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TITLE: Outcome of infants with 10-min Apgar score of 0-1 in a low-resource setting

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ABSTRACT

Background: In high resource settings, postponing the interruption of cardio-pulmonary resuscitation from 10 to 20 minutes after birth has been recently suggested, but data from low-resource settings are lacking. We investigated the outcome of newborns with Apgar score of 0-1 at 10 minutes of resuscitative efforts in a low-resource setting.

Methods: This observational sub-study from the NeoSupra trial included all 49 late preterm/full-term newborns with Apgar score of 0-1 at 10 minutes of resuscitation. The study was carried out at Mulago National Referral Hospital (Kampala, Uganda) between May 2018 and August 2019. Outcome measures were mortality and hypoxic–ischemic encephalopathy in the first week of life. All resuscitations were video-recorded and daily reviewed by trial researchers.

Results: Median duration of resuscitation was 32 minutes (interquartile range 17-37). Advanced resuscitation was provided to 21/49 neonates (43%). Overall, 48 neonates (98%) died within two days of life (44 in the delivery room, three at the first day and one at the second day) and one survived at one week with severe hypoxic–ischemic encephalopathy.

Conclusion: Our study adds information from a low-resource setting to the recent evidence from high-resource settings about prolonging the resuscitation in infants with Apgar scores of 0-1 at 10 minutes. The vast majority died in in the delivery room despite prolonged resuscitative efforts. We confirm that duration of resuscitation should be tailored to the setting, while the focus in low-resource settings should be improving the quality of antenatal and immediately-after-birth care.

INTRODUCTION

Apgar score is a clinical tool that is used worldwide to describe neonatal status immediately after birth (1). In addition, this score can help the health care staff drive the resuscitation process and may influence the decision to interrupt the resuscitative efforts in case of an Apgar score of 0 (absence of detectable heart rate and other signs of life) at 10 minutes (2). Nonetheless, such neonates may show further improvements because of inadequate heart rate detection or fetal/neonatal adaptive response to transition (3,4).

The appropriate duration of cardio-pulmonary resuscitation (CPR) in neonates with absent or incomplete response is a continuous matter of debate, because of the trade-off between survival (stopping too early when return of spontaneous circulation is still achievable) and neurodevelopmental outcome (persisting too long may grant survival but with significant neurodevelopmental impairment).

In 2015, the International Liaison Committee on Resuscitation (ILCOR) suggested that the decision of discontinuing CPR after 10 minutes of sustained resuscitative efforts, when the heart rate was still undetectable, could be reasonable but was left to the health care provider (2). However, the low level of evidence resulted in a weak recommendation. In 2020, the ILCOR revised the previous recommendation and suggested considering a change of goals of care if the newborn has not responded to recommended steps of resuscitation as appropriate to the given setting (5). This change was based on additional information from recent literature but was still considered a weak recommendation based on very low-certainty evidence (6). Furthermore, the evidence came from studies conducted in high-resource settings, thus such indications should be customized in low-resource settings where the quality of antenatal and neonatal care is limited, neuroprotective strategies not accessible, and advanced and prolonged resuscitative efforts may not be an option

(6,7). Data on outcome of newborns receiving prolonged resuscitation in low resource settings is needed to provide information about the possible customization of these recommendations.

This study aimed to investigate the outcome of newborns with an Apgar score of 0-1 at 10 minutes of resuscitative efforts in a low-resource setting.

METHODS

Study design

This is an observational sub-study from the NeoSupra trial (8) describing characteristics and outcome of newborns with an Apgar score of 0-1 at 10 minutes of life. The study was carried out at the Department of Obstetrics and Gynecology, Mulago National Referral Hospital, Kawempe Division in Kampala, Uganda between May 2018 and August 2019. The neonatal intensive care unit (NICU) offered supplemental oxygen and nasal continuous positive airway pressure, while mechanical ventilators, continuous monitoring and therapeutic hypothermia were not available. The trial protocol was approved by the Uganda National Council for Science and Technology (MHREC 1168) and the Regional Committee for Medical and Health Research Ethics (REK South East ref. n. 2017/989) in Norway. Mothers of eligible infants gave written consent to participate in the trial and use data for scientific purpose.

Patients

In the trial, newborns with gestational age ≥34 weeks, expected birth weight ≥2000 g and need for positive pressure ventilation at birth were eligible for inclusion. Neonates with major malformations (incompatible with sustained life or affecting the airways) and stillbirths were excluded (8). In this sub-study, we selected the subset of newborns with an Apgar score of 0-1 at 10 minutes of life.

