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Graduate School of Business
Center for Health Administration Studies (CHAS)
1101 East 58th Street, Walker 111
Chicago, Illinois 60637
(312) 702-7104

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JOHN LANTOS, M.D.
Instructor, Department of Pediatrics
Fellow, Department of Medicine and Clinical Ethics
The University of Chicago

"Decisions about CPR for Very Low Birthweight Babies"

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SPECIAL ARTICLE

SURVIVAL AFTER CARDIOPULMONARY RESUSCITATION IN BABIES OF VERY LOW BIRTH WEIGHT

Is CPR Futile Therapy?

JOHN D. LANTOS, M.D., STEVEN H. MILES, M.D., MARC D. SILVERSTEIN, M.D., AND CAROL B. STOCKING, PH.D.

Abstract We conducted a retrospective study of outcome after cardiopulmonary resuscitation (CPR) in babies of very low birth weight. Of 158 such babies (birth weight, <1500 g) admitted to a neonatal intensive care unit in 1985, 49 (31 percent) underwent CPR. Low birth weight, low Apgar scores, birth asphyxia, pulmonary interstitial emphysema, hyaline membrane disease, and severe intraventricular hemorrhage were associated with the need for CPR. None of the 38 babies who received CPR in the first three days of life survived. Four of the 11 babies who received CPR after the first 72 hours survived. Three of the four survivors had residual neurologic deficits.

Survival rates after CPR in infants of very low birth weight are lower than those in older children or adults. CPR may therefore be considered a nonvalidated therapy in this population. If the results of our study are confirmed, CPR should not be instituted automatically in very-low-birth-weight babies as though it were a validated treatment. Instead, it should be administered upon parents' advance informed consent to experimental treatment. (N Engl J Med 1988; 318:91-5.)

BABIES of very low birth weight (<1500 g)[1] account for 50 percent of all neonatal deaths, even though they represent only 1.15 percent of all live births in the United States.[2] Survival of babies in this weight range has improved dramatically over the past 15 years as a result of advances in neonatal intensive care.[3,4] Improvements in survival have been accompanied by questions about the efficacy of neonatal intensive care,[5] the limits of viability,[6] and the reliability of predictions of prognosis when used to justify the withholding of neonatal intensive care.[7]

The development of criteria for determining which babies will benefit from aggressive treatment and which babies will not survive even with aggressive treatment has proved difficult. Many neonatologists feel compelled to treat all babies aggressively at birth and to withdraw care only if dire complications such as massive intracranial hemorrhage or renal failure develop.[8] Some institutions have policies that govern the recommendation of aggressive treatment for babies[9]; others leave this to the discretion of the attending neonatologist.[10]

In pediatrics and neonatology, doctors assume that patients should have all the available therapy that is not futile, and the effectiveness of therapy replaces patient preference as the primary factor governing decisions to use or discontinue therapy. Unlike competent adult patients, infants cannot be asked to decide whether to accept or reject therapeutic interventions on the basis of information about the benefits and burdens of treatment and the consequences of nontreatment. Because of this, it is imperative that physicians know the effectiveness of therapies for various subpopulations in the neonatal intensive care unit.

Cardiopulmonary resuscitation (CPR) in the neonatal intensive care unit involves mechanical ventilation and the administration of intravenous inotropic agents to neonates with intractable bradycardia and hypotension; true cardiac arrest is relatively rare in neonates. The effectiveness of CPR has not been as well studied in babies of very low birth weight as it has in older children. Studies of outcome after CPR in children have found survival rates ranging from 5 to 75 percent. Outcomes have been much better after respiratory arrests unaccompanied by cardiac arrest than after cardiac arrests, with 44 to 75 percent of patients surviving until discharge from the hospital[11,12] as compared with 5 to 31 percent surviving after cardiac arrest.[13,14] A study of neonate survival after CPR found that the overall rate of survival until discharge was 14 percent; 7 percent of babies were still alive one year after discharge.[15] Prognostic factors that correlated with death after CPR were gestational age less than 37 weeks, postnatal age at the time of arrest less than 48 hours, renal failure, and sepsis. Birth weight of less than 1500 g also correlated with death, but outcome data were not further stratified according to birth weight.

