Tidsskriftet
DEN NORSKE LEGEFORENING

Outcomes following neonatal cardiopulmonary resuscitation

OVERSIKTSARTIKKEL

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BACKGROUND

Cardiopulmonary resuscitation of an infant that is critically ill at birth will end in either survival or death. Those that survive may develop complications in the immediate postnatal period, or subsequently in infancy or at school age. Hypoxic ischaemic encephalopathy is a disorder characterised by neurological symptoms in neonates that have experienced perinatal hypoxia. The condition is classified as mild, moderate or severe. We wished to provide an overview of short- and long-term outcomes following resuscitation at birth.

METHOD

We searched the Medline database for outcomes following resuscitation at birth.

RESULTS

We identified 15 indexed, peer-reviewed original articles and two meta-analyses of outcomes following resuscitation at birth or following perinatal asphyxia. Hypoxic ischaemic encephalopathy affects 38 % of patients to a mild or moderate degree, and 23 % to a severe degree. Mortality ranges from 10 % in high-income countries to 28 % in low-income countries. Survivors often develop motor, cognitive and sensory developmental disabilities. In some cases, these are first discovered at school entry, when more complex skills are required.

INTERPRETATION

Functional impairment at school age is strongly correlated with functional status in infancy. Changes in the algorithms for resuscitation, and routine use of therapeutic hypothermia, have reduced the risk of serious sequelae following hypoxic ischaemic encephalopathy.

Neonates that fail to breathe for themselves and/or have a slow heart rate immediately after birth should, according to Norwegian and international guidelines, undergo cardiopulmonary resuscitation in accordance with clearly defined algorithms (1). These are divided into various steps: drying, warming and stimulation, bag-valve-mask ventilation, cardiopulmonary resuscitation with chest compressions and ventilations, and possibly adrenaline (1–3).

Approximately 10 % of infants born at or near term require tactile stimulation to begin breathing (2), while 3 % will require respiratory support such as bag-valve-mask ventilation. A further 0.1 % will require treatment with chest compressions and/or adrenaline (1, 4). The Apgar score after five and ten minutes is often used retrospectively to identify infants that have experienced perinatal asphyxia. The score is based on evaluation of respiration, heart rate, skin tone, reflexes and muscle tone, and can range from 0 (no sign of life) to 10 (infant is in very good health). Owing to major subjective differences in scoring, the pH of umbilical cord blood is used to supplement the diagnosis (5).

Perinatal asphyxia accounts for one in every four (23 %) neonatal deaths worldwide, and 99 % of these occur in low-income countries (6). Perinatal asphyxia is a condition in which insufficient oxygen supply before, during or after birth leads to cardiorespiratory depression, hypotension and reduced tissue perfusion with subsequent organ damage (7).

At the cellular level, oxygen deficiency in the brain leads to anaerobic metabolism and primary cell death with reduced energy production, acidosis and accumulation of intracellular substances, secondary cell death with failure of mitochondrial energy production, and delayed cell death months after the event in association with chronic inflammation and epigenomic changes, see Figure 1 (8).

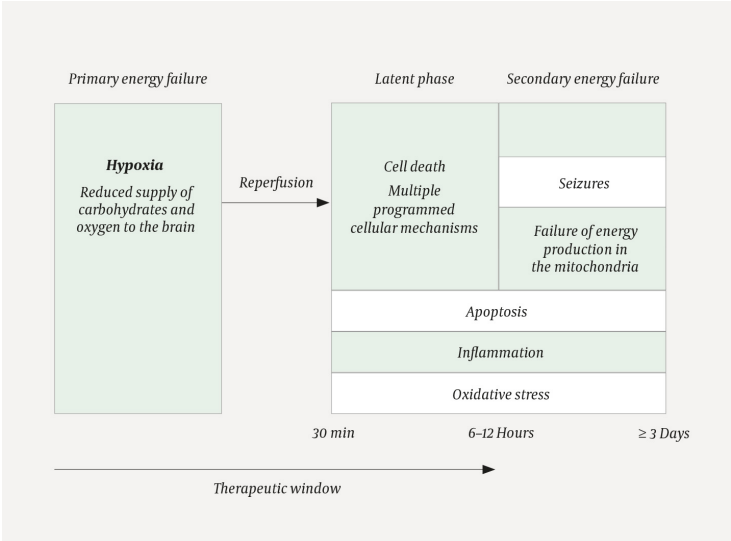

Figure 1 *The metabolic phases following perinatal asphyxia (8). In the primary phase, a failure of energy supply to the brain is followed by reoxygenation and restoration of cellular functions. A cascade of cellular mechanisms leads to renewed failure of mitochondrial energy production following a 'latent phase' of 6–24 hours, and can cause significant damage. The interval between the primary and secondary phases of energy failure is a window for active therapeutic hypothermia.*

