Neonatal Resuscitation Research Priorities in Low- and Middle-Income Countries

Vivek V. Shukla 1,2 and Somashekhar M. Nimbalkar 2

1University of Alabama at Birmingham, Birmingham, Alabama, USA
2Bhaikaka University, Karamsad, Gujarat, India

Correspondence should be addressed to Vivek V. Shukla; viveks3985@gmail.com

Received 25 July 2021; Revised 5 November 2021; Accepted 15 November 2021; Published 25 November 2021

Academic Editor: Lavjay Butani

Several critical physiological changes occur during birth. Optimal and timely resuscitation is essential to avoid morbidity and mortality. The International Liaison Committee on Resuscitation (ILCOR) is a multinational committee that publishes evidence-based consensus and treatment recommendations for resuscitation in various scenarios including that for neonatal resuscitation. The majority of perinatal deaths occur in low- and middle-income countries (LMICs); however, there is limited research output from LMICs to generate evidence-based practice recommendations specific for LMICs. The current review identifies key areas of neonatal resuscitation-related research needed from LMICs to inform evidence-based resuscitation of neonates in LMICs.

1. Introduction

Extraterine transition at birth and survival depends on several critical interlinked physiologic changes, including increase in systemic vascular resistance, decrease in pulmonary vascular resistance, closure of right to left shunts, alveolar fluid absorption and clearance, increase in metabolic demand, and endocrine changes [1–4]. The extraterine transition in term newborns occurs spontaneously in about 85% [5], 10% need stimulation [6], 5% need positive pressure ventilation, 2% need intubation, and 0.1% need chest compressions [7, 8]. Cardiopulmonary resuscitation is needed for a relatively small proportion of newborns [7]; however, the absolute number is high when seen in the context of the total number of births [9]. Timely and appropriate resuscitation can prevent long-term morbidity and neonatal death [5, 10, 11].

2. Resuscitation Guidelines

The International Liaison Committee on Resuscitation (ILCOR) is a committee of 8 international resuscitation councils, the majority of which are from high-income countries, which publishes evidence-based consensus and treatment recommendations for neonatal resuscitation [12, 13]. The most recent guidelines are the 2020 International Consensus on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) Science with Treatment Recommendations (CoSTR) for neonatal life support (NLS) with thorough evidence evaluation (Table 1) [14].

2.1. Perinatal Mortality in Low- and Middle-Income Countries

The global perinatal and neonatal deaths are estimated to be 4 million per year, and of that, about 98% occur in low- and middle-income countries (LMICs) [15–17]. Despite the sustained focus on reducing neonatal mortality by various international and local health organizations, neonatal deaths have increased in the relative contribution for under-5 child deaths [18]. Intrapartum asphyxia accounts for about 2 million stillbirths and neonatal deaths/year [17, 19–21] and results in long-term neurodevelopmental disabilities in about 1 million survivors/year [22] with a loss of about 41 million disability-adjusted life years/year [23]. Failure to initiate breathing after birth is the primary reason for death and disability in infants with birth asphyxia [24]. Lack of access to optimal resuscitation at birth is a preventable
cause of death that is responsible for the majority of the perinatal and neonatal deaths in LMICs [10, 11, 25].

2.2. Resuscitation-Related Research in LMICs. The majority of resuscitation-related research that informs ILCOR neonatal resuscitation recommendations is from high-income countries. In the current ILCOR NLS-CoSTR, only 20 of a total of 96 of the referenced original science studies are from LMICs [14], and the majority of them are small sample size studies that have a limited grade of evidence. Interventional research can help identify the best management approach for a given disease or condition. This highlights the urgent need for enhancing resuscitation-related research for improving perinatal and neonatal outcomes in LMICs.

2.3. Why More Resuscitation-Related Research Is Needed from LMICs. The evidence from interventional research is specific for the environment and patient characteristics that it is tested and cannot be simply extrapolated to other settings. The research from high-income countries may not be applicable to low resource settings of LMICs because of differences in nutritional, environmental, socioeconomic, and genetic factors. Also, the ancillary resources and trained healthcare providers needed for a specific intervention may not be available. The application of the intervention without appropriate monitoring and follow-up may result in an increase in the risk of adverse outcomes. For example, several therapeutic hypothermia trials from high-income countries show benefits in survival and neurodevelopmental outcomes [26–28], establishing its role as a standard of care in infants with perinatal hypoxic-ischemic encephalopathy in high-income countries. However, as shown in the recently completed therapeutic hypothermia trial from LMICs, including infants from public sector neonatal units, infants in the therapeutic hypothermia group had increased mortality without any difference in severe disability in survivors.

