

OBSTETRICS

The long-term outcome in surviving infants with Apgar zero at 10 minutes: a systematic review of the literature and hospital-based cohort

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OBJECTIVE: The purpose of this study was to investigate the outcomes of infants who had Apgar scores of zero at 10 minutes and were resuscitated successfully.

STUDY DESIGN: The literature was reviewed systematically to identify the outcomes of cases; in addition, the perinatal database at the John Radcliffe Hospital, Oxford, was used to identify similar cases. Eligible infants were identified through hospital records, and outcomes of all infants with an Apgar score of zero at 10 minutes, who were born between January 1991 and December 2004, were reviewed.

RESULTS: Eighty-five cases were identified from the literature. With the Oxford database, 9 of 83,065 infants (0.12/1000 births) met our study criteria. Six of the 9 infants died before leaving hospital. One infant with severe quadriplegia and microcephaly died at 11 months

of age. One infant at follow-up examination at 5 years had severe spastic quadriplegia with severe global delay. One infant with grade 2 hypoxic-ischemic encephalopathy, who was born with severe anemia that was corrected promptly at birth, had mild disability at follow-up examination at 2 years. Thus, death or severe disability occurred in 8 of 9 infants. Combining the results of metaanalysis of published data with our results of 94 infants, 88 infants (94%) either died or were handicapped severely; 2 infants (2%) were handicapped moderately, and 1 infant (1%) was handicapped mildly. For 3 infants (3%), the long-term outcome could not be determined.

CONCLUSION: The outcome of infants with an Apgar score of zero at 10 minutes is almost universally poor.

Key words: Apgar score, outcome, resuscitation, stillborn

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The frequency of apparently stillborn infants (Apgar zero at 1 minute) who are resuscitated ranges successfully from 0.5-1.26 per 1000 deliveries.^{1,2} The decision to resuscitate an infant who is born in this condition is usually straight

forward, but the decision to stop resuscitation if the infant continues to be unresponsive is more difficult. Prolongation of resuscitation may delay death or result in the survival of a severely handicapped infant. Previous case series and case reports have shown an Apgar score of zero at 10 minutes to be an important risk factor for subsequent death or disability.¹⁻⁷

Both the American Heart Association⁸ and the United Kingdom Resuscitation Council⁹ recently revised their neonatal resuscitation guidelines in this situation; it is now recommended that if there are no signs of life after 10 minutes of adequate resuscitation then withdrawal of resuscitation be considered. This is in contrast to previous guidelines^{10,11} and was based on a series with relatively few cases,^{1,2} in which it was not always clear whether infants with congenital abnormalities had been excluded. The limitations of the supporting evidence may undermine the implementation of the guide-

lines. It is of the utmost importance that the best evidence is available, both to underpin the guideline to help health professionals resuscitate appropriately and to avoid the creation of "a fate worse than death."¹²

The purpose of this study was to investigate the outcomes of all babies with an Apgar score of zero at 10 minutes and were resuscitated successfully, with both a systematic review and a 14-year period of prospectively collected records from the John Radcliffe Hospital, Oxford, UK.

METHODS

We searched Medline (1966-April 2005) for publications that had examined the association between low Apgar scores and neonatal outcome. The MeSH headings used were *Apgar score*, *resuscitation*, and *cardiopulmonary resuscitation*; the text key words searched for were *Apgar*, *resuscitation*, *ten minutes*, and *10 minutes*. From the abstracts that were identified,

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TABLE 1

Summary of outcome studies of infants who were resuscitated successfully and admitted to the neonatal intensive care unit with an Apgar score of zero at 10 minutes

| Study | Infants (n) | Death (n) | Severe disability (n) | Moderate disability (n) | Mild disability (n) |
|------------------------------|-------------|-----------|-----------------------|-------------------------|---------------------|
| Patel and Beeby ³ | 29 | 20 | 8 | 1 | 0 |
| Jain et al ² | 27* | 26 | 0 | 0 | 0 |
| Haddad et al ¹ | 16† | 14 | 0 | 0 | 0 |
| Thornberg et al ⁵ | 5 | 5 | 0 | 0 | 0 |
| Casalaz et al ⁴ | 4 | 3 | 1 | 0 | 0 |
| Koppe et al ⁶ | 3 | 3 | 0 | 0 | 0 |
| Socol et al ⁷ | 1 | 0 | 0 | 1 | 0 |
| This study | 9 | 7 | 1 | 0 | 1 |
| TOTAL | 94 | 78 | 10 | 2 | 1 |

* One survivor was reported with cerebral palsy, although the severity and length of follow-up period were not described.