Hypoxic ischaemic encephalopathy (HIE) occurs in 70 % of neonates that survive severe perinatal asphyxia, often defined as umbilical cord pH < 7.0, Apgar score < 3 at five minutes of age, need for resuscitation at ten minutes of age, and neurological symptoms. The latter typically include seizures and abnormal muscle tone and reflexes in the neonate (9). These resolve in some cases, whereas in others, permanent brain damage may occur. The initial neurological examination, together with the umbilical cord pH, Apgar score and requirement for cardiopulmonary resuscitation, is used to determine the need for treatment. The condition is often graded as mild, moderate or severe using the staging scale developed by Sarnat and Sarnat in 1976 (10). Staging is performed on the basis of clinical and electrophysiological findings in six main categories: level of consciousness, neuromuscular control, complex reflexes, autonomic function, presence of seizures, and electroencephalography (EEG), see Figure 2 (10).

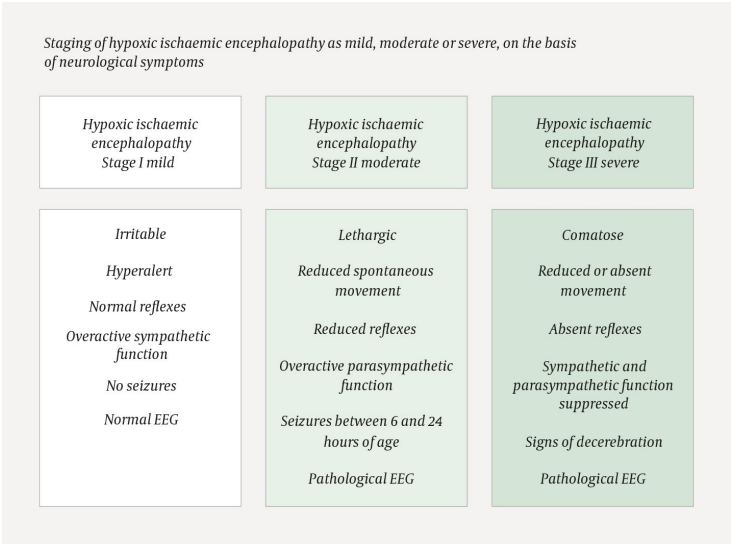

Figure 2 *Neurological symptoms in the various stages of hypoxic ischaemic encephalopathy. Modified from Sarnat and Sarnat (10).*

Neonates that require resuscitation immediately after birth are almost always hypoxic with a combined respiratory and metabolic acidosis. A key factor in resuscitation is therefore the rapid initiation of effective ventilation that leads to increasing heart rate and chest expansion (1, 11). Effective ventilations are difficult to perform, and a suboptimal technique may result in an insufficient clinical response in the infant. It is not uncommon for chest

compressions to be initiated in cases of persistently low heart rate following ineffective ventilation (12).

One study showed that 24 out of 39 (62 %) infants received chest compressions as a result of preceding ineffective ventilation, and five out of 39 (13 %) owing to an incorrectly positioned intubation tube (13). Conversely, hypocapnia, i.e. low levels of carbon dioxide in the blood due to overventilation, increases the risk of intraventricular haemorrhage and hypoxia-induced brain injury. Here, the use of large tidal volumes or overly frequent ventilations may be responsible (14, 15).

Reoxygenation after asphyxia is associated with increased production of oxygen free radicals. This may lead to oxidative stress and exacerbate brain injury following resuscitation. Neonates now receive 21 % oxygen upon initiation of assisted ventilation, rather than 100 % oxygen as was used prior to 2010. This has probably improved survival rates and reduced the incidence of hypoxia-induced brain injury following perinatal asphyxia (16).

Ethical challenges

If there are no signs of life after ten minutes of effective cardiopulmonary resuscitation, it is appropriate to consider discontinuing resuscitation (2). One study showed that, in cases where this limit was exceeded, 88 out of 94 (94 %) patients either died or had severe motor impairments (17).