Procedures

Details about trial procedures have been previously reported (8). Briefly, all midwives who were involved in neonatal resuscitation participated in a 1-day Helping Babies Breathe (HBB, 2nd edition) course (9) including an additional module for using the laryngeal mask airway. Neonates were cared for following an updated Mulago Hospital neonatal resuscitation flowchart based on Helping Babies Breathe program. Heart rate was assessed by using a stethoscope. HBB-trained health staff on duty performed basic resuscitation (initial steps, facemask/ laryngeal mask ventilation), while advanced resuscitation (endotracheal intubation, chest compressions, medications) was initiated by a physician when available (2). The severity of hypoxic–ischemic encephalopathy was assessed using the Thompson score by a trial doctor masked to the ventilation device (10). All resuscitations were video-recorded and daily reviewed by trial researchers.

Data collection

Maternal and neonatal characteristics (including Apgar score at 1, 5 and 10 minutes), information on resuscitation interventions and outcome (NICU admission, Thompson score, mortality) were retrieved from the database of the main trial. Research assistants monitored each resuscitation and collected times and data in the main trial (8). Moderate-to-severe hypoxic–ischemic encephalopathy (HIE) was based on a Thompson score of 11 or higher at day 1 to 5 during hospitalization.

Data analysis

Categorical data were summarized as number and percentage, whereas continuous data were summarized as median and interquartile range. This sub-study had a descriptive purpose and mainly involved descriptive statistics. In addition, the comparison between infants who received vs. those who did not receive advanced resuscitation was added to provide more information to the reader. The comparisons were performed using Mann-Whitney test (continuous data) and Chi Square test or

Fisher's exact test (categorical data). All tests were 2-sided and a p-value less than 0.05 was considered statistically significant. Data were analyzed using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria) (11).

RESULTS

Among the 1,163 newborns who were included in the main trial, 49 (4.2%) had an Apgar score of 0-1 at 10 minutes of life. Maternal and neonatal characteristics are reported in Table 1. Advanced resuscitation was provided to 21 neonates (43%). Forty-four neonates (90%) deceased in the delivery room (no Thompson score available), while five (10%) were admitted to the NICU (one neonate with Apgar 0 and four neonates with Apgar 1 at 10 minutes). Three of them (6%) died within 24 hours (Thompson score of 15 and 19 in two neonates; not available in one neonate) and one (2%) died at two days of life (Thompson score of 16). Only one neonate was alive at the end of the study period (7 days) and recorded Thompson scores of 13-8-9-12-14 from day 1 to 5 (Figure 1).

When comparing infants who received vs. those who did not receive advanced resuscitation, we did not find statistically significant differences in mortality and characteristics, apart from primiparous mothers and delivery through cesarean section, which were more frequent in infants who received advanced resuscitation (Table 2).

DISCUSSION

Our findings showed an unfavorable outcome of late preterm/full-term infants with Apgar score of 0-1 at 10 minutes of resuscitation efforts in a low-resource setting. The vast majority died in the delivery room despite prolonged resuscitative efforts, and the only survivor at 7 days of age experienced a severe HIE.

To our knowledge, this is the first detailed report on such infants in low-resource settings. A recent ILCOR review of the dedicated literature identified 16 studies from high-resource settings (United States, United Kingdom, Australia, Canada, Japan) including 579 infants in need for CPR at 10 minutes after birth (6), thus highlighting the lack of information from middle- and low-resource settings. In the subset of 350 infants with ≥36 weeks gestation, the review reported an overall survival of 54% and survival without moderate/severe impairment of 14%. The authors concluded that such infants are at high risk for mortality and neuro-disability, but survival without neuro-disability is possible. Unfortunately, our findings suggest that such conclusion is unlikely in settings with limited quality of antenatal, perinatal and postnatal care (including mechanical ventilation and neuroprotective strategies). Our data revealed an overall unfavorable outcome (death or HIE) in all late preterm/full-term infants with Apgar score of 0-1 at 10 minutes, who were burdened by 96% mortality within 24 hours of life. Of note, the presence of a caregiver capable to provide advanced resuscitation did not impact the mortality.

