The effect of respiratory management on neurodevelopmental outcome in preterm infants
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GENERAL DISCUSSION

This thesis provides insight into what interventions might further improve respiratory care of preterm infants admitted to the neonatal intensive care unit (NICU). For some of the suggested improvements, it provides evidence of feasibility and improvement of short- and long-term outcomes. Furthermore, this thesis identifies the knowledge gaps in non-invasive respiratory care, providing hypothesis to explore in future studies. Therefore, the results of this thesis are important for patients, parents, researchers and health care professionals.

As described in Chapter 1, preterm infants are at high risk of respiratory failure due to the immaturity of the respiratory system and control of breathing. Initially, invasive mechanical ventilation (IMV) was the preferred mode of respiratory support for preterm infants to restore gas exchange and/or control of breathing. However, IMV can also injure the lung which may lead to the development of the most common complication of preterm birth: bronchopulmonary dysplasia (BPD). The disease BPD has evolved over time and so have the criteria to define and classify its severity. Nowadays BPD is diagnosed when an infant cumulatively requires more than 28 days of supplemental oxygen (mild BPD). If, in addition to this, the infant needs < 30% supplemental oxygen at 36 weeks postmenstrual age (PMA), BPD is classified as moderate, and if the infant needs ≥ 30% oxygen or positive pressure support at 36 weeks PMA, as severe BPD. BPD is associated with prolonged primary hospitalization, pulmonary complications such as recurrent infections, asthma and wheezing throughout childhood. Furthermore, BPD increases the risk of neurodevelopmental impairment (NDI) later in life. In addition to BPD, IMV is also associated with an increased risk of neurodevelopmental impairment, e.g. the longer the duration of IMV, the greater the risk.

It is clear that reducing IMV may have important benefits on patient outcome, especially concerning the risk of BPD and adverse long-term neurodevelopmental outcome. Alternative and successful modes of non-invasive respiratory support are nasal continuous positive airway pressure (nCPAP) or nasal intermittent positive pressure ventilation (nIPPV). In addition, pharmacological interventions such as caffeine and doxapram can be used in treating apnea of prematurity (AOP). The NICU of the Emma Children’s Hospital/Academic Medical Center (AMC) in Amsterdam has implemented a strict non-invasive respiratory policy over the past years, in order to reduce mechanical ventilation and subsequently BPD and NDI. The aims of this thesis were (1) to assess the feasibility of this strict non-invasive respiratory policy and its effect on NDI, (2) to assess whether previously found associations between both mechanical ventilation and BPD with neurodevelopmental outcome still existed in this era of non-invasive respiratory management, and (3) to summarize the existing evidence on the pharmacologic agents used in avoiding IMV, i.e. the optimum dose of caffeine and safety and efficacy of doxapram treatment.
The non-invasive respiratory policy

In **Chapter 2**, the feasibility and effectiveness of a local non-invasive respiratory policy is assessed by comparing outcomes of an epoch before to an epoch after implementation of this new policy. We conclude that a non-invasive respiratory policy is feasible, as shown by the reduction in both the need for IMV (35% vs 43% never ventilated) and the total duration of IMV (0.5 days vs 1.5 days). This is accompanied by an increased use of non-invasive support and respiratory stimulants such as caffeine and doxapram in the epoch after implementing a non-invasive respiratory policy. The non-invasive strategy also results in a trend towards less BPD and a significant improvement in the combined outcome measure mortality or neurodevelopmental impairment (NDI) at two years corrected age (CA). The already low incidence of BPD (23%) in the cohort subjected to more IMV in the first epoch of the study can be an explanation for finding only a trend towards a reduced risk of BPD in the non-invasive cohort. The incidence in the first epoch is considerably less than the reported 40% in a large cohort of infants born in the United States of America (USA) between 1993 and 2012. It is important to acknowledge that the retrospective design of the study prevents us stating firm conclusions. The results may have been biased by the shift in active treatment from 25 to 24 weeks GA between the two epochs, although a sensitivity analysis does not indicate this. Furthermore, conversion between different versions of the Bayley Scales of Infant Development (BSID) may not be optimal. Despite these limitations, our findings show that a reduction in IMV duration might have a positive effect on long-term neurodevelopmental outcome, which is highly clinically relevant.

