WHO recommendation on the prophylactic administration of surfactant in preterm newborns

17 November 2015

Recommendation

Administration of surfactant before the onset of respiratory distress syndrome (prophylactic administration) in preterm newborns is not recommended.

(Strong recommendation based on low-quality evidence)

Publication history

First published: November 2015

Updated: No update planned

Assessed as up-to-date: November 2015

Remarks

- The GDG did not recommend prophylactic administration of surfactants despite evidence of benefit in older studies because:

  — the control group in these older studies did not receive continuous positive airway pressure (CPAP), which is now part of standard care; and

  — recent studies in which CPAP was given to control group did not show any evidence of benefit for prophylactic surfactant administration, and a possibility of harm could not be ruled out.

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 who have or are at risk of respiratory distress syndrome (P), is surfactant therapy (I), compared with routine care without surfactants (C), effective in reducing adverse newborn outcomes (O)? If so:
  - How early should the surfactant therapy be started?
  - Should surfactants be given for prophylaxis in newborns where respiratory distress syndrome has not yet set in, or selectively when existing respiratory distress is worsening?
  - Which types of surfactant are effective – animal-derived or synthetic; protein-containing or protein-free?
Evidence summary

Prophylactic versus rescue surfactant therapy for respiratory distress syndrome (RDS) in preterm neonates

Evidence for this recommendation was based on a Cochrane review that evaluated the effects of prophylactic administration of surfactants compared with selective rescue therapy on mortality and morbidity in preterm newborns with or without evidence of RDS (13).

The review included 11 studies, all from intensive care units of hospitals in HICs, and all using animal-derived surfactants. Surfactants were administered with or without CPAP; two studies routinely administered CPAP to stabilize babies in the comparison arm, whereas the other nine were conducted in the pre-CPAP era.

Neonatal death: The use of prophylactic surfactant administration was not associated with benefit in terms of neonatal death (RR 0.89, 95% CI 0.76–1.04; 10 studies, 4507 preterm neonates). However, there was substantial heterogeneity among studies depending on whether the control group receive CPAP or not. In recent studies in which CPAP was given to control infants, prophylactic administration of surfactants did not reduce neonatal death (RR 1.24, 95% CI 0.97–1.58; 2 studies, 1746 neonates). However, in eight older studies where CPAP was not administered to control infants, the mortality reduction was significant (RR 0.69, 95% CI 0.56–0.85; 2761 neonates). The findings were similar for in-hospital mortality outcomes as reported in five studies. There was a trend towards a reduction in risk of in-hospital mortality with the use of prophylactic surfactant administration compared to selective therapy (RR 0.79, 95% CI 0.63–1.00; 5 studies, 1458 neonates). One of these five studies used CPAP for control infants, and reported a relative risk of 1.76 (95% CI 0.79–3.94; 428 neonates).

Severe neonatal morbidity: The pooled effect across all 11 studies that reported morbidity outcomes did not provide evidence of a difference between intervention and control groups for air leaks (RR 0.86, 95% CI 0.71–1.04), sepsis (RR 0.83, 95% CI 0.64–1.08) or severe IVH (RR 0.87, 95% CI 0.74–1.04). However, the nine older studies in which control group infants did not receive CPAP showed a reduced risk of air leaks (RR 0.79, 95% CI 0.63–0.98; 8 studies, 2760 neonates) and sepsis (RR 0.1, 95% CI 0.03–0.33; 5 studies, 2013 neonates) in the intervention group.

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 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:


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**


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