Neonatal Resuscitation: State of the Art

Daniele Trevisanuto, MD[1] Alfonso Galderisi, MD[1]

[1] Department of Woman's and Child's Health, University of Padova, Padova, Italy

Address for correspondence Daniele Trevisanuto, MD, Department of Woman's and Child's Health, University of Padova, Padova, Italy (e-mail: daniele.trevisanuto@unipd.it).

Am J Perinatol 2019;36(suppl S2):S29–S32.

Abstract

The objective of this study is to revise novel evidence and forthcoming clinical trials that focused on the gap of knowledge raised during the 2015 guidelines for neonatal resuscitation. Literature search on main topics on neonatal resuscitation published after 2015 edition of the consensus on science and guidelines was performed. Only relevant articles (mainly randomized controlled trials [RCTs] and meta-analyses) were included and presented as descriptive review. In the past years, new RCTs and/or meta-analyses have become available on umbilical cord clamping and umbilical cord milking, oxygen concentrations to start resuscitation in term and preterm infants, use of laryngeal mask, sustained lung inflation, less invasive surfactant administration, and heart rate assessment. Despite the increasing available literature on neonatal resuscitation in the past years, many interventions are still performed without robust scientific evidence. Adequately powered and well-designed RCTs are needed to optimize management of neonates at birth.

Keywords

- neonatal resuscitation
- oxygen concentration
- preterm infant
- thermal
- umbilical cord clamping
- ventilation

The agenda of the International Liaison Committee on Resuscitation Neonatal Work Group relies on periodic consensus on science that revises novel evidence for the gap of knowledge in neonatal resuscitation and represents the basis for guidelines.[1–3] The consensus is expected to set the pace for forthcoming guidelines in a timely manner, as well as to encourage studies targeting critical areas for the lack of robust evidence or the absence of trials.

Herein, we revised novel evidence and forthcoming clinical trials that focused on the gap of knowledge raised during the 2015 guidelines as well as during the following consensus with the ultimate scope of providing an update in the initial steps of neonatal resuscitation (cord clamping and thermoregulation), ventilation and oxygenation, and heart rate (HR) assessment. These areas represented major gaps of knowledge in the past guidelines for neonatal resuscitation and have informed neonatal research of the past years.[1]

Each task has been described with respect to the examined gap of knowledge ("spotlight"), the "current recommendation," and "novel evidence" in the area.

Cord Clamping and Initial Steps

Spotlight: Umbilical cord milking (UCM) and delayed cord clamping (DCC) to improve short-term neonatal outcomes and long-term neurodevelopment.

Current recommendations: Guidelines suggest "against" the routine use of cord milking for infants <29 weeks gestation, due to the lack of evidence for its benefit and acknowledge that "cord milking may be considered on an individualized basis or in a research setting as it may improve initial mean blood pressure, hematological indices and intracranial hemorrhage" with "no evidence for improvement or safety in long-term outcomes."[1] DCC for longer than 30 seconds is recommended in both term and preterm infants who do not require resuscitation at birth[1] because it reduces intraventricular hemorrhage of any grade, the need for transfusion and the incidence of necrotizing enterocolitis,[1] in the absence of effect on long-term neurodevelopment. However, DCC is not recommended for infants requiring neonatal resuscitation due to the absence of studies including newborns requiring neonatal resuscitation.

DOI https://doi.org/10.1055/s-0039-1691797.
ISSN 0735-1631.

Novel evidence: Katheria et al demonstrated that UCM increased language and cognitive scores at the 2-year Bayley scale evaluation in infants born <32 weeks' gestation, as compared with their peers managed with DCC, in a randomized controlled trial (RCT) conducted on 197 neonates.[4] Despite these results support UCM as an effective alternative to DCC, further research is needed to define the role of UCM on long-term outcomes.

Findings from a large Swedish longitudinal study reported that DCC improves fine motor and social domains at 4 years of age in full-term neonates, as assessed by the use of Wechsler Preschool and Primary Scale of Intelligence-III and Movement Assessment Battery for Children scores.[5] A recent meta-analysis on 18 RCTs conducted in 2,834 infants <37 week's gestation showed that DDC reduces hospital mortality of ~30%. Same size effect was found in the subgroup of 996 infants ≤28 weeks' gestation.[6] This evidence is expected to strengthen the recommendation for DCC in preterm neonates.