Several studies have explored the effect of (duration of) IMV and BPD on neurodevelopmental outcome in preterm infants. One study found an increased risk on NDI after protracted ventilation (median duration of 18 IMV days) in preterm infants born between 1995 and 1998. Another study reported an increased risk of NDI at 18 months corrected age with worsening BPD severity. As shown in Chapter 2, current respiratory support practice is much more non-invasive than respiratory practice in the late 90s. The question rises whether the association found between IMV and NDI two decades ago still applies to the current practice with a median IMV duration of less than one day. This question is addressed in **Chapter 3**, including a cohort of preterm infants born between 2010 and 2015, ventilated with a median duration of 0.5 days. We show that the association between IMV duration and NDI at 24 months CA still exists in an era of non-invasive respiratory management, with a 7% increased risk on NDI per additional day of IMV. This suggests that the association between IMV duration and NDI might even be larger compared to the 18% increase per week ventilation found by Walsh et al. However, the results must be interpreted carefully as there may have been other explanations for this increase in risk. First, the definition of NDI was broader in this chapter compared to Walsh et al. Using a stricter definition from this previous study will limit the number of
the infants with NDI considerably. A second explanation can be the changed indication to start IMV. Twenty years ago, preterm infants were considered to be too immature or too compromised to be offered non-invasive support and were therefore primarily treated with IMV. Nowadays, most infants, including the extremely preterm infants, are offered non-invasive support as the primary mode of support. Only the most severely ill patients will fail this mode of support and will be started on IMV. This selected group of patients ending up on IMV probably has a higher risk of NDI later in life.

The effect of having a diagnosis of BPD on neurodevelopmental outcome has mainly been assessed with a binary definition of BPD. To our knowledge, only two studies reported on the association between BPD severity and neurodevelopmental outcome at two year corrected age (CA), with conflicting results. The association between severity of BPD and neurodevelopmental outcome at five years CA has not been assessed yet. It is important to know whether the neurodevelopmental outcome at two years is sufficient to predict neurodevelopmental outcome later in life. If not, studies might need to consider prolonging follow up. It has already been shown that in the general preterm population the correlation between follow up assessment at two and five years is only fair. Since infants with BPD already have a higher risk on white matter damage and neurodevelopmental impairment, this correlation might be stronger in BPD infants, and might be dependent on the severity of BPD. Therefore, in Chapter 4, the correlation between BDP severity and two and five years CA neurodevelopmental outcome is assessed in a cohort of infants born between 2006 and 2012. Including 543 patients, with 13% having mild BPD, 9% having moderate BPD and 10% having severe BPD, the level of BPD severity is associated with increasing risk on adverse outcome, with the largest effect seen in infants with severe BPD. The correlation between adverse neurodevelopmental outcome at two and five years is only fair in all levels of BPD severity, corresponding with the correlation in infants without BPD. This emphasizes the importance of classifying the severity of BPD at neonatal age and the implementation of prolonged follow up in these BPD infants.

In 2017, a study by Doyle et al. reported no improvement in respiratory function at the age of eight, while the duration of mechanical ventilation was reduced from a median of 21 days in 1991-1992 to 10 days in 2005. They suggested that the focus on non-invasive support might not results in better outcome. In Chapter 5, we propose a different explanation based on the respiratory management and outcomes of three local cohorts of babies born between 24-28 weeks of gestation. The median duration of mechanical ventilation in 2004-2005 is 5.9 days, decreasing to 1.8 days in 2010-2011 and 0.8 days in 2013-2014. The rate of BPD is considerably lower in the Amsterdam cohort (36% in 2004-2005) compared to the cohort described in the study by Doyle et al. (56% in 2005). We therefore suggest that a further reduction in IMV duration is necessary to achieve improved short-term (e.g. BPD) and possibly also long-term lung function.
Pharmacologic agents used in a non-invasive respiratory policy

As shown in Chapter 2, the introduction of a non-invasive respiratory policy leads to the increased use of caffeine therapy. However, the optimum dose of caffeine is yet to be established. Chapter 6 summarizes all randomized controlled trials comparing different dosages of caffeine. Meta-analysis shows a significant decrease in BPD, the combined outcome mortality or BPD and failure to extubate in infants who received a higher caffeine dose for > 14 days. Meta-analysis shows no differences in mortality alone and NDI between the different caffeine dosages. However, the caffeine regimens differ considerably between the included studies, with the definition of a high maintenance dose ranging between 5-30 mg.kg\(^{-1}\).d\(^{-1}\) and the duration of different caffeine dosage ranging between 36 hours to the total duration of NICU admission. Also, the quality of these studies is deemed low to very low. Therefore, an optimum dose of caffeine cannot be determined based on the current evidence, although there are indications that a higher caffeine dose might improve outcome.

