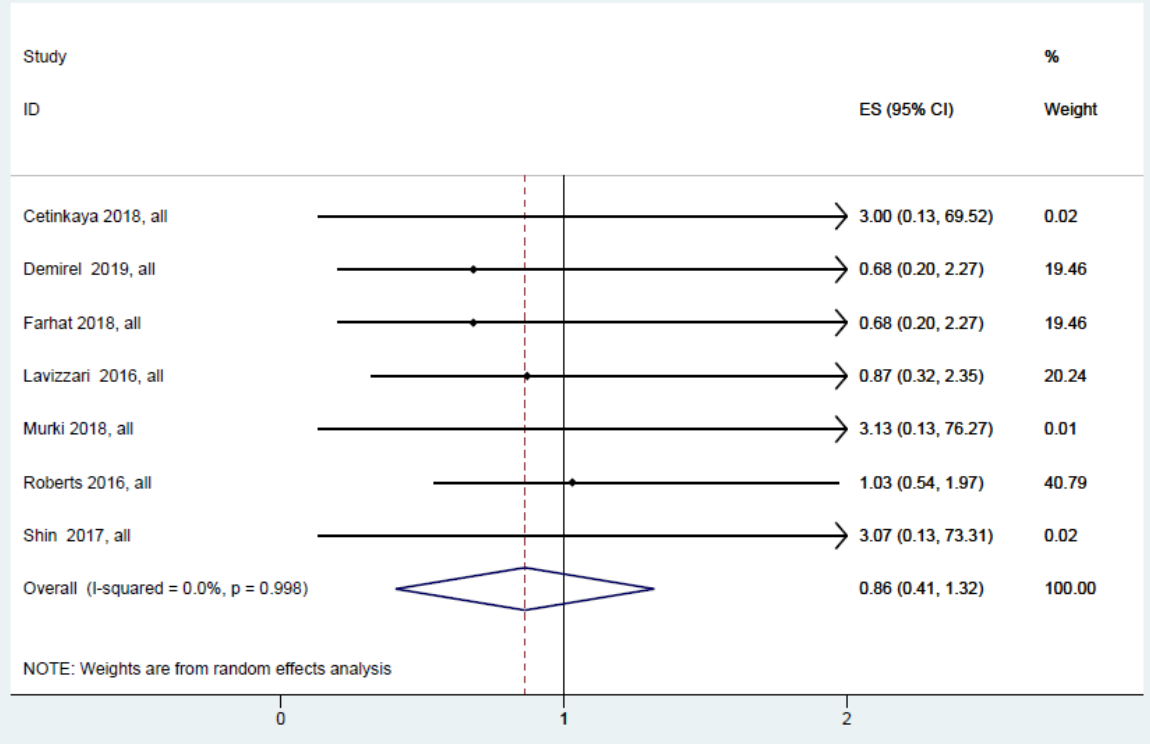
Appendix 5. Meta-analysis on secondary outcomes using HFNC versus CPAP for primary support in preterm infants.