Most patients in the neonatal intensive care unit weigh less than 1500 g and are born at less than 37 weeks' gestation. Many require CPR in the first 48 hours of life. More refined prognostic criteria for survival or death after CPR in babies of very low birth weight would help neonatologists decide whether or not they should administer CPR to such patients. With this in mind, we designed our study to define further the effectiveness of CPR in subpopulations of very-low-birth-weight infants.

From the Center for Clinical Medical Ethics, the Department of Pediatrics, and the Section of General Internal Medicine at the University of Chicago Pritzker School of Medicine. Address reprint requests to Dr. Lantos at the Center for Clinical Medical Ethics, Box 72, University of Chicago Hospitals, 5841 S. Maryland Ave., Chicago, IL 60637.

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METHODS

We reviewed the charts of all very-low-birth-weight babies admitted to the neonatal intensive care unit at University of Chicago Medical Center's Lying-In Hospital, an inner-city tertiary care academic medical center, between January 1, 1985, and December 31, 1985. For each patient, categorical data were collected concerning race, sex, maternal age and parity, type of insurance, prenatal care, place of birth (University of Chicago, other hospital, or home), and type of delivery (vaginal or cesarean section). Examination of obstetrical records revealed that problems during maternal labor and delivery included variable or late decelerations of the fetal heart rate, preeclampsia, eclampsia, cord prolapse, meconium staining, delivery of twins, and prolonged rupture of membranes (>24 hours) with or without maternal fever. For each baby, we recorded birth weight, estimated gestational age, Apgar scores, and admission diagnoses as described in the chart by the senior admitting physician. When available, diagnoses based on chest radiographs and head sonograms were recorded. Diagnoses at the time of hospital discharge or death were obtained from discharge summaries in medical charts or from death certificates.

Information about six specific resuscitation interventions — the use of epinephrine, bicarbonate, atropine, chest compressions, vasopressor infusions, and emergency intubation — was obtained from physicians' orders, physicians' notes, nurses' notes, medication records, and records of cardiac arrest. Any baby who had a record of cardiac arrest in his or her chart or who received at least one dose of intravenous epinephrine or atropine and mechanical ventilation for bradycardia or hypotension was classified as having had CPR. Interventions commonly used to correct transient hypotension, apnea, or bradycardia, such as fluid bolus or gentle stimulation, were not recorded as CPR.

Babies who were resuscitated in the delivery room but did not require CPR after admission to the neonatal intensive care unit were included in the study as nonrecipients of CPR. Twelve babies admitted to the neonatal intensive care unit after they were 12 hours of age and six babies with incomplete charts were excluded from the study.

Outcome was evaluated only in terms of survival until hospital discharge or death, with note made of the neurologic status of survivors at discharge.

Categorical variables were analyzed with use of the chi-square test. Student's t-test was used to compare means. The Wilcoxon rank-sum test was used to compare the birth weights of infants who needed CPR with the birth weights of those who did not, and to compare the birth weights of infants who survived with those of infants who did not survive. Significant univariate predictors of survival or the need for CPR were analyzed with use of the Cochran–Mantel–Haenszel chi-square test, with control for the effect of birth weight. Confidence intervals for proportions in which the numerator was zero were determined by the method of Hanley.[16] Data analysis was done with SAS/PC software[17] on an AT&T PC6300 computer.

The study was approved by the institutional review board of the University of Chicago Division of Biological Sciences.

RESULTS

One hundred seventy-six babies of very low birth weight were admitted to the neonatal intensive care unit during the study period, and 158 of their charts contained sufficient information for analysis.

