WHO recommendation on the time for starting continuous positive airway pressure therapy for newborns with respiratory distress syndrome

17 November 2015

Recommendation

Continuous positive airway pressure therapy for newborns with respiratory distress syndrome should be started as soon as the diagnosis is made.

(Strong recommendation based on very low-quality evidence)

Publication history

First published: November 2015

Updated: No update planned

Assessed as up-to-date: November 2015

Remarks

- In view of the high proportion of neonatal deaths that are caused by respiratory distress syndrome, the GDG made a strong recommendation despite the low quality of the evidence showing the benefits of early continuous positive airway pressure (CPAP) therapy.

Background

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life. (1) Globally, it is the leading cause of perinatal and neonatal mortality and morbidity. (2) Preterm infants are particularly vulnerable to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high risk of infection. (3-5) With the increasing contribution of neonatal deaths to overall child mortality, it is critical to address the determinants of poor outcomes related to preterm birth to achieve further reductions in child mortality. (6-8)
Infant mortality and morbidity from preterm birth can be reduced through interventions delivered to the mother before or during pregnancy, and to the preterm infant after birth. (9) Interventions can be directed at all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation programme) or aimed at minimizing the risk in women with known risk factors (e.g. progestational agents, cervical cerclage). (10) However, the most beneficial set of maternal interventions are those that are aimed at improving outcomes for preterm infants when preterm birth is inevitable (e.g. antenatal corticosteroids, magnesium sulfate and antibiotic prophylaxis). (9) Special care of the preterm newborn to prevent and treat complications of prematurity is also critical to newborn survival. In high-income countries, reductions in mortality rates in infants that were born preterm have been driven largely by improved care and, more importantly, by appropriate policy changes.

Methods

The recommendations were developed using standard operating procedures in accordance with the process described in the WHO handbook for guideline development (11). Briefly, these included (i) identification of priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

The scientific evidence underpinning the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (12). Up-to-date systematic reviews were used to prepare evidence profiles for the priority questions. WHO then convened a Technical Consultation in May 2014 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendations based on the evidence profiles.

In November 2014, an online consultation of the GDG was conducted to review and revise the recommendations in the light of the findings of a large implementation trial of antenatal corticosteroids in low-resource countries.

Further information on procedures for developing this recommendation are available [here](#).

Recommendation question

For this recommendation, we aimed to answer the following question:

- In newly born preterm babies with or at risk of respiratory distress syndrome (P), is continuous positive airway pressure (I), compared with routine care (C), effective in preventing adverse newborn outcomes? If so:
  - Under what conditions and when should continuous positive airway pressure be provided?
  - What are the indications for additional interventions?

Evidence summary

Early versus late initiation of continuous positive airway pressure (CPAP) therapy for respiratory distress syndrome (RDS) in preterm infants:
Evidence on the timing of initiation of CPAP therapy for preterm newborns with RDS was derived from a Cochrane review by Ho et al. (13).

This review included five randomized trials and one quasi-randomized trial, all from HICs. The included studies were conducted between the mid-1970s and the early 1980s, before the era of surfactant treatment. Criteria for enrolment differed somewhat between trials but essentially all preterm babies with radiological or clinical features of RDS were included. The intervention involved initiation of CPAP therapy (either with continuous distending pressure or continuous negative pressure) immediately following the diagnosis of RDS, and these neonates required fraction of inspired oxygen (FiO2) between 0.3 and 0.7. In the comparison arm, CPAP was initiated only when RDS was worsening and babies required relatively higher FiO2 (between 0.5 and 1.0). An updated search in May 2014 identified one additional RCT (60), conducted in Iran in 2013. In the study, early CPAP was defined as CPAP initiated within 5 minutes of birth, and late CPAP was that initiated at least 30 minutes after birth. This trial was the largest of all the seven studies included and contributed over 30% of the total preterm newborns in the review.

**Neonatal death:** Only two trials (involving 61 preterm babies) reported mortality in the neonatal period. The trials suggested no evidence of a reduction in neonatal mortality with early initiation of CPAP as compared to delayed initiation (RR 0.93, 95% CI 0.13–6.81). All seven trials reported the effect of early initiation of CPAP on in-hospital neonatal mortality. However, with a total of only 237 preterm babies included in this analysis, the evidence for mortality reduction from the pooled results was inconclusive: 13.8% of those initiated early on CPAP died in-hospital, as compared to 18.8% of those receiving delayed CPAP (RR 0.70, 95% CI 0.40–1.24).

**Severe neonatal morbidity:** Six studies (involving 165 neonates) showed that early rather than delayed initiation of CPAP therapy was associated with reduced risk of respiratory failure requiring mechanical ventilation (17.8% versus 31.5%; RR 0.55, 95% CI 0.32–0.96). Only one study (60) reported on the need for surfactant therapy and the incidence of sepsis in neonates on early or late CPAP. Early initiation was associated with a 36% lower risk of complications requiring surfactant therapy (RR 0.64, 95% CI 0.44–0.93) and a 54% lower incidence of sepsis (RR 0.46, 95% CI 0.27–0.79). Finally, the incidence of IVH was also lower with the use of early CPAP compared with delayed CPAP (58.3 versus 83.0%, P = 0.037). However, there was no conclusive evidence of reduction in the risks of BPD (RR 0.70, 95% CI 0.12–3.98) or air leaks (RR 0.84, 95% CI 0.37–1.91).

Further information and considerations related to this recommendation can be found in the WHO guidelines, available at:

http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1

http://apps.who.int/iris/bitstream/handle/10665/183038/WHO_RHR_15.17_eng.pdf?sequence=1

**Implementation considerations**

- The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
- A set of interventions should be established to ensure that an enabling environment is created for the
use of the recommendations, and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.

- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

Research implications

The GDG identified that further research on the following high-priority questions is needed:

- What is the best modality for providing CPAP? e.g. nasal intermittent positive pressure ventilation, nasal flow cannulas, etc.
- What is the role of CPAP for babies with apnoea of prematurity that persists despite giving methylxanthines/caffeine?
- What is the efficacy of surfactants in a context where antenatal corticosteroids and early CPAP is provided (without immediate obligatory mechanical ventilation) for babies who are at risk of respiratory distress syndrome (e.g. InSURE – intubation, surfactant replacement therapy and extubation)?

Related links

WHO recommendations on interventions to improve preterm birth outcomes (2015) – [full document](#) and [evidence tables](#)

Supporting systematic reviews:

[Early versus delayed initiation of continuous distending pressure for respiratory distress syndrome in preterm infants](#)

Other links of interest

[Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors](#)

[Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice](#)

[WHO Programmes: Sexual and Reproductive health](#)

[Maternal Health](#)

[Infant, Newborn Health](#)

References

13. †Ho JJ, Henderson-Smart DJ, Davis PG. Early versus delayed initiation of continuous distending pressure for respiratory distress syndrome in preterm infants. Cochrane

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