In high resource settings, stopping the resuscitative efforts before 10 minutes could harm some infants who may survive without neuro-disability, and considering a change in goals of care has recently been suggested if the newborn has not responded to recommended steps of resuscitation as are appropriate to the given setting (5,12,13). Hence, this decision should be tailored according to clinical aspects (including gestational age, presumed etiology, therapeutic options, and reversibility of the situation) and the parents' willing (who should be informed about the potential risk of morbidity) (6). In our study, we found an overall unfavorable outcome despite an average duration of resuscitation of 30 minutes, thus we confirm that the discussion on discontinuing resuscitation and changing the goals of care should be tailored to the setting (2,5). Of note, improving survival of asphyxiated newborns implies the potential burden of chronic health care due to long-term

neurological disability and impairment (6,15). This burden is even more relevant in settings where the resources and the access to the health care system are limited (16).

The main strength of this study is the quality of data thanks to the presence of a research assistant, the use of a clinical tool for the evaluation of HIE (Thompson score) and the videorecording of all resuscitations. Nonetheless, some limitations should be considered when interpreting the results. First, some study features (single center, small sample size and eligibility criteria) limited the generalizability of the findings. Second, the implementation of the main trial was likely to improve midwife skills (8), thus reducing the incidence of Apgar score of 0-1 at 10 minutes. Third, advanced resuscitation could be provided to less than half of infants (when a physician was available), but this is a common situation in low-resource settings.

CONCLUSIONS

Our study adds information from a low-resource setting to the recent evidence from high-resource settings about prolonging the resuscitation in infants with Apgar scores of 0-1 at 10 minutes. The vast majority died in in the delivery room despite prolonged resuscitative efforts. We confirm that the discussion on discontinuing resuscitation and changing the goals of care should be tailored to the setting. In low-resource settings, the focus should be improving the quality of antenatal and immediately-after-birth care.

Contributors' Statement:

Mr. Cavallin was contributed to data analysis, data interpretation, and writing of the manuscript.

Dr. Myrnerts Höök contributed to data collection, data interpretation, and critically reviewed the manuscript.

Dr. Pejovic contributed to data collection, data interpretation, and critically reviewed the manuscript.

Dr. Byamugisha contributed to data collection, data interpretation, and critically reviewed the manuscript.

Dr. Nankunda contributed to data collection, data interpretation, and critically reviewed the manuscript.

Prof. Tylleskär conceived the study, and contributed to data interpretation, and writing of the manuscript.

Prof. Trevisanuto conceived the study, and contributed to data interpretation, and writing of the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- In high resource settings, postponing the interruption of cardio-pulmonary resuscitation from 10 to 20 minutes after birth has been recently suggested.
- Outcome of newborns with Apgar score of 0-1 at 10 minutes of resuscitative efforts in low-resource setting is unknown.

WHAT THIS STUDY ADDS

- The vast majority of newborns with Apgar score of 0-1 at 10 minutes died in in the delivery room despite prolonged resuscitative efforts.
- The discussion on discontinuing resuscitation and changing the goals of care should be tailored to the setting.
- In low-resource settings, the focus should be improving the quality of antenatal and immediately-after-birth care.

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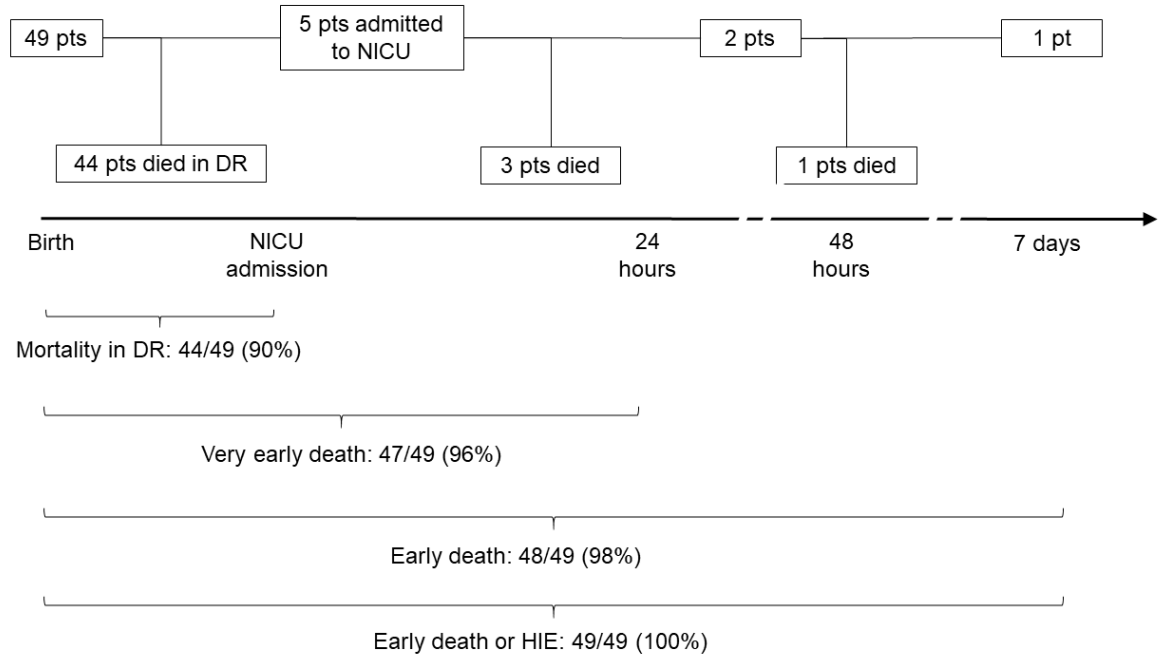
FIGURE