In newborns born at term at risk for resuscitation, Katheria et al showed that 5-minute DCC could be accomplished safely without compromising the ability to perform resuscitation and was associated with increased saturations, decreased fractional cerebral tissue oxygen extraction, and greater blood pressure at 12 hours of life when compared with the group that received 1-minute DDC.[7] Despite these infants were considered at risk of resuscitation, their median (interquartile range) 5-minute Apgar score was 9 (9–9). Efficacy and safety of DDC in newborns needing resuscitation at birth remain to be established.[7]

Spotlight: Intrauterine "thermostability" need to be replaced by extrauterine "thermoregulation" at birth by the use of differential strategies that include room temperature, radiant infant warmer, thermal mattress, plastic wrap, cap, and humidified and heated gases.[1,8] The different contribution of each of them, as well as the new strategies to optimize thermoregulation after birth represent a current gap of knowledge.

Current recommendations: Hypothermia (<36°C) increases morbidity and mortality in preterm neonates[9–11]; therefore, guidelines recommend to maintain nonasphyxiated infants between 36.5 and 37.5°C.[1] Thermal mattress, plastic wrap, cap, and infant warmer, in addition to the environmental controlled temperature, are the tools to achieve such a goal. Their use (individual or combined) is recommended in infants less than 32 weeks' gestation, although the optimal intervention to achieve the established target is debated.[8,12]

Novel evidence: Thermal servocontrol systems could represent a new promising instrument to achieve target temperature in delivery room. This system relies on a probe, positioned on newborn skin for temperature sensing, that drives automated adjustment of cradle temperature with a feedforward mechanism. A RCT in preterm neonates (birth weight less than 1,500 g and/or a gestational age less than 30 + 6 weeks) (NCT03844204) is ongoing. The primary outcome is the proportion of neonates in the normal thermal range (36.5–37.5°C) at neonatal intensive care unit (NICU) admission, and the intervention group will be positioned on the infant warmer with the servocontrol mechanism, while in the control group, the temperature of the infant warmer will be manually set at maximum of power output. This trial is expected to provide novel evidence regarding a new tool to achieve thermostability after delivery in preterm neonates. Indeed, it has been described how the relationship between admission temperature and morbidity/mortality is U-shaped with both hypothermia (<36.5°C) and hyperthermia (>37.2°C) is associated with adverse neonatal outcome.[11]

Ventilation and Oxygenation

Spotlight: Optimizing need for initial oxygen concentrations in resuscitation of preterm newborns.

Current recommendations: During resuscitation of preterm neonates (<35 weeks' gestation), a lower oxygen concentration (21–30%) is recommended to initiate resuscitation. Higher oxygen concentrations are not recommended to prevent early exposure to additional oxygen in the absence of benefit.[1]

Novel evidence: A meta-analysis on 10 RCTs and 4 cohort studies including 5,697 preterm (<35 weeks' gestation) infants showed no statistically significant benefits or harms starting with lower FiO_2 (≤0.50) compared with higher FiO_2 (>0.50) in short-term and long-term mortalities, neurodevelopmental impairment, or other key preterm morbidities.[13] These results confirm 2015 recommendations that suggest starting resuscitation with low oxygen concentrations (FiO_2 0.21–0.30), Of note, the majority of newborns ≤32 weeks' gestation will require oxygen supplementation at birth.

Spotlight: Optimizing interface for noninvasive ventilation.

Current recommendations: Guidelines suggest in favor of continuous positive airway pressure during neonatal resuscitation in spontaneously breathing term or preterm infant, while, in the absence of respiratory effort, positive end-expiratory pressure need to be considered. The lack of raise in HR remains the guide to evaluate the respiratory support intervention and to drive ventilation-corrective steps.[14] We fall short of evidence regarding the optimal interface to be used for the initial steps of neonatal resuscitation, although positive-pressure ventilation can be effectively delivered through flow-inflating bag, self-inflating bag, or T-piece resuscitator, with self-inflating bag to be considered only in the absence of compressed gas source. Alternative interfaces, as laryngeal mask airway (LMA) are indicated in late preterm and term infants,[1] although evidence for their use in smaller infants is lacking. The ideal noninvasive respiratory support, as well as the first choice interface, is still highly debated.