Table 1: 2020 CoSTR topics reviewed and evidence evaluation process [14].

| Sr. no. | Topic                                      | Subtopic                                      | Process               | Studies from LMICs |
|--------|--------------------------------------------|----------------------------------------------|-----------------------|--------------------|
| 1      | Anticipation and preparation                | Prediction of need of respiratory support in the delivery room | Evidence update       | No                 |
|        |                                             | Effect of briefing/debriefing following neonatal resuscitation | Scoping review        | No                 |
| 2      | Initial assessment and intervention         | Warming adjuncts                              | Evidence update       | No                 |
|        |                                             | Suctioning of clear fluid                    | Scoping review        | No                 |
|        |                                             | Tracheal intubation and suction of nonvigorou meconium-stained newborns | Systematic review     | Yes                |
| 3      | Physiological monitoring and feedback devices | Heart rate monitoring during neonatal resuscitation | Evidence update       | No                 |
|        |                                             | Sustained inflation                           | Systematic review     | Yes                |
|        |                                             | Positive end-expiratory pressure (PEEP) versus no PEEP | Evidence update       | No                 |
|        |                                             | Continuous positive airway pressure (CPAP) versus intermittent PPV | Evidence update       | No                 |
| 4      | Ventilation and oxygenation                 | T-piece resuscitator versus self-inflating bag for ventilation | Scoping review        | Yes                |
|        |                                             | Oxygen for preterm resuscitation             | 2019 CoSTR publication | No                 |
|        |                                             | Oxygen for term resuscitation                | 2019 CoSTR publication | No                 |
| 5      | Circulatory support                         | CPR ratios for neonatal resuscitation        | Evidence update       | No                 |
|        |                                             | 2-thumb versus 2-finger compressions for neonatal resuscitation | Evidence update       | No                 |
| 6      | Drug and fluid administration                | Epinephrine (adrenaline) for neonatal resuscitation | Systematic review     | No                 |
|        |                                             | Intravascular versus umbilical vein for emergency access | Systematic review     | No                 |
|        |                                             | Volume infusion during neonatal resuscitation | Evidence update       | No                 |
|        |                                             | Sodium bicarbonate during neonatal resuscitation | Evidence update       | No                 |
| 7      | Prognostication during CPR                  | Impact of duration of intensive resuscitation | Systematic review     | No                 |
| 8      | Postresuscitation care                       | Rewarming of hypothermic newborns            | Evidence update       | No                 |
|        |                                             | Induced hypothermia in settings with limited resources | Evidence update       | Yes                |
|        |                                             | Postresuscitation glucose management         | Evidence update       | No                 |
and availability of resources should be ensured, as resources
remaining availability of adequately trained healthcare providers
and the effectiveness of interventions, prior to adoption for a given set-
be carefully introduced while monitoring the responses for
vidual settings within LMICs [30–34]. Interventions should
Evidence from LMICs.
2.4. Areas of Resuscitation-Related Research Needing More
Evidence from LMICs. Insufficient evidence from LMICs
has led to knowledge gaps that are major barriers to the
improvement of perinatal and neonatal outcomes in LMICs. There are several areas of neonatal resuscitation-related
research that need better evidence from LMICs. Some of
the research gaps include optimal oxygenation targets for
resuscitation of preterm infants, therapeutic hypothermia
for infants with perinatal depression from centers with
higher levels of care, delivery of respiratory support at
specific gestational age groups and testing of various inter-
faces, optimal thresholds, method, route, doses, and timing of
various resuscitation-related interventions like chest com-
pressions, epinephrine, volume expanders, and inotropes
[14]. As outcomes of infants who are enrolled in inter-
vensional trials and the survivors getting admitted for intensive
care may not be representative of the overall population, it
is also essential to set up a collaborative registry of infants
needing resuscitation at delivery from multiple institutes
to better evaluate the outcomes of all infants with various
conditions and those receiving different interventions. In
addition to reporting hospital outcomes, efforts should be
made to evaluate the long-term outcomes of infants
enrolled in interventional trials, including 2-year neurode-
velopmental and school-age outcomes using standardized
assessment tools.

2.5. Future Directions. There needs to be a sustained effort
towards improving the amount and quality of neonatal
resuscitation-related research for informing evidence-based
strategies from LMICs. Strengthening research infrastruc-
ture and supporting investigators with enhanced govern-
mental and philanthropic research funding can help
support quality neonatal research from LMICs. The creation
of international, national, and interinstitutional research
networks for collaboration, peer evaluation of research pro-
jects, and monitoring of ongoing projects can help stream-
line research efforts in LMICs. Efforts targeted towards
training and mentoring early career investigators from
LMICs can harness and promote the expertise and training
needed for neonatal research.

Data Availability

No original data was used in the current review.

Conflicts of Interest

All authors have indicated they have no potential conflicts of
interest to disclose.

Authors’ Contributions

VVS conceptualized and drafted the initial manuscript and
reviewed and revised the manuscript. SMN conceptualized,
reviewed, and revised the manuscript. All authors approved
the final manuscript for submission and agree to be account-
able for all aspects of the work.

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