† Two survivors were reported, both with hypoxic-ischemic encephalopathy. One infant remained an inpatient at 3 months of age with multiple bowel perforations, and the other was discharged at 53 days with bronchopulmonary dysplasia, meconium aspiration syndrome, and pulmonary hypertension.

we studied the eligible articles and their reference lists. Only articles that provided the outcomes of infants with an Apgar score of zero at ten minutes were included in the analysis.

We identified all singleton and multiple infants with an Apgar score of zero at 10 minutes of age who were subsequently successfully resuscitated and were transferred to the neonatal intensive care unit. All babies were delivered at ≥ 24 weeks of gestation at the John Radcliffe Hospital, Oxford, UK, during the period January 1, 1991, to December 31, 2004. Infants with congenital abnormalities were excluded. The population was identified from the OXMAT (Oxford Materials) database. In addition, all infants with an Apgar score of zero at 5 minutes that were identified as 10-minute Apgar scores were not always included when OXMAT was first introduced. Cases were confirmed by an examination of the maternal and neonatal clinical records. Data were abstracted from the maternal and neonatal notes. Follow-up data were provided from the hospital pediatric records.

For each woman, data on age, parity, antenatal complications, gestational age at delivery, peripartum complications, and mode of delivery were collected. For each infant, data that included birthweight; Apgar scores at 1, 5, and 10 minutes; arterial and venous cord pH and

base excess; outcomes, and postmortem findings were collected.

RESULTS

Our literature search identified 33 studies. After we screened abstracts, we read 25 papers that were found to be relevant to this study. Eighteen papers were excluded because the outcomes of infants with an Apgar score of zero at 10 minutes could not be determined from the data. This left 7 studies in which the outcomes of infants with an Apgar score of zero at 10 minutes were known. The results of these studies combined with our results are shown in Table 1. Of the 94 infants, 88 infants (94%) either died or were severely handicapped; 2 infants (2%) were moderately handicapped, and 1 infant (1%) was mildly handicapped. In 3 cases (3%), the long-term outcome could not be determined.

During the 14-year study period, there were 83,065 deliveries at ≥ 24 weeks of gestation. There were 416 stillbirths for which resuscitation was not attempted because intrauterine death was anticipated, which provides a stillbirth rate of 5.0 per 1000 births at ≥ 24 weeks of gestation. During the study period, resuscitation was attempted for 62 infants with an Apgar score of zero at 1 minute (Figure).

Seventeen infants had an Apgar score of zero at 10 minutes, and 11 other infants had an Apgar score of zero at 5 minutes. Eight of the 17 infants who were identified with an Apgar score of zero at 10 minutes were excluded after and inspection of their medical records. In 5 infants, there were major congenital abnormalities (all died); 3 infants were eventually stillborn after resuscitation beyond 10 minutes; in 3 other infants, resuscitation was not attempted or was abandoned at < 10 minutes because of a combination of being extremely premature and small for gestational age. One of the 11 infants with an Apgar score of zero at 5 minutes was found, after case note review, to have an Apgar score of zero at 10 minutes and was also resuscitated. Therefore, a total of 9 infants were included in the study; a summary of the outcomes are shown in Table 2. Six of the 9 infants died before discharge from hospital. One infant with severe quadriplegia and microcephaly died at 11 months of age. One infant at follow-up examination at 5 years has severe spastic quadriplegia with severe global delay. The single infant with mild motor delay at 2 years of age was born with acute anemia as a consequence of a vasa praevia and was given a transfusion at delivery during the immediate resuscitation. This infant had grade 2 hypoxic-ischemic encephalopathy and

had periventricular leukomalacia and was discharged from the hospital at 55 days old.

