Delayed Cord Clamping in Newborns Born at Term at Risk for Resuscitation: A Feasibility Randomized Clinical Trial

Anup C. Katheria, MD[1], Melissa K. Brown, RRT[1], Arij Faksh, DO[2], Kasim O. Hassen, RRT[1], Wade Rich, RRT[1], Danielle Lazarus, RRT[1], Jane Steen, RN[1], Shahram Sean Daneshmand, MD[2], and Neil N. Finer, MD[1]

Infants may benefit if resuscitation could be provided with an intact umbilical cord. Infants identified at risk for resuscitation were randomized to 1- or 5-minute cord clamping. The 5-minute group had greater cerebral oxygenation and blood pressure. Studies are needed to determine whether this translates into improved outcomes. *(J Pediatr 2017;187:313-7).*

Trial registration ClinicalTrials.gov: NCT02827409.

Delayed cord clamping (DCC) in newborns born at term has not been shown to affect neonatal death or morbidity outcomes.[1,2] Because of the complexity of providing supportive interventions with the umbilical cord intact, most subjects in published studies have not required resuscitation. This has prompted the American Academy of Pediatrics and the International Liaison Committee on Resuscitation to acknowledge that there is insufficient evidence to recommend an approach to cord clamping for newborns who require resuscitation at birth.[3,4]

The timing of "late" cord clamping is variable, ranging from 30 seconds to 5 minutes or to when the cord stops pulsating. Currently, infants requiring resuscitation do not benefit from DCC because of the practice of removing the infant from the mother to perform resuscitation. The primary driver of cutting the cord of an unstable infant is the determined need for resuscitation intervention. Recently, we and others have demonstrated the benefits of using a bedside trolley (LifeStart; Inditherm Medical, Rotherham, United Kingdom) that allows resuscitation interventions to be initiated while the cord remains intact for 60-90 seconds.[5-7] We have shown that DCC for 5 minutes improves cardiac output in healthy infants born at term after vaginal birth.[8] Infants at risk for resuscitation may benefit from extended placental transfusion by increased blood volume and potentially improved outcomes. The establishment of ventilation before cord clamping facilitates the transition from fetal circulation and gas exchange in the lung, which is critical for adequate oxygenation of the brain.[9] We hypothesized that in infants born at term at risk for resuscitation, 5-minute DCC with the use of resuscitation interventions compared with 1-minute DCC (or sooner if requiring resuscitation) would improve transition at birth and increase cerebral tissue oxygen saturation (StO_2) as measured by near-infrared spectroscopy at 12 hours of life.

BP	Blood pressure
DCC	Delayed cord clamping
FTOE	Fractional cerebral tissue oxygen extraction
HR	Heart rate
NICU	Neonatal intensive care unit
SpO_2	Peripheral arterial oxygen saturation
StO_2	Cerebral tissue oxygen saturation

Methods

We conducted a randomized controlled trial (ClinicalTrials.gov: NCT02827409) of vaginally delivered neonates ≥37 weeks' gestational age who required the attendance of a neonatal provider (neonatal nurse practitioner, advance life support nurse, and/or physician) because of an at-risk delivery. The institutional review board of Sharp Health Care approved the study. At our institution, the criteria for the attendance of a neonatal provider included infants with a fetal heart rate (HR) tracing showing minimal-absent variability, recurrent fetal HR decelerations, prolonged tachycardia or bradycardia, shoulder dystocia, fetal malpresentation, vacuum- or forceps-assisted vaginal delivery, and meconium-stained amniotic fluid. Exclusion criteria were planned or progression toward cesarean delivery, multiple gestations, or known congenital anomalies (**Figure 1**; available at www.jpeds.com). If there was a placental abruption, nonreducible nuchal cord or a cord accident, or avulsion at the time of delivery, the infant was excluded.

Subjects were identified by prescreening mothers in labor and delivery by research coordinators or by notification of the research team from the neonatal or obstetrical provider. Written informed consent was obtained from the parent by an investigator before delivery. Because the neonatal team needed to be adjacent to the mother to provide resuscitation, they could not be blinded to the intervention.