Fourteen of the 158 babies (9 percent) died after unsuccessful attempts to intubate them with a 2.5-mm endotracheal tube. These babies were described in the medical records as "too small to intubate" or "not viable." Each of their records was analyzed separately.

The remaining 144 viable babies had an average (±SD) birth weight of 1031±298 g and an average gestational age of 28±3.0 weeks. Fifty-four percent of the babies were male, 82 percent were black, and 66 percent were either uninsured or insured by Medicaid. The distribution according to birth weight, estimated gestational age, race, and sex is shown in Table 1.

Characteristics of Cardiac Arrests

Forty-nine of 144 viable babies received CPR. All 49 had records of cardiac arrest in their charts. All received intravenous epinephrine and mechanical ventilation as part of their resuscitation. All CPR recipients were on cardiorespiratory monitors at the time of their cardiac arrest. No baby without a record of cardiac arrest received intravenous epinephrine in the neonatal intensive care unit. Other interventions administered as part of CPR were atropine (27 of 49 babies), vasopressor infusions (18 of 49), chest compressions (14 of 49), and emergency intubation (3 of 49). The 46 babies who did not require emergency intubation were already intubated at the time their CPR began.

Certain interventions that may be thought of as constituting resuscitation — such as fluid boluses for hypotension, bag-and-mask ventilation for apnea, or even elective intubation — were routine in the neonatal intensive care unit but were not recorded in this study. CPR was usually begun only after these interventions had failed.

Clinical Course

Mortality rates decreased with increasing birth weight (P<0.01), from 28 of 32 babies (88 percent) with birth weights between 500 and 750 g to 6 of 46 (14 percent) babies with birth weights between 1250 and 1500 g. The relation between mortality and birth weight is shown in Figure 1.

Each intrapartum problem, admission diagnosis,

Table 1. Race, Sex, Birth Weight, and Maturity of 144 Babies of Very Low Birth Weight.

CHARACTERISTIC	FREQUENCY	PERCENT
Race/sex		
Black/male	62	43
Black/female	56	39
White/male	16	11
White/female	10	7
Totals	144	100
Birth weight (g)		
<500	2	1.4
500–749	30	20.8
750–999	31	21.5
1000–1249	36	25.0
1250–1499	45	31.3
Totals	144	100
Estimated gestational age (wk)		
<24	5	3
24–27	48	34
28–31	71	49
32–35	15	11
>35	2	1
Unknown	3	2
Totals	144	100

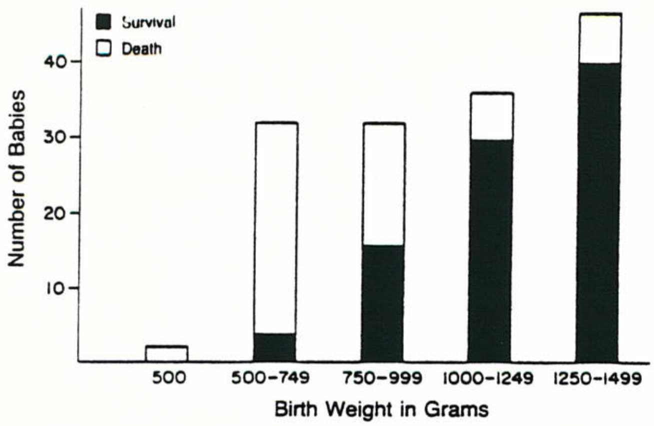

Figure 1. Outcome According to Birth Weight.

radiologic diagnosis, and discharge diagnosis was analyzed as a separate variable to determine which correlated with the need for CPR.

We determined that there was no correlation between the type of delivery, place of delivery, or any single intrapartum problem and the eventual need for CPR. The proportion of babies requiring CPR was the same for those with no intrapartum problems as it was for those with one or more intrapartum problems.

Babies with one-minute Apgar scores of less than 5 were significantly more likely to require CPR than those with scores of 5 or higher ($P<0.01$). Five-minute Apgar scores of less than 5 were not significantly associated with the need for CPR.