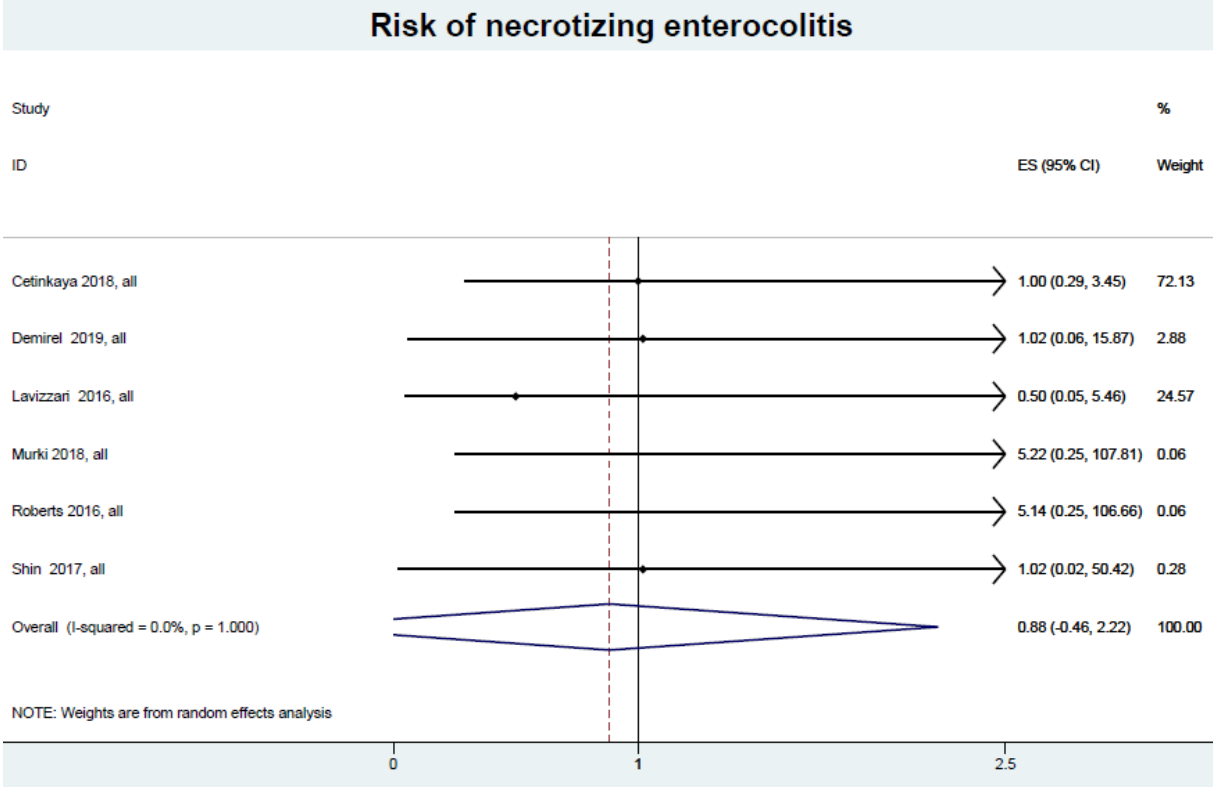
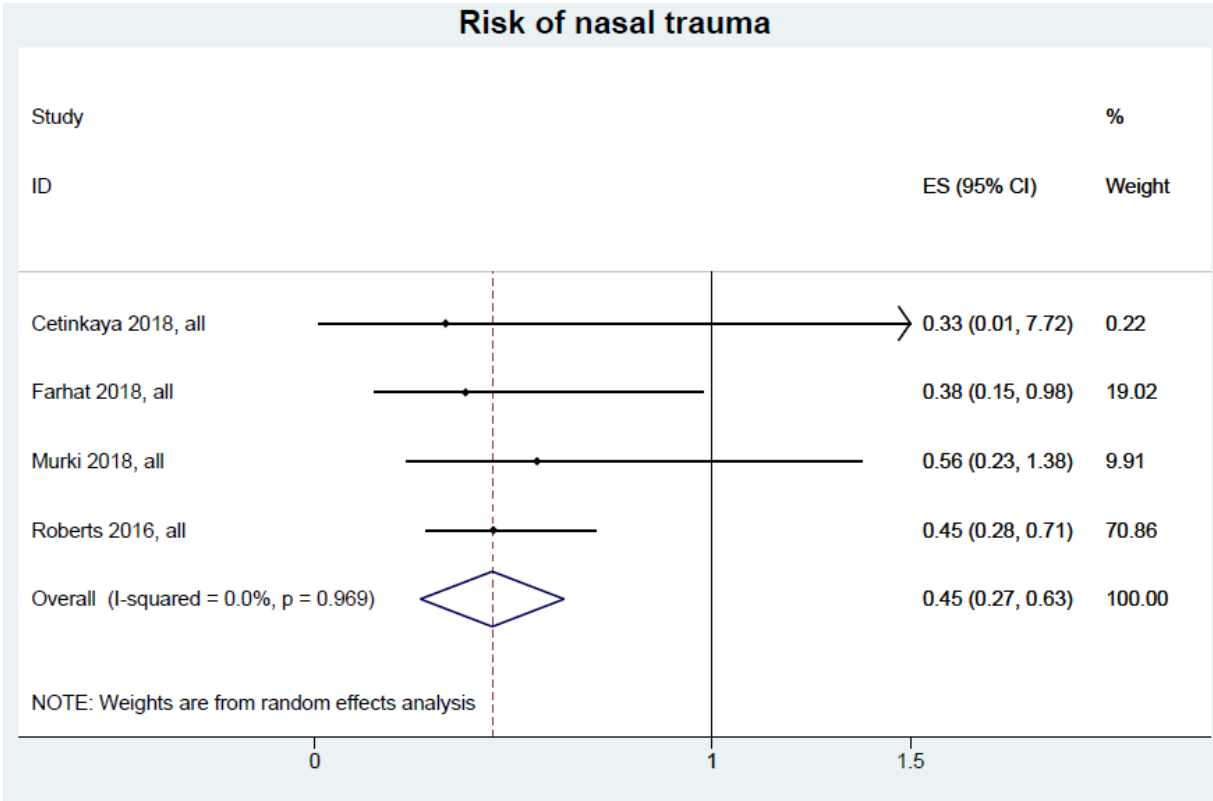