At delivery, the attending team randomized (via computer-generated sequentially numbered opaque envelopes) each infant to receive 1-minute or 5-minute DCC. Infants randomized to the 1-minute group had their umbilical cord clamped and cut by 1 minute and were placed either on the mother's abdomen or, if depressed the cord was cut immediately (within seconds), they were transitioned to the radiant warmer. Resuscitation was defined as receiving stimulation to breathe, blow by oxygen,

From the [1]Department of Perinatology, Neonatal Research Institute at Sharp Mary Birch Hospital for Women and Newborns, San Diego, CA; and [2]San Diego Perinatology, Sharp Mary Birch Hospital for Women and Newborns, San Diego, CA

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or positive pressure ventilation by endotracheal tube or mask. After the cord was cut, a pulse oximeter (Radical-7; Masimo Corporation, Irvine, California) was placed on a preductal site by the respiratory therapist. HR was first determined by a handheld Doppler probe (2 MHz, Sonoline B; Crucial Medical Systems, Shenzhen, China) and then by the pulse oximeter, which also displayed the peripheral oxygenation (SpO_2). A member of the research team attending the delivery called out both values. Data were downloaded from the pulse oximeter following delivery. Clamping time was determined by the Apgar timer and recorded.

Infants randomized to the 5-minute group were placed on the mother's abdomen if vigorous. Otherwise, they were placed on the LifeStart bed, which was equipped with resuscitation tools (**Figure 2**; available at www.jpeds.com) (oxygen/air blender, Neopuff Infant T-Piece Resuscitator [Fisher & Paykel Healthcare, Auckland New Zealand], portable suction). Resuscitation interventions (warm dry and stimulate initially if apneic, oxygen and/or ventilation if needed based on spontaneous breathing, SpO_2, or HR) were equivalent to the 1-minute group. If the infant did not have adequate breathing (continued need for ventilation or oxygen), clamping was delayed past the 5-minute cutoff until the infant transitioned (stable HR and SpO_2), the cord stopped pulsating, or the placenta was delivered. The research team documented all resuscitation measures at the time of the intervention.

Demographics and follow-up data were collected from all infants either in the neonatal intensive care unit (NICU) or the postpartum floor at 12 hours of life by the research team, who were blinded to the infants' group assignment. This included the primary endpoint, the StO_2, which was obtained via near-infrared spectroscopy (Foresite Monitor; Casmed, Branford, Connecticut) from a sensor placed on the forehead. The fractional cerebral tissue oxygen extraction (FTOE) was calculated ($SpO_2 - StO_2/SpO_2$) and recorded. Noninvasive blood pressure (BP) (Dash 3000; General Electric, Fairfield, Connecticut), HR, SpO_2, and a noninvasive hemoglobin from the oximeter acquired with the Rainbow R1-20L adhesive sensor (Masimo Corporation) also were collected at 12 hours of life.

A previous study of early and late cord clamping in infants born preterm demonstrated a 3% difference in StO_2 at 24 hours of age (68 and 71, respectively).[10] Based on these previous data, at least 13 infants in each group would be required to achieve a power of 95% and an alpha of 0.05. Given that only a percentage of infants in the trial were expected to require extensive resuscitation, a larger sample of 60 subjects (n = 30 in each arm) was chosen.

We performed statistical analyses using PASW Statistics 22.0 (SPSS Inc, Chicago, Illinois). Normally distributed continuous outcome variables were compared with the unpaired Student *t* test, and nonparametric continuous outcome variables were analyzed with the Mann-Whitney *U* test. For repeated measurements tests, R (R Foundation for Statistical Computing, Vienna, Austria) and lme4 (linear mixed-effects models using Eigen and S4) were used to perform linear mixed-effects regression (lmer) analysis of the relationship between the respective treatments. Two-sided $P < .05$ was considered significant.

Table I. Demographics

Demographics	1-Minute DCC group (n = 30)	5-Minute DCC group (n = 30)	*P* value
Gestational age, wk, mean ± SD	39 ± 1.0	39 ± 1.0	.41
Birth weight, g, mean ± SD	3399 ± 510	3440 ± 523	.39
Male, n (%)	16 (53)	17 (56)	.99
Nonreassuring fetal HR, n (%)	14 (47)	13 (43)	.99
Meconium-stained amniotic fluid, n (%)	19 (63)	19 (63)	.99
Instrumentation needed for delivery, n (%)	6 (20)	2 (7)	.25
Time to cord clamping, s, mean ± SD	69 ± 35	348 ± 115	<.001
Cord pulsating when clamped, n (%)	27 (90)	6 (20)	<.001
Time to first breath/cry, s, mean ± SD	36 ± 61	25 ± 42	.43
Breathing before cord clamping, n (%)	25 (83)	30 (100)	.05
1-Minute Apgar, median (Q1, Q3)	8 (8, 8)	8 (9, 9)	.39
5-Minute Apgar, median (Q1,Q3)	8 (8, 8)	9 (9, 9)	.16

Q, quartile.