Birth weight was significantly associated with the need for CPR ($P<0.01$), as shown in Figure 2.

Twenty-nine babies (20 percent) had an admission diagnosis of birth asphyxia, and a larger proportion of these babies received CPR than did babies without birth asphyxia ($P<0.05$).

One hundred thirty-two babies (92 percent) had a radiologic diagnosis of hyaline membrane disease, and 47 (33 percent) had pulmonary interstitial emphysema. These diagnoses were predictors of the need for CPR ($P<0.05$).

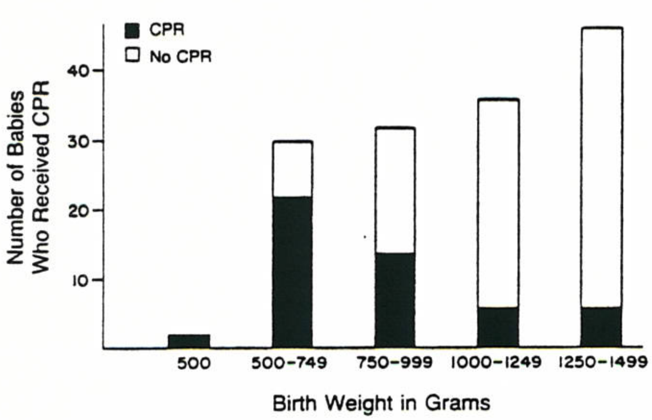

Figure 2. The Need for CPR According to Birth Weight.

Twenty-four babies (17 percent) had subependymal or intraventricular hemorrhage on ultrasound examination. Seventeen (12 percent) had a final diagnosis of intracerebral, or Grade IV, intraventricular hemorrhage. Six of the 17 babies with a final diagnosis of Grade IV intraventricular hemorrhage died before sonograms were obtained; the diagnosis was based on a clinical course (neurologic decompensation, a drop in the hematocrit, a bulging fontanelle) that led to a clinical diagnosis of severe intracranial hemorrhage. The babies with a final diagnosis of Grade IV intraventricular hemorrhage were more likely to have received CPR than the other babies ($P<0.01$).

The univariate predictors of the need for CPR are shown in Table 2. When analysis of the univariate predictors for CPR was controlled for the effect of birth weight, none of the admission diagnoses or clinical factors associated with the need for CPR remained statistically significant.

Outcome after CPR

Four of 49 babies (8 percent) who required CPR during their hospital stay survived to leave the hospital. Eighty-three of 95 babies (87 percent) who did not receive CPR survived.

The only variable that was significantly associated with survival after CPR was the interval from admission to the neonatal intensive care unit until the first CPR episode. None of the 38 babies who received CPR in the first 72 hours of life survived. Four of 11 babies who received CPR after 72 hours survived. Neither birth weight nor any of the variables used to describe the clinical course had a statistically significant effect on the outcome after CPR. Relations between birth weight, the need for CPR, the interval until the first CPR, and outcome are shown in Figure 3. The upper limit of the 95 percent confidence interval for survival after CPR in the first 72 hours of life is 7 percent.[16]

Three of the four survivors and none of the nonsurvivors required emergency intubation or reintubation at the time of CPR. Three survivors received only one dose of epinephrine, and one survivor received two doses of epinephrine. None of the 30 babies who received more than two doses of intravenous epinephrine during hospitalization survived to leave the hospital.

In two of the survivors, cardiac arrest occurred after accidental extubation, in one at 37 and in the other at 40 days of age. One of these babies was discharged after 68 days with a Grade IV intraventricular hemorrhage. The other baby was discharged at 113 days of age with final diagnoses of severe bronchopulmonary dysplasia, resolved *Staphylococcus epidermidis* meningitis with residual hypertonicity, retinopathy of prematurity with apparently normal vision, and non-A, non-B hepatitis. A third survivor received CPR at 15 days of age during an episode of sepsis. He had *S. epidermidis* meningitis with bilateral subdural hemorrhages. He

Table 2. Variables Associated with the Need for CPR.