Figure 1. Timeline of study patients. DR: delivery room. NICU: neonatal intensive care unit.

HIE: moderate-to-severe hypoxic–ischemic encephalopathy (based on a Thompson score of 11

or higher at day 1 to 5 during hospitalization). Figure created by authors.

TABLES

Table 1. Characteristics of neonates with an Apgar score of 0-1 at 10 minutes of life.

Maternal and delivery characteristics	N (%) or median (interquartile range)
Maternal age, years	22 (20-26)
At least one antenatal visit	49 (100%)
Primiparous	30 (61%)
Amniotic fluid: Clear amniotic fluid Meconium stained and/or foul smelling	8 (16%) 41 (84%)
Mode of delivery: Vaginal delivery Vaginal delivery by vacuum extraction Cesarean section	18 (37%) 1 (2%) 30 (61%)
Neonatal characteristics	**N (%) or median (interquartile range)**
Males	27 (55%)
Multiple birth	1 (2%)
Birth weight, grams	3200 (2960-3400)
Time to resuscitation table, seconds	39 (26-59)
Apgar score at 1 minute of life	1 (1-2)
Apgar score at 5 minutes of life	1 (1-2)
Apgar score at 10 minutes of life: 0 1	17 (35%) 32 (65%)
Resuscitation interventions	**N (%)**
Ventilation device: Laryngeal mask Facemask	29 (59%) 20 (41%)
Tracheal intubation	6 (12%)
Chest compressions	15 (31%)
Intravenous drugs	7 (14%)
Duration of resuscitation, minutes [a]	32 (17-37)

[a] The duration of resuscitation ranged from 10 to 44 minutes.

Table 2. Comparison between infants who received vs. those who did not receive advanced resuscitation

Variable	Infants who received advanced resuscitation (n=21)	Infants who did not receive advanced resuscitation (n=28)	p-value
Maternal and delivery characteristics	**N (%) or median (interquartile range)**	**N (%) or median (interquartile range)**	
Maternal age, years	20 (20-24)	23 (20-28)	0.43
At least one antenatal visit	21 (100%)	28 (100%)	-
Primiparous	17 (81%)	13 (46%)	0.02
Amniotic fluid:			0.99
Clear amniotic fluid	3 (14%)	5 (18%)	
Meconium stained and/or foul smelling	18 (86%)	23 (82%)	
Mode of delivery:			0.04
Vaginal delivery	4 (19%)	14 (50%)	
Vaginal delivery by vacuum extraction	1 (5%)	0 (0%)	
Cesarean section	16 (76%)	14 (50%)	
Neonatal characteristics	**N (%) or median (interquartile range)**	**N (%) or median (interquartile range)**	
Males	11 (52%)	16 (57%)	0.78
Multiple birth	0 (0%)	1 (4%)	0.99
Birth weight, grams	3200 (3000-3500)	3200 (2908-3400)	0.35
Time to resuscitation table, seconds	40 (26-56)	34 (22-100)	0.93
Apgar score at 1 minute of life	1 (1-2)	1 (1-2)	0.99
Apgar score at 5 minutes of life	1 (1-2)	1 (1-2)	0.47
Apgar score at 10 minutes of life:			0.07
0	4 (19%)	13 (46%)	
1	17 (81%)	15 (54%)	
Resuscitation interventions	**N (%)**	**N (%)**	
Ventilation device:			0.78
Laryngeal mask	13 (62%)	16 (57%)	
Facemask	8 (38%)	12 (43%)	
Duration of resuscitation, minutes [a]	34 (30-40)	29 (16-35)	0.11
Mortality	**N (%)**	**N (%)**	
Mortality in the delivery room	19 (90%)	25 (89%)	0.99
Mortality in the delivery room or neonatal intensive care unit	21 (100%)	27 (96%)	0.99