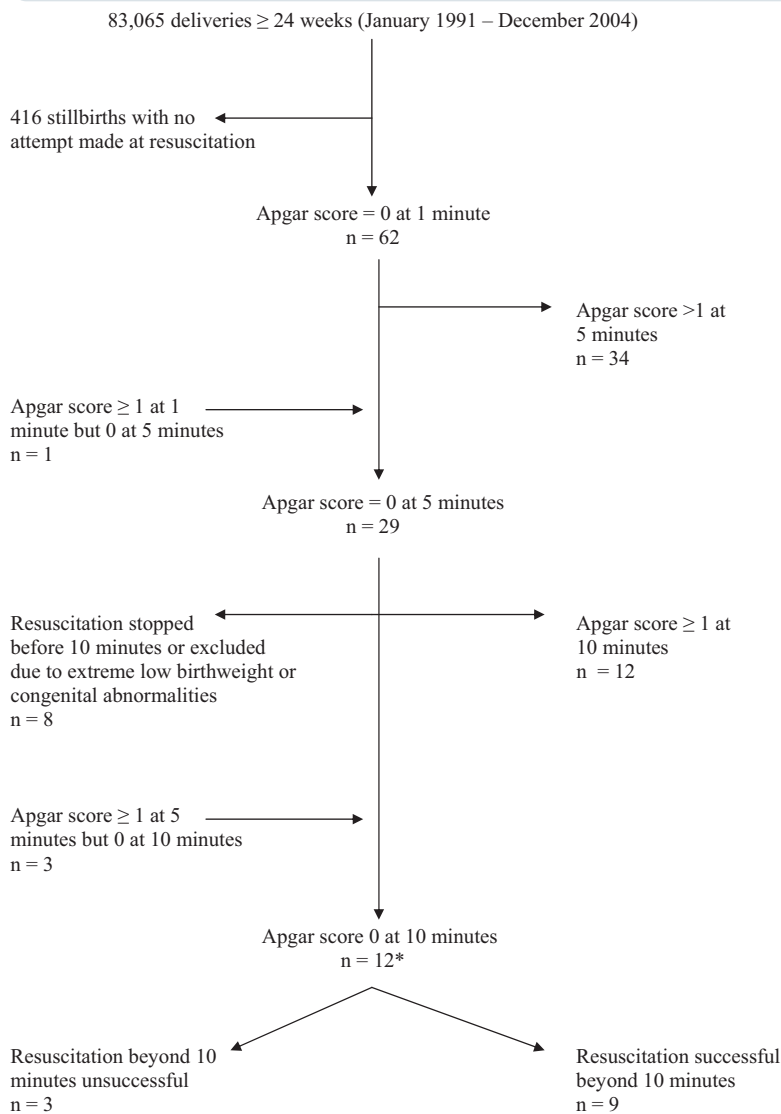
COMMENT

We present the unique combination of a systematic review of the literature and a prospective cohort study. Our purpose was to evaluate the outcomes of infants who were resuscitated successfully after an Apgar score of zero at 10 minutes. This issue is of great relevance to all caregivers who are involved in intrapartum care. The evidence for prolonged resuscitation has been based mainly on experimental work from the 1960s on fetal lambs.¹³ This showed that terminal apnea occurred 20 minutes after hypoxia was induced, but recovery was still possible if resuscitation was undertaken at this stage.¹⁴ However, this situation is not comparable to that of a baby who has no response to systematic attempts at resuscitation after 20 minutes, where the hypoxia is likely to have been more prolonged.

Most of the existing literature has focused on the outcome of apparently stillborn babies (Apgar score of zero at 1 minute) or on the outcome after birth asphyxia. There are 7 published studies in which the outcomes after successful resuscitation of infants with an Apgar score of zero at 10 minutes can be extracted,¹⁻⁷ with a range of between 1 and 29 infant outcomes reported. One limitation is that these are observational studies and therefore may be subject to reporting bias. All of these studies corroborate our findings. The 2 largest studies report the outcomes of 29 and 27 infants, respectively.^{2,3} However, it is not clear whether infants with congenital abnormalities were excluded in either. In a population-based study by Patel and Beeby,³ infants of at least 36 weeks of gestation with an Apgar score of zero at 10 minutes and who were resuscitated successfully were identified. The authors stated that babies in this category in non-tertiary hospitals who died before transfer would be lost to their study, which therefore may have underestimated the mortality rate. Twenty (69%) of the 29

FIGURE

Outcome of apparently stillborn infants who were born in Oxford between January 1991 and December 2004



infants died before discharge from hospital. Eight of the 9 babies who survived had severe disability, and 1 baby had moderate disability, although the length of the follow-up period was not stated. Jain et al,² in a study of the outcome of apparently stillborn infants, reported the outcome of 27 infants who were resuscitated successfully after an Apgar score of zero at 10 minutes. All except 1 baby died. The survivor has cerebral palsy, although the severity and length of the follow-up period were not described.