Clinical Finding	Relative Risk	95% Confidence Interval
Grade IV intraventricular hemorrhage*	8.2	2.5–26.9
Hyaline membrane disease†	6.3	1.4–28.0
Pulmonary interstitial emphysema‡	3.5	1.6–7.5
Birth asphyxia§	3.1	1.3–7.1
1-minute Apgar <5	2.7	1.3–5.5

*Discharge diagnosis; 6 of 13 patients did not undergo ultrasonography

†Admission diagnosis or chest-radiograph diagnosis.

‡Chest-radiograph diagnosis.

§Admission diagnosis.

was discharged at 114 days of age with seizures. Only one survivor, who had cardiac arrest at six days of age immediately after a double-volume exchange transfusion for hyperbilirubinemia, was neurologically intact at discharge.

Decisions Not to Resuscitate

Eighteen of the 144 viable babies (13 percent) died without receiving epinephrine at the time of death. For 5 of these 18 babies there was a written "do not resuscitate" order, for 9 there was a decision documented in the doctor's notes that resuscitation should be withheld but there was no "do not resuscitate" order, and for four there was no documentation of decisions to withhold treatment but the babies did not receive CPR at the time of death.

The average birth weight of the 14 babies considered too small to intubate was 370±125 g and their average gestational age was 22±1.4 weeks. Birth weights in this group ranged from 220 to 590 g, with four babies weighing over 500 g. After attempted intubation was unsuccessful, all 14 babies were admitted to the nursery and received basic nursing care. All the babies in this group died within three hours.

Discussion

We found that very-low-birth-weight infants given CPR in the first few days of life may have outcomes that are markedly worse than those reported for either older children or adults. The severity of illness in our study population seemed comparable to that in other studies of very-low-birth-weight babies. Thirty-two to 54 percent of babies of very low birth weight have pulmonary interstitial emphysema,[18,19] as compared with our 32 percent. Between 9 and 16 percent of babies of less than 35 weeks' gestation are reported to have Grade IV intraventricular hemorrhage,[20,21] as compared with our finding of 12 percent. Reported survival rates among infants weighing less than 750 g at birth range between 5 and 45 percent[22,23]; our 12 percent survival rate in this weight group was low but consistent with the rates in other studies. The improvement in survival with increasing birth weight demonstrated in our study is comparable to that seen in other studies.[1,24,25]

The setting and interventions of CPR in very-low-birth-weight babies differ from those seen in adults and children. True cardiac arrest is rare in the neonatal intensive care unit. Bradycardia is common and often responds to gentle stimulation. Hypotension is treated initially with a fluid bolus. Severe apnea or respiratory arrest may be reversed with bag-and-mask ventilation or with nonemergency intubation, often before it leads to cardiac arrest and the need for pharmacologic stimulation.[26] In the neonatal intensive care unit, CPR entails the intravenous administration of inotropic agents to babies receiving mechanical ventilation and is initiated only after stimulation and fluid challenge have failed. Instead of being a discrete event, "cardiopulmonary arrest" in the neonatal intensive care unit is a constellation of physiologic derangements that occurs at the end of the spectrum of cardiopulmonary instability. The poor outcome of CPR in the neonatal intensive care unit may reflect both the seriousness of underlying conditions that affect babies of very low birth weight and the aggressiveness of care that babies receive before the initiation of CPR.

CPR in babies of very low birth weight, especially in the first 72 hours of life, may be considered an unproved and virtually futile therapy. Futile therapies — those that offer no immediate or long-term benefit to the patient — may not be considered either medically indicated or ethically obligatory. According to federal legislation passed in 1984, treatment is not legally required if "the provision of such treatment would be virtually futile in terms of the survival of the infant and . . . would be inhumane."[27] Unfortunately, no clinical definitions of futility are included in the legislation.