Risk of air leak syndrome

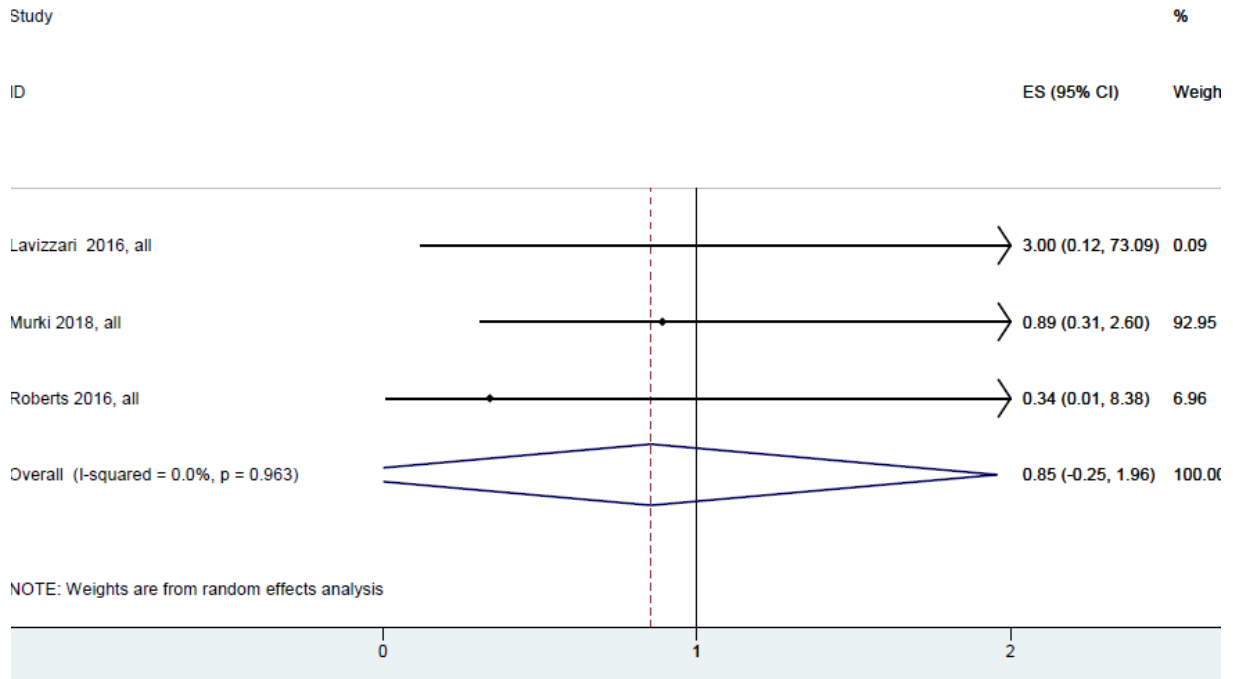


Risk of bronchopulmonary dysplasia

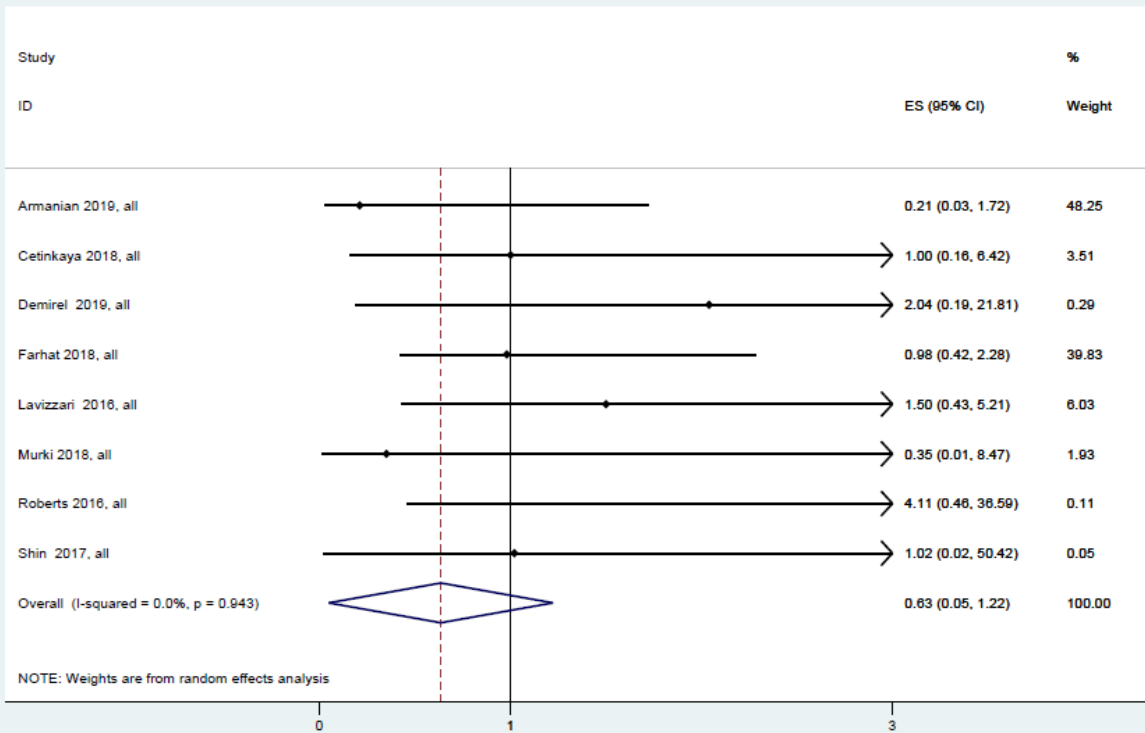