Results

Sixty infants were randomized (n = 30 per group) from August 2016 to September 2016. The mean times for DCC in the 1-minute and 5-minute groups were 1 minute, 9 seconds and 5 minutes, 48 seconds, respectively ($P < .001$, **Table I**). The rates of resuscitation for 1- and 5-minute groups were 63 (19/30) and 43 (13/30) ($P = .20$, **Figure 3**). There were 8 infants who required admission to the NICU (6 in the 1-minute and 2 in the 5-minute group, $P = .25$) for poor transition and/or tachypnea. No infants were diagnosed with hypoxic ischemic encephalopathy or required therapeutic hypothermia. Two infants (1-minute group) required oxygen at the 12-hour endpoint. One required 26% oxygen, 2-liter high flow nasal cannula. The second infant developed severe persistent pulmonary hypertension and was transferred at 24 hours of life. There were no differences between groups in HR (**Figure 3**) or SpO_2 (**Figure 3**) for the first 5 minutes in the overall group, but infants undergoing 5-minute DCC who did not receive supplemental oxygen or positive pressure ventilation had greater SpO_2 levels at 3 and 4 minutes of life ($P = .03$, **Figure 3**). There were no differences in postnatal noninvasive hemoglobin, bilirubin, SpO_2, or HR at 12 hours of life. Infants in the 5-minute group had greater mean BP (53 ± 13 vs 47 ± 7, $P = .02$), StO_2 (82 ± 5 vs 79 ± 7, $P = .02$), and decreased FTOE (0.15 ± .05 vs 0.18 ± .06, $P = .03$, **Table II**) compared with the 1-minute cord-clamping group.

Discussion

This randomized clinical trial evaluated 1 vs 5 minutes of DCC in newborns born at term at risk for resuscitation. We demonstrated that 5-minute DCC could be accomplished safely without compromising the ability to perform resuscitation and was associated with increased StO_2, decreased FTOE, and greater BP at 12 hours of life. Immediate improvements in postnatal transition, such as greater SpO_2, were identified in newborns not requiring supplemental oxygen or positive pressure