Novel evidence: A recent Cochrane review including seven RCTs (five comparing LMA with bag-mask ventilation and three comparing LMA with endotracheal tube) demonstrated that LMA reduced the need for intubation (5 studies, 661 infants), the ventilation times, and the admission to the NICU. In studies that allowed LMA rescue of infants failing with bag-mask ventilation, it was possible to avoid intubation in the majority.[15]

These findings confirm that LMA represents a useful emergency tool in delivery room and all health care providers should be trained on LMA use. Smaller sizes LMA for preterm infants are needed.

Spotlight: Sustained lung inflation (SLI).

Table 1 Interventions, gaps of knowledge, novelties, and expected impact on future guidelines on neonatal resuscitation

Interventions	Gaps of knowledge	Novelties	Expected impact on future guidelines
Umbilical cord management	Cord clamping: DCC and milking	DCC improves long-term cognitive outcome in full-term infants; is feasible in neonates at risk of resuscitation; reduces mortality in preterm infants UCM seems to improve long-term outcomes compared with DCC in preterm infants[7]	–
Initial steps	Temperature: lack of preferential strategy to optimize postnatal thermoregulation	Servocontrol system (NCT03844204)	Ongoing trial
Ventilation and initial oxygen concentrations	LMA in term and preterm infants	LMA reduces intubation, ventilatory times, and NICU admission compared with face mask[15]	–
	SLI is not recommended	SLI increases mortality and does not improve BPD risk at 36 weeks[17]	Recommendation against SLI
	Oxygen need: high or low FiO_2?	Starting resuscitation with low FiO_2 ($\leq$0.50) or high FiO_2 (>05.0) does not impact mortality and neurodevelopmental impairment[13]	–
Monitoring	HR assessment: three lead ECG has been suggested with low level of evidence	NeoTapAdvancedSupport[20] (NCT03730025)	New devices may help heart rate assessment and communication

Abbreviations: DCC, delayed cord clamping; ECG, electrocardiogram; HR, heart rate; LMA, laryngeal mask airway; NICU, neonatal intensive care unit; SLI, sustained lung inflation; UCM, umbilical cord milking.

Current recommendations: Current guidelines suggest against SLI for supporting preterm infants at birth.[1]

Novel evidence: SLI is not recommended after pivotal trial stopped for increased mortality.[16] Four hundred sixty infants born at less than 26 weeks' gestation failed to prove superiority of SLI as compared with intermittent positive pressure ventilation on the risk of bronchopulmonary dysplasia (BPD) or mortality at 36 weeks' gestation. Although the trial could have been underpowered for one of the two primary outcomes (BPD risk at 36 weeks' gestation), the increased mortality prevents SLI use in preterm infants.[17]

Spotlight: Less invasive surfactant administration (LISA) at birth.

Current recommendations: LISA allows surfactant administration by the insertion of a thin catheter in trachea in the absence of needing for intubation. LISA was associated with the lowest likelihood of the composite outcome of death or BPD at 36 weeks' postmenstrual age.[18,19] While LISA is not mentioned in current neonatal guidelines, its use "should be considered" in spontaneously breathing preterm neonates with respiratory distress syndrome.[18]

Heart Rate Assessment

Spotlight: HR is the most important clinical indicator during neonatal resuscitation. HR can be assessed by four modalities: umbilical cord palpation, palpation of peripheral pulses, auscultation by using stethoscope, and three-lead electrocardiogram (ECG).

Current recommendations: Three-lead ECG has been suggested after 2015 guidelines with very low quality of evidence, based on five nonrandomized clinical trials.[1,2] Alternative ways to assess HR during neonatal resuscitation are a current gap of knowledge.

Novel evidence: Neo Tap Advanced Support (NeoTapAS) is a mobile application, based on a screen tapping method that calculates the HR. In a simulation study conducted on 160 measurements of HR, the mean difference between communicated and set HR was 1 beat per minute, suggesting NeoTap as a potential new tool to rapidly and accurately assess HR in delivery room.[20] In a neonatal resuscitation-simulated scenario, NeoTapAS reduced the time to the first HR communication and the time of initiation of chest compressions and administration of adrenaline compared with mental computation (NCT03730025).

Conclusion

Consensus on science is an ongoing process and is the basis for forthcoming guidelines. Despite increasing literature on neonatal resuscitation has become available in the past years, many interventions are still performed without robust scientific evidence (►**Table 1**). The knowledge of the gaps will help design large RCTs to optimize interventions in delivery room.

Conflict of Interest
None declared.

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