Clinical definitions of futility will most likely involve statistical estimations of a treatment's chances of success rather than an absolute prediction of its failure. A treatment could be considered virtually futile if the probability of benefit to the patient was very low. Data such as those presented here would allow such judgments to be made on a factual rather than an intuitive basis and would give empirical content to the

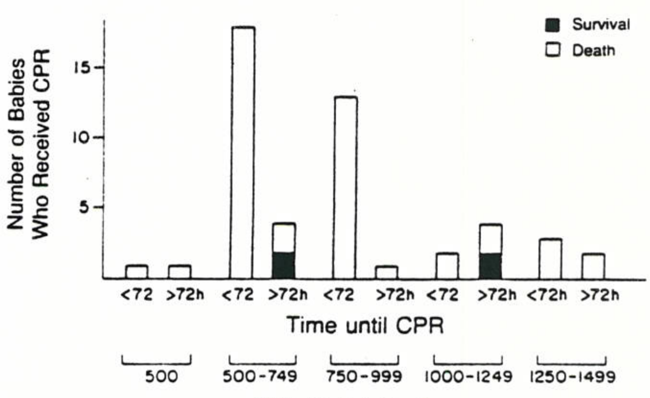

Figure 3. The Incidence of CPR and Outcome after CPR, According to Birth Weight and the Interval until the First Resuscitation.

vague notion of futility. Argument would then center on the appropriate statistical definition of futility. Our data allow statistically valid predictions of survival rates of up to 7 percent among very-low-birth-weight babies in the first 72 hours of life. This retrospective study at one center may not reflect the experience of other centers. Larger multicenter studies should be undertaken to establish the reproducibility of these findings.

Therapies of limited or unproved value, or those called into question by new data, have been defined as "innovative" or "nonvalidated."[28] The ethical obligations of medical professionals to protect vulnerable patients from clinical trials involving such therapies differ from the ethical obligations that govern the use of proved therapies.[29]

The finding that CPR is a nonvalidated therapy in babies of very low birth weight would have consequences for the presumption that favors the use of CPR in such patients in the first days of life. Practically, it would mean that very-low-birth-weight babies should not be subject to a standing order for CPR during the first days of life. Aggressive support could still be given to such babies, but the need for CPR would be taken as a sign of impending death, and no additional cardiovascular support would be warranted. This conclusion, based on the finding of medical futility, would preempt argument about the sanctity of life or the quality of life — issues that have clouded discussion of the ethics of withholding treatment from neonates.[30]

Another approach to CPR as a nonvalidated therapy would be to offer it to babies of very low birth weight as a potentially life-saving, but experimental, therapy. Consent to a standing order for CPR could then be obtained after discussions with parents that focused on their willingness to allow their children to participate in clinical trials. It would also be necessary, after some discussion of risks and benefits, to obtain the parents' informed consent for investigative resuscitation techniques. Refusal to consent would be viewed as unwillingness to participate in research rather than refusal of life-prolonging treatment. Parental refusal to consent would lead to actions identical to those that result from a policy of withholding CPR from all very-low-birth-weight babies for the first 72 hours of life, but the ethical rationale would be considerably different.

The ethical analysis of the problem of withholding care from newborns must include consideration of the innovative nature of much of neonatology. The problems that are most vexing for neonatologists exist because of a conflict between the obligation to provide treatment that may be in the best interest of the patient and the obligation to protect vulnerable persons from the hazards of medical experimentation. One way to resolve this conflict is to use new or unproved neonatal interventions in accordance with the ethical guidelines that have been developed for the evaluation of innovative therapies. Studies of the effectiveness of neonatal intensive care should focus on predictors of outcome for various subpopulations of infants. In this way, decision making can be more individualized, and it may be possible to untangle our conflicting ethical obligations.

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