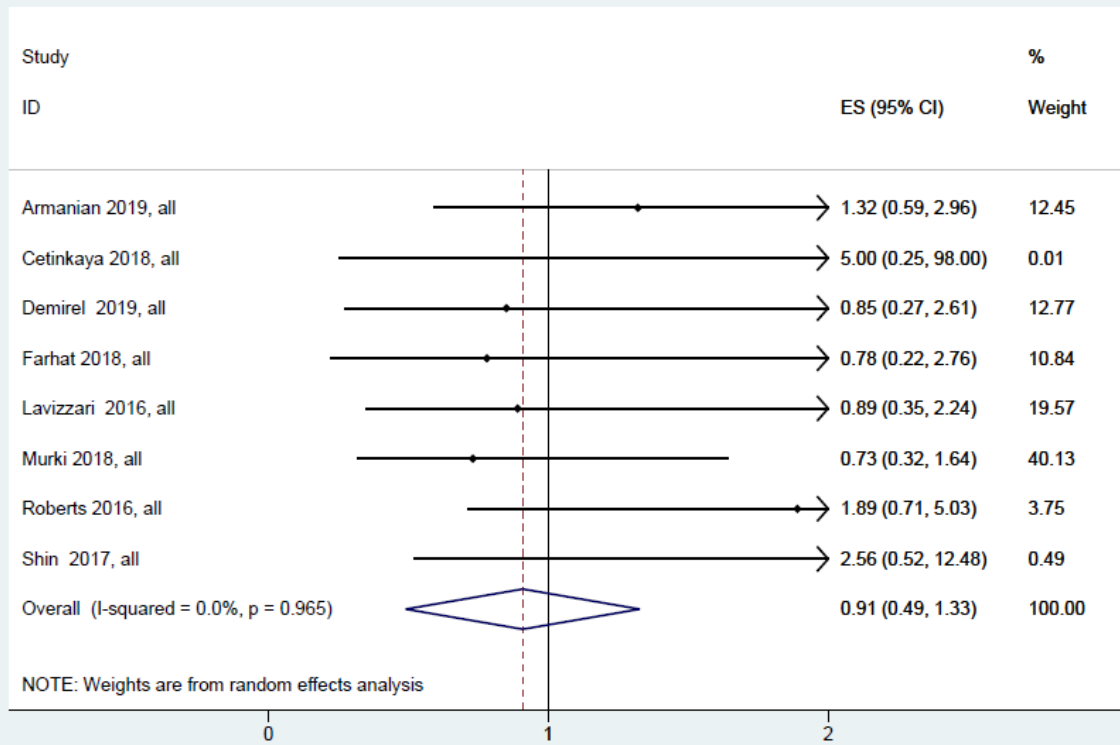
Risk of retinopathy of prematurity



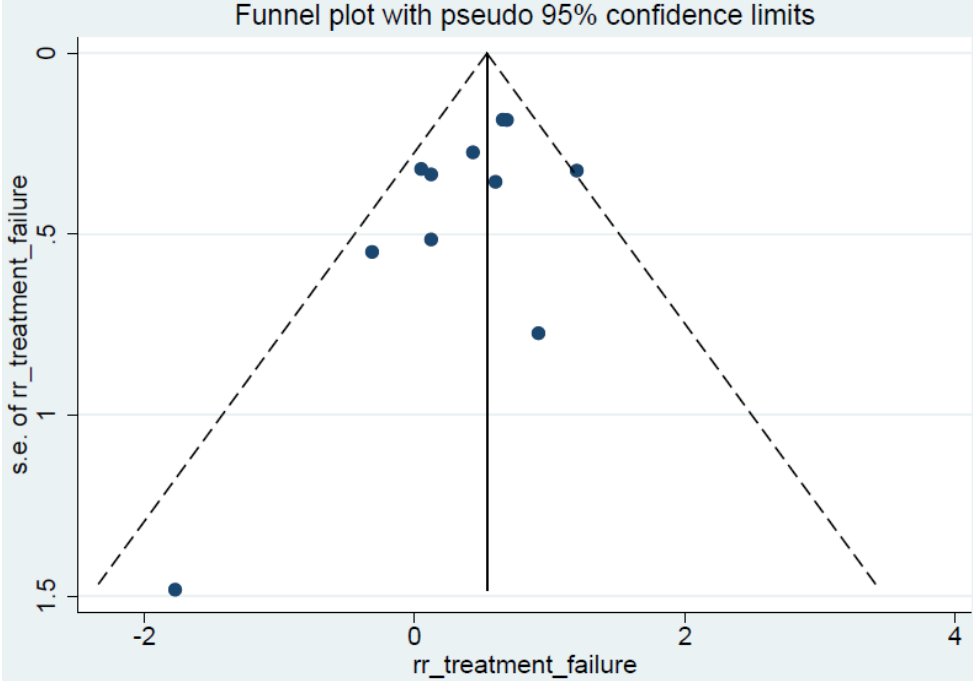
Risk of intraventricular hemorrhage



Risk of patent ductus aortus



Appendix 6. Funnel plot for meta-analysis of relative risk of treatment failure using HFNC compared to CPAP in primary respiratory support for preterm infants.