In cases where the infant has had a heart beat (bradycardia) and/or shown signs of independent respiration but does not improve after ten minutes of effective treatment, the decision can be a difficult balancing act. The risk of discontinuing treatment prematurely while it is still possible to achieve spontaneous circulation and survival must always be weighed against the risk of major neurological injury or of postponing the decision to discontinue treatment (2). Survival and complications after cardiopulmonary resuscitation can therefore be a direct consequence of the decisions and actions of healthcare personnel.

A key ethical question with respect to resuscitation is whether the treatment would cause such great suffering for the infant that it should be discontinued. For this reason, it is important to have accurate knowledge of the clinical outcomes that can be expected in infants that undergo treatment in the neonatal period (18).

Three main factors predict the outcome for a neonate following perinatal asphyxia and resuscitation: the severity of the perinatal asphyxia and hypoxic ischaemic encephalopathy, the quality of the treatment received, and the subsequent medical treatment in the neonatal unit.

The aim of this article is to classify and provide an overview of short- and long-term outcomes following resuscitation at birth.

Method

We searched the Medline database for the keywords ‘resuscitation’, ‘asphyxia neonatorum’, ‘hypoxic-ischemic brain injury’, ‘infant’, ‘treatment outcome/diagnosis’, ‘short-term’, ‘long-term’, and ‘apgar score’. The keywords were combined in several ways; see Table 1 for combinations and the number of hits. Only publications in English were included.

Table 1

Overview of keywords and search strings applied to Medline-indexed articles

Keyword	Search string
Resuscitation	‘exp Resuscitation’, ‘resuscitat*.mp’, ‘cardiopulmonary resuscitation .mp’, ‘(resuscitation adj2 delivery adj2 room).mp’

Keyword	Search string
Asphyxia neonatarum	'Asphyxia neonatorum/', '(asphyxi* adj3 neonat*).mp', '(hirth* adj3 asphyxia*).mp'
Hypoxic-ischemic brain injury	'Hypoxia-ischemia, brain/', 'hypoxic-ischemicencephalopathy.mp', '(neurology* adj3 disabil*).mp'
Infant	'exp Infant, Newborn/', 'neonat* or baby or babies.mp', 'Term birth/', '(delivery adj3 room).mp'
Treatment outcome/diagnosis	'treatment outcome/', 'outcome*.mp', 'exp Diagnosis/', 'diagnos*.mp', 'diagnosis.fs'
Short-term	'((«short term» or shortterm) adj5 (consequence* or outcome* or diagnosis*)).mp'
Long-term	'((«long term» or longterm) adj5 (consequence* or outcome* or diagnosis*)).mp'
Apgar score	'Apgar score/', 'apgar.mp'

Initially, no restrictions were applied with respect to year of publication. However, when reviewing the titles and abstracts, we ultimately decided to include only studies after 2004, since these were the most relevant. This decision was partly to do with definitions, and also because comparison of results has only recently become possible. The search was terminated on 15 January 2017. We also included articles from a literature database created during the first author's PhD period and the UpToDate library. The first author selected relevant articles for inclusion.

We identified relevant articles using a PICO analysis (P = Patient/Problem, I = Intervention, C = Comparison, O = Outcome) (19). Infants born at or near term without established spontaneous respiration at birth (P) who received resuscitation (I) were compared to healthy neonates that did not require resuscitation (C), with respect to clinical outcomes after short and/or long observation periods (O). The search yielded 203 articles in which Apgar scores were studied in neonates with hypoxic ischaemic encephalopathy and/or resuscitation following asphyxia. Of these, 13 articles included short-term follow-up, and 31 articles long-term follow-up, but none included both. Short-term outcomes included survival and clinical symptoms. Long-term outcomes included survival, absence of sequelae, or motor, cognitive and/or sensory late effects. Short-term outcomes were examined immediately after birth. Long-term outcomes were examined at 18 months and 6–7 years of age.

Studies that examined short- or long-term mortality and/or sequelae following resuscitation at birth were also included. The relevance of the articles was first assessed based on their title and abstract. Relevant articles were read in full, and 15 original articles and two meta-analyses were included. The remaining references in this article relate to background information and mechanisms of brain injury.