Two other studies reported on the outcome after unexpected apparent stillbirth. First, in a study by Haddad et al,¹

the outcomes of 16 infants who were resuscitated successfully after Apgar scores of zero at 1, 5, and 10 minutes were examined. Fourteen infants (88%) died before discharge from hospital. One survivor had hypoxic-ischemic encephalopathy and multiple bowel perforations and was still an inpatient at 3 months of age. The other survivor was diagnosed with hypoxic-ischemic encephalopathy, bronchopulmonary dysplasia, meconium aspiration syndrome, and secondary pulmonary hypertension and was discharged at 53 days of age. No further follow-up evaluation was reported. Casalaz et al⁴ reported the outcomes of 4

TABLE 2

Clinical details of infants with an Apgar score of zero at 10 minutes who were resuscitated and admitted to neonatal intensive care

| Case | Gestation (wk) | Birthweight (g) | Peripartum event | Mode of delivery | Cord pH | | Outcome |
|------|----------------|-----------------|--|-----------------------------|----------|--------|---|
| | | | | | Arterial | Venous | |
| 1 | 32 | 1745 | Abruption | Cesarean section | 6.67 | 6.8 | Spastic quadriplegia, microcephaly, died at 11 mo |
| 2 | 36 | 2097 | Abnormal cardiotocogram | Cesarean section | 6.88 | 8.0 | Died day 3 |
| 3* | 30 | 1400 | Vasa praevia | Forceps | 7.05 | 7.0 | Periventricular leukomalacia, mild disability age 2 y |
| 4 | 39 | 3590 | Abruption | Ventouse | 6.60 | 4.0 | Died day 2 |
| 5 | 40 | 2759 | Vasa praevia | Spontaneous vertex delivery | 6.84 | 7.2 | Died day 4 |
| 6 | 37 | 2836 | Failed ventouse | Cesarean section | 7.15 | 8.0 | Spastic quadriplegia, severe global delay |
| 7 | 39 | 3977 | Group B streptococcus, meconium, abnormal cardiotocogram | Cesarean section | 6.67 | 7.16 | Died day 2 |
| 8 | 39 | 2975 | Meconium, abnormal cardiotocogram | Cesarean section | 6.76 | 6.96 | Died at 14 h |
| 9 | 41 | 2789 | Bradycardia | Breech | 6.84 | 6.92 | Died at 6 h |

* Severe anemia; received transfusion during resuscitation attempts.

infants who had an Apgar score of zero at 10 minutes. Three of the 4 infants died at <1 week of age, and 1 infant survived the neonatal period severely disabled with dyskinetic spastic quadriplegia.

Three studies have looked at the outcome after birth asphyxia. Thornberg et al,⁵ in a Swedish population study, followed 227 term infants with birth asphyxia (Apgar score, <7 at 5 minutes). Five infants had an Apgar score of zero at 10 minutes. Four infants had seizures; all of the infants had severe hypoxic-ischemic encephalopathy, and all of the infants died, although the age at which death occurred is not reported. However, Apgar scores at 1, 5, and 10 minutes are given only for those infants who died or had neurologic sequelae. Apgar scores are not given for the 1 infant who had cardiopulmonary resuscitation but is reported as having a normal outcome. Koppe and Kleiverda⁶ followed 54 severely asphyxiated infants, which was not defined, who were born at >37 weeks of gestation with a birthweight greater than 2500 g. They reported the outcome of 3 infants with a zero Apgar score at 10 min-

utes and for whom spontaneous respiration did not occur until ≥ 30 minutes after birth. All 3 infants died. This study was carried out in the Netherlands between 1965 and 1975 and may not reflect modern neonatal management. The third study reports the long-term outcome of 28 infants who were born at ≥ 34 weeks of gestation with a 5-minute Apgar score of ≤ 3 .⁷ One infant had an Apgar score of zero at 10 minutes and had newborn encephalopathy, an abnormal computed tomography scan, and pulmonary dysfunction. Abnormal psychomotor function was reported at long-term follow-up evaluation.

The numbers in the present study are small compared with some others, because we excluded infants with congenital abnormalities. Our findings show that the outcomes, even for congenitally normal infants with an Apgar score of zero at 10 minutes, are very poor and even worse if infants with congenital abnormalities are considered. Taken together, our data with those of all available previous studies show that the outcomes for infants who do not re-

spond to cardiopulmonary resuscitation by 10 minutes of age are extremely poor, with a very low chance of surviving without severe disability. These findings present strong evidence that adequate resuscitation beyond 10 minutes is not justified. ■

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