Service de la formation
3ème cycle - Pôle 3

Conclusions

Nous proposons que l'oxygénothérapie aux lunettes haut débit ne soit pas utilisée à la place de la ventilation en pression positive continue en primo-thérapie dans le syndrome de détresse respiratoire du nouveau-né prématuré, et ce quel que soit l'âge gestationnel de naissance. De nouvelles études randomisées contrôlées sont nécessaires pour évaluer l'influence du traitement par surfactant sur l'efficacité de l'OLHD, ainsi que des études visant des populations d'extrêmes prématurées <28 semaines d'âge gestationnel.

Clermont-Ferrand, le 31/08/2020
Pierre CLAVELOU
Doyen - Directeur



Clermont-Ferrand, le 26/08/2020
Le Président du Jury

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Pr Etienne MERLIN
Service de Pédiatrie Générale
RPPS 10004043138

High Flow Nasal Cannula (HFNC) versus Continuous Positive Airway Pressure (CPAP) for primary respiratory support in preterm infants: a meta-analysis

Résumé

Introduction : L'efficacité et la tolérance de l'oxygénothérapie aux lunettes haut débit (OLHD) chez le nouveau-né prématuré ont été démontrées en relais post extubation, mais les données concernant l'OLHD en primo-thérapie dans le syndrome de détresse respiratoire du nouveau-né prématuré sont insuffisantes et discordantes. Nous avons mené une revue systématique et méta-analyse d'études contrôlées randomisées pour évaluer l'efficacité et la tolérance de l'OLHD comparée à la ventilation spontanée en pression expiratoire positive (CPAP) en primo-thérapie du syndrome de détresse respiratoire du nouveau-né prématuré dans les 24 premières heures de vie, ainsi qu'une analyse en sous-groupe par âge gestationnel et étudier l'impact des paramètres cliniques.

Méthode : Les études contrôlées randomisées ont été recherchées dans les bases de données PubMed, Cochrane Library, Embase, et CINHAL jusqu'au 25 août 2020, avec comme critère de jugement principal l'échec du traitement. Nous avons calculé les risques relatifs en intention de traiter et effectué des méta-analyses en utilisant un modèle à effet aléatoire (modèle de DerSimonian-Laird). L'hétérogénéité a été évaluée à partir d'une analyse des funnel-plots et du test d'hétérogénéité de I².

Résultats : 10 études ont été incluses, pour un total de 1830 patients. L'âge gestationnel de naissance des patients inclus allait de 28 à 37 semaines de gestation. Les débits d'OLHD allaient de 2-5L/min à 5-8 L/min. Les modes de CPAP utilisés étaient sur ventilateur, à bulle ou les deux, pour des pressions allant de 2 à 8 mmHg. Le traitement par surfactant était autorisé dans 7 études sur 10. Notre méta-analyse montre une multiplication de 1.42 du risque d'échec de traitement avec l'OLHD comparée à la CPAP (95CI 1.07 to 1.79, I²=25.4%) sans différence en fonction des groupes d'âge gestationnel. Les méta-régressions n'ont pas démontré d'impact des paramètres cliniques sur les résultats: l'âge gestationnel, le poids de naissance, le débit de l'OLHD, le mode de CPAP ou l'utilisation de surfactant.

Conclusion : Nous proposons que l'OLHD ne soit pas utilisée à la place de la CPAP en primo-thérapie dans le syndrome de détresse respiratoire du nouveau-né prématuré, et ce quel que soit l'âge gestationnel de naissance.

Mots-clés

HFNC, CPAP, primary respiratory support, preterm, meta-analysis.

Membres du Jury

Président : Monsieur MERLIN Etienne, Professeur, UFR de Médecine et des Professions paramédicales de Clermont-Ferrand

Monsieur DUTHEIL Frédéric, Professeur, UFR de Médecine et des Professions paramédicales de Clermont-Ferrand

Madame COSTE Karen, MCU, CHU Clermont-Ferrand, Pédiatrie

Madame SAVY Nadia, PH, CHU Clermont-Ferrand, Pédiatrie

Madame REMERAND Ganaelle, PH, CHU Clermont-Ferrand, Pédiatrie

Madame EGRON Carole, PH, CHU Clermont-Ferrand, Pédiatrie

Date de la soutenance : 22 Septembre 2020.