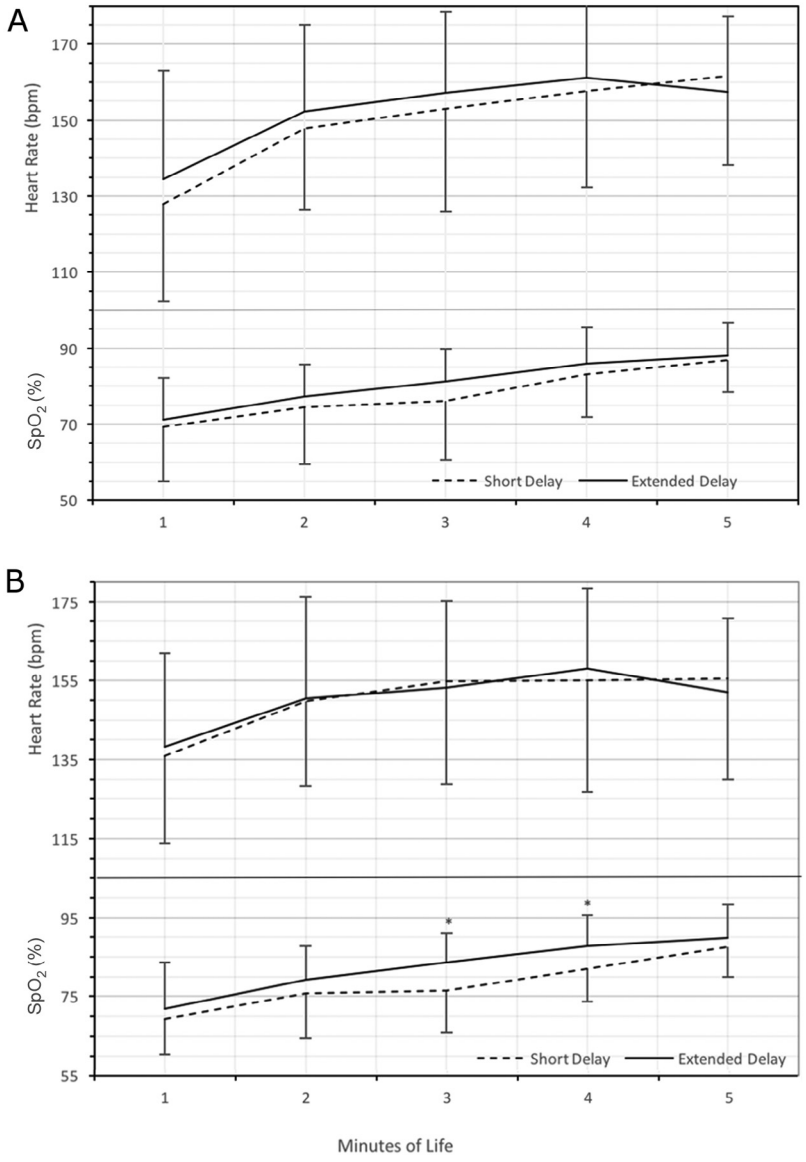

Figure 3. **A,** HR and SpO_2 over the initial 5 minutes of life in all subjects. **B,** HR and SpO_2 over the initial 5 minutes of life in subjects not requiring supplemental oxygen or positive pressure ventilation.

ventilation. Although the number of resuscitation interventions was low and not significantly different, there was a trend for less resuscitation and improved Apgar scores in the 5-minute DCC group. We believe the longer delay yielded a greater blood volume and increased pulmonary circulation and cardiac output, allowing greater oxygen delivery to the tissues and decreased need for resuscitation interventions.

BP increases normally after birth, and a wide range of values are observed at any specific hour of life.[11-13] Mean BP values were significantly greater at 12 hours of life in the infants in the 5-minute DCC group. We did not have the power to correlate BP to outcomes. Asphyxiated infants born at term developing intraventricular hemorrhage present more frequently with hypotension.[14] Although the BP values in this study were within normal limits, a 5-minute DCC combined with resuscitation interventions as needed may have beneficial effects on infants who have significant cardiac dysfunction such as those with asphyxia.

Infants in the 5-minute group showed an increase in cerebral StO_2 and a decrease in FTOE, which could be consistent with a greater placental transfer.[8] Cerebral StO_2 correlates with cerebral blood flow in neonates born at term.[15] Baenziger et al[10] reported increased StO_2 for the first 24 hours in infants born premature who received 60-90 seconds of DCC as compared with immediate cord clamping. Both lower StO_2 and increased FTOE have been associated with reduced hemoglobin and brain injury. El-Dib et al[16] studied 72 infants born premature and demonstrated by regression models that cerebral FTOE correlated negatively with hemoglobin and increased in patients with either periventricular leukomalacia or severe intraventricular hemorrhage. In addition, a lower BP and StO_2 also may be linked to poor outcomes. Alderliesten et al[17] studied

Table II. Neonatal outcomes

Outcomes	1-Minute DCC group (n = 30)	5-Minute DCC group (n = 30)	*P* value
Rate of resuscitation, n (%)	19 (63)	13 (43)	.20
Required only stimulation to breathe, n (%)	9 (30)	8 (27)	.99
Required supplemental oxygen, n (%)	15 (50)	8 (27)	.11
Required mask positive pressure ventilation, n (%)	5 (17)	2 (7)	.42
Required intubation, n (%)	1 (3)	1 (3)	.99
Required chest compressions or epinephrine, n (%)	0	0	.99
NICU admission, n (%)	6 (20)	2 (7)	.25
Mean blood pressure, 12 h, mean ± SD	47 ± 7	53 ± 13	.02
HR, 12 h, mean ± SD	125 ± 14	121 ± 14	.33
SpO_2, 12 h, mean ± SD	97 ± 3	98 ± 3	.34
Hemoglobin from oximeter, 12 h, mean ± SD	14.1 ± 1.8	15.4 ± 2.7	.06
Cerebral oxygenation, 12 h, mean ± SD	79 ± 7	82 ± 5	.02
FTOE, 12 h, mean ± SD	0.18 ± 0.06	0.15 ± 0.05	.03
24-h bilirubin level (serum or transcutaneous), mean ± SD	6.09 ± 2.5	5.7 ± 2.1	.56
Discharge weight, mean ± SD	3489 ± 1346	3471 ± 1343	.96
Number of days hospitalized, mean ± SD	3.4 ± 1.8	3 ± 1.0	.23
Breastfeeding at discharge, n (%)	30 (100)	27 (90)	.24

neonates born premature with hypotension and found low StO_2 was correlated with poor neurodevelopmental outcome.