When treatment with caffeine for central apnea is insufficient, doxapram treatment can be added as adjunctive treatment, to stimulate the respiratory center in the brain\(^{10}\). However, there are large differences in the prescription rates between centers. For example, the use of doxapram decreased in the USA between 2005 and 2010\(^{20}\), while Chapter 2 of this thesis shows an increased use of doxapram over time in a single center in the Netherlands. The reason behind this difference is that the safety of doxapram treatment is questioned by studies reporting on short-term adverse events such as hypertension and gastro-intestinal disturbances\(^{21-23}\), but also mental developmental delay on the long-term\(^{24}\). However, observational studies investigating doxapram are always confounded by indication: the infants who receive doxapram always have a higher incidence of AOP and other short-term morbidities. The studies reporting on long-term adverse effects of doxapram do not correct for these confounders\(^{24, 25}\).

To evaluate the risk on adverse neurodevelopmental outcome after doxapram therapy, a case-control study including 142 doxapram-treated infants and 284 non-treated infants is performed in Chapter 7. This study suggests that doxapram treatment is not associated with an increased risk on NDI at 24 months CA and might even be associated with a benefit on the outcome mortality or NDI at 24 months CA. Even though this association persists after correction for confounders and after multiple sensitivity analyses, a case control study will never provide the highest level of evidence\(^{26}\), because it is not possible to identify and subsequently correct for all confounders.

Due to the conflicting results of previously published reports on doxapram and those reported in Chapter 7, the aim of Chapter 8 is to identify, appraise and summarize all randomized and non-randomized evidence on doxapram treatment. Four randomized controlled trials (RCTs) and 28 observational studies are identified, with considerable heterogeneity between study populations and design, dosage regimens and outcome
measures. All studies reporting on apnea show a positive effect after doxapram treatment, with most of them not showing adverse effects of doxapram treatment. Due to the heterogeneity in study designs and outcome measures, meta-analysis cannot be performed. In the case series, a large variety of adverse effects is reported, mostly when using doses > 1.5 mg.kg⁻¹.h⁻¹. The interpretation of these reports is difficult, due to the small sample size, the lack of a control group, and a high risk of bias in the individual studies. Therefore, the overall applicability of this review is low, and it remains unclear whether the beneficial effects of doxapram will outweigh the adverse effects.

CONCLUSIONS

The aim of this thesis was to evaluate the effect of respiratory management on neurodevelopmental outcome. Based on this thesis, several conclusions can be drawn.

First, this thesis demonstrates that the implementation of a non-invasive respiratory support policy is feasible and might be associated with improved neurodevelopmental outcome even in extremely preterm infants. This is supported by our finding that – in this new era of non-invasive respiratory management – every additional day of IMV is associated with an increased risk of adverse neurodevelopmental outcome at two years of age.

Second, BPD is associated with an adverse neurodevelopmental outcome at two and five years of age. In addition, increasing severity results in an increased risk of NDI. Similar to the general population, the correlation between two and five years neurodevelopmental outcome is only fair, emphasizing the importance of following up this high-risk population to at least 5 years of age.

Finally, there is only limited evidence supporting the use of a higher dose of caffeine and doxapram in the treatment of AOP.
FUTURE PERSPECTIVES

Implications for clinical practice

For daily practice, Chapter 2, 3, and 5 emphasize the importance of pursuing a non-invasive respiratory strategy in preterm infants. These chapters show a potential reduction in neurodevelopmental impairment when such a strategy is implemented. Chapter 4 shows that prolonged follow-up until at least five years is needed to assess the long-term neurodevelopmental outcome of BPD patients. In this non-invasive respiratory strategy, infants might benefit from a higher dose of the respiratory stimulant caffeine, although the gathered evidence in Chapter 6 is inconclusive. If this higher dose is used in daily practice, it is important to monitor the infant closely for possible side effects such as tachycardia. Although Chapter 7 could not find an increased risk on adverse neurodevelopmental outcome after doxapram treatment, Chapter 8 shows that the routine use of doxapram for central apnea treatment cannot be recommended yet, since it is unclear whether the benefits will outweigh the adverse effects.

Implications for research

The conclusions of the systematic reviews on caffeine and doxapram both state that the level of evidence is not high enough to draw accurate conclusions. Therefore, new randomized trials are needed. First, in the case of the optimal caffeine dosage, beneficial results are seen when a higher maintenance dose is administered for a prolonged period. In order to provide conclusive evidence on the optimal caffeine dose, a large multicenter blinded RCT should compare a high maintenance dose caffeine citrate (e.g. 20 mg.kg$^{-1}$.d$^{-1}$) to a low maintenance dose caffeine citrate (e.g. 10 mg.kg$^{-1}$.d$^{-1}$) for more than 14 days in preterm infants at risk for adverse pulmonary and neurodevelopmental outcomes. The loading dose of the trial should be carefully considered, since one study reported an increased risk on cerebellar hemorrhage after a high loading dose (i.e. 80 mg.kg$^{-1}$ in 36 hours$^{27}$). Primary outcome measures should be BPD severity at 36 weeks PMA, defined according to the international standards, and neurodevelopmental outcome. The study should be adequately powered to detect small but clinically relevant effects.