Newborns who don't establish adequate respirations before DCC are more likely to have increased morbidity and death.[18] Although the majority of infants in our trial did not need extensive resuscitation (mostly stimulation and/or oxygen), the mean time for onset of breathing was greater than 20 seconds in both arms. There were 5 infants in the 1-minute group who were still not breathing by 1 minute. Infants in both arms who were not breathing initially may have had early cord clamping before the onset of breathing had we not placed the baby on the trolley and performed stimulation to encourage breathing. Although there was no difference in the onset of breathing between groups, providing stimulation or resuscitation during DCC may provide benefit in infants who otherwise have inadequate breathing or spontaneous ventilation before clamping of the umbilical cord.

There are limitations to our trial. This was a pilot study, so small physiological improvements should not be interpreted as clinical improvement and evidence for a change in practice. The design of the intervention did not allow for blinding of the clinical team at the bedside. Several of our measurements were taken at a single time point: StO_2, hemoglobin, and BP were collected only at 12 hours of life, and a continuous measurement may have yielded a different result.[19] A lack of difference in hemoglobin, bilirubin, and SpO_2 at 12 hours may have been due to our small sample size. We also found that our method of identifying potential subjects at risk did not accurately predict an infant who would require resuscitation, and overall few infants require aggressive resuscitation. There were several infants who were excluded or not approached because they progressed to cesarean delivery for fetal distress or other indications. Hence, it is possible we may have missed a sicker population that could have had greater benefit from a placental transfusion. We chose not to include infants delivered via cesarean because waiting 5 minutes until cord clamping has not been well studied in the operative field, due to an open uterus, prolonged anesthetic, and there could have been theoretical maternal morbidity such as blood loss. Furthermore, the mode of delivery may alter the efficacy of a placental transfusion. DCC also results in decreased placental transfusion compared with cord milking at cesarean delivery, as shown by markers such as hemoglobin, systemic blood flow, BP, and urine output.[20] Cord milking may be a useful alternative in a situation in which resuscitation is required at cesarean delivery, but this needs further study. The trial included a large proportion of meconium deliveries; however, many infants responded to tactile stimulation or positive pressure ventilation, and none of them required intubation.

Neonates requiring resuscitation may benefit the most from a longer placental transfusion, which allows more time for blood to return to the newborn after birth. Positive pressure ventilation has been shown to stabilize transition in a preterm lamb model.[21] It has been suggested that fetal blood volume loss to the placenta may occur as the infant descends into the birth canal when shoulder dystocia or a tight nuchal cord occur.[19,22] The mechanism is thought to be related to the squeeze of the infant as it traverses the tight birth canal, which places pressure on the umbilical cord.[22] Within the cord, the muscular-walled, high-pressure arteries continue to move blood from the fetus to the placenta, whereas return flow from the placenta to the fetus in the thin-walled vein is impeded.[23] This may result in a net transfer of blood volume from the fetus to the placenta during birth. DCC can facilitate cardiovascular transition by establishing pulmonary blood flow as a replacement preload before the placenta is removed from the circulation and may help avoid adding a hypovolemic ischemic insult to an already-asphyxiated infant.[9] Conversely, it is unclear whether infants already in asystole would be able to receive a placental transfusion or whether it would contribute to further fetal blood loss. Further study is needed in infants who are compromised and hemodynamically unstable to better understand the risk/benefit of DCC in these infants.