Second, in the case of doxapram, a placebo-controlled multicenter RCT is needed to assess the efficacy and safety of doxapram treatment for AOP in preterm infants. Following the publications in this thesis, underlining the clinical gap of knowledge in neonatology, a ZonMW grant application was submitted for such a large RCT. All 10 Dutch NICUs have agreed to participate in this future trial.

Third, due to the observational character of the studies in Chapters 2, 3, 4, 5, and 7, conclusive high-quality evidence of a beneficial effect of non-invasive respiratory support cannot be given$^{28}$. Some clinicians are wondering whether aiming towards a
non-invasive respiratory support strategy at all costs is the most effective strategy, or might even be a harmful strategy, by allowing more hypoxic episodes and higher carbon dioxide levels. For example, Doyle et al. showed that reducing mechanical ventilation duration did not improve lung function at eight years\textsuperscript{19}. To provide high quality evidence on this subject, an RCT comparing two contrasting respiratory strategies could be performed, including infants with a gestational age < 28 weeks. The non-invasive respiratory treatment group should avoid intubation and mechanical ventilation as much as possible. For this, accepting higher PaCO\textsubscript{2} levels and a higher rate of AOP while adopting a more liberal use of high dose caffeine citrate and doxapram should be implemented. In the invasive respiratory treatment group, intubation and mechanical ventilation should be used to treat hypoxia, hypercapnia and AOP when proven therapies such as non-invasive support and regular dosed caffeine treatment fail to correct these conditions. The primary outcome measure of this RCT should be BPD, defined according to international standards. Secondary outcome measures should be neurodevelopmental outcome at two and at five years.

Finally, for optimal guidance in clinical decision making, it is important to keep evaluating the effects of current neonatal practice, not only after two years, but also after five years, to assess the true long-term outcome of preterm infants. In might even be necessary to prolong follow up even further to eight years. The correlation between two, five and eight year follow up outcome should also be assessed.
SUMMARY

Chapter 1 provides an overview of the immature respiratory system, the adverse effects of invasive mechanical ventilation, including BPD, the effects of IMV and BPD on long-term neurodevelopmental outcome, and the possible interventions to support a preterm infants with a non-invasive respiratory policy.

In Chapter 2, the feasibility and efficacy of implementing a non-invasive respiratory support policy is evaluated by comparing two cohorts of preterm infants, one before and one after implementation. The results show that a non-invasive respiratory support policy can be implemented successfully with a reduction in both the need and duration of IMV. This policy is associated with a trend to less BPD and an improved neurodevelopmental outcome.

In this current era of non-invasive respiratory management, the association between mechanical ventilation duration and neurodevelopmental outcome at the age of two is explored in Chapter 3. We found that the duration of mechanical ventilation is still negatively correlated with adverse neurodevelopmental outcome.

Chapter 4 shows that the severity of BPD is independently associated with NDI at two and five years. Furthermore, the correlation between neurodevelopmental outcome at the age of two and five is only fair in infants with BPD, emphasizing the importance of prolonged follow up of this high risk population.

Chapter 5 argues that improvement in lung function at eight years might only be seen when a profound reduction in IMV duration is achieved.

In order to achieve an optimal non-invasive respiratory strategy, pharmacologic stimulant are used. Chapter 6 summarizes and appraises all RCTs reporting on different caffeine dosages. Meta-analyses show that a higher caffeine dose could be beneficial in reducing mortality and adverse pulmonary outcome, but due to the low level of evidence and the heterogeneity between the trials, the optimum dose of caffeine cannot be determined.

When apnea persists during caffeine treatment, adding doxapram can be considered the next step in the treatment of central apnea. Chapter 7 evaluates the risk on adverse neurodevelopmental outcome after doxapram therapy by comparing doxapram-treated infants with non-treated infants. In contrast to previous studies, a positive association between doxapram treatment and neurodevelopmental outcome was found.
Next, all randomized and non-randomized evidence on doxapram is summarized in **Chapter 8**, but unfortunately, no firm conclusions can be drawn on safety and efficacy of doxapram treatment, due to the heterogeneity of study designs and low quality of published evidence.

**Chapter 9** contains the general discussion, future perspectives and English summary. A Dutch summary can be found in **Chapter 10**.
REFERENCES