In this pilot randomized clinical trial, we found that a 5-minute interval for DCC is feasible in newborns born at term at risk for resuscitation. Infants with DCC may benefit from improved hemodynamics, as demonstrated by an increased BP, StO_2, and decreased FTOE. Future studies are needed to determine whether these benefits translate into decreased admission into the NICU and improved long-term neurodevelopmental outcomes. ■

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Reprint requests: Anup C. Katheria, MD, Neonatal Research Institute at Sharp Mary Birch Hospital for Women and Newborns, 8555 Aero Dr, Suite 104, San Diego, CA 92123. E-mail: anup.katheria@sharp.com

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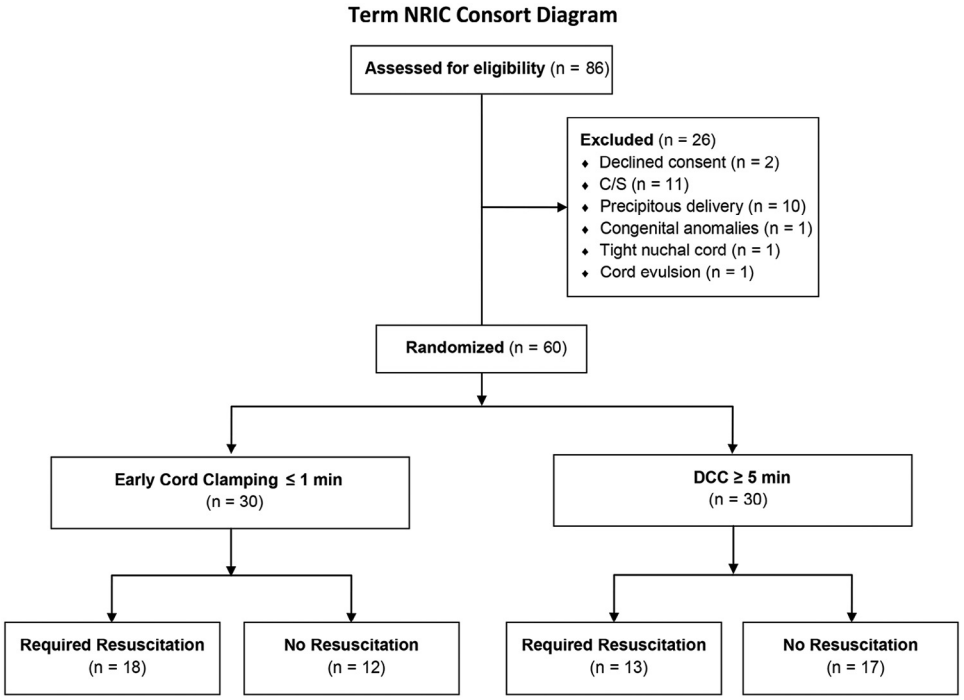

Figure 1. CONSORT diagram. *C/S*, cesarean delivery; *NRIC*, Neonatal Resuscitation with Intact Cord.

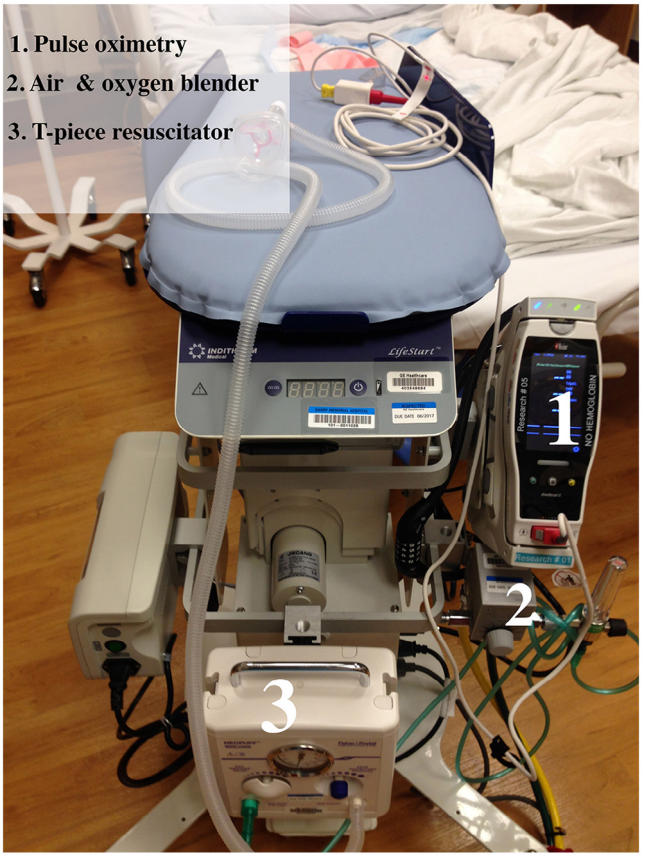

Figure 2. LifeStart bed equipped with resuscitation equipment.