Results

SHORT-TERM OUTCOMES FOLLOWING RESUSCITATION

The outcomes for a critically ill infant shortly after birth, often following resuscitation, are death, survival with rapid recovery, or the need for intensive treatment. Correctly performed resuscitation should quickly lead to spontaneous circulation and independent respiration. By contrast, ineffective ventilation attempts and chest compressions may exacerbate hypoxic injury.

In the aforementioned review from 2007, 85 % of neonates that received intensive treatment but were without signs of life after ten minutes, died, while 93 % of those that survived developed moderate to severe disability (17). However, a more recent study found that 30 % of neonates treated at birth and without signs of life showed normal development at 1–2 years of age (20). The difference between these two studies may be explained in part by the switch to using 21 % oxygen rather than 100 %, and by the use of therapeutic hypothermia in the most recent study.

A meta-analysis including 184 countries and more than four million births found that the incidence of postnatal hypoxic ischaemic encephalopathy was 1–8 per 1 000 live births in high-income countries and five times higher in low-income countries (6). Of all live-born infants with hypoxic ischaemic encephalopathy, 38 % were affected to a mild or a moderate degree, and 23 % to a severe degree (45 studies, n = 2 340) (6). Mortality was 10 % in high-income countries and 28 % in low-income countries, with risk of mortality highest in serious cases of the condition (31 studies, n = 2 639) (6).

LONG-TERM OUTCOMES

A range of measuring instruments for clinical assessment, radiology, physiology and biochemical analyses are used to predict long-term outcomes for neonates with hypoxic ischaemic encephalopathy.

Based on the Sarnat classification system (10), many more neonates with a moderate to severe form of the condition developed neurological injury than those with a mild form (21, 22).

Over the last few decades, the introduction of therapeutic hypothermia in high-income countries has improved outcomes for neonates with hypoxic ischaemic encephalopathy born at or near term. This has been shown in a number of studies comparing outcomes for these infants with those for control infants that did not receive therapeutic hypothermia (23–29).

Worldwide more than one million infants that survive perinatal asphyxia develop motor, cognitive and/or sensory impairments in early childhood or at school age (6). A meta-analysis comparing therapeutic hypothermia with no treatment (21) included six randomised clinical trials and a pilot study (total n = 1 214) (23–29). Severe neurodevelopmental disability was defined as motor cerebral palsy (CP) and cognitive developmental delay based on the 'Mental Developmental Index' in the Bayley Scales of Infant and Toddler Development, version II (21). Language, emotional development and social skills were also evaluated. Risk of death and/or severe disability at 18 to 22 months of age was markedly reduced after therapeutic hypothermia (21).

The results also revealed that the number of infants that must be treated to prevent death and/or severe developmental impairment in one infant (i.e. the number needed to treat, NNT) is seven. Hypothermia had greater efficacy in neonates with moderate, as opposed to severe, hypoxic ischaemic encephalopathy. This emphasises the need to optimise neuroprotective treatment, including through earlier initiation of therapeutic hypothermia. It will also be important to improve selection of neonates with hypoxic ischaemic encephalopathy that may benefit from the treatment. Selection is currently based on the severity of clinical symptoms and on blood gas values, including pH. It is possible that therapeutic hypothermia in combination with allopurinol, melatonin and/or erythropoietin (EPO) may offer greater neuroprotection; however, this has yet to be established for certain (30–33).

Cerebral palsy is a disorder of muscle control resulting from brain injury in the neonate. The following criteria should be fulfilled for cerebral palsy to be considered a consequence of hypoxic ischaemic encephalopathy: pH < 7 in umbilical artery blood, moderate to severe hypoxic ischaemic encephalopathy and spastic dyskinetic tetraplegia (34). Infants that underwent therapeutic hypothermia in the acute phase had a 16 % increased rate of survival without disability at the age of 18 months (21). In addition, the incidence of cerebral palsy was reduced by 12 %, cognitive impairments by 12 % and blindness by 4 % (21). However, there was no difference in the incidence of deafness.

Three randomised clinical trials examined children at 6–7 years of age and recorded motor, cognitive and/or sensory impairments (35–37). The combined outcome variable of death or IQ < 70 was observed in 47 % of children in the hypothermia group versus 62 % in the control group (37, 38). The results were greatly influenced by outcomes at 18–22 months of age, with

80 % of those that were severely affected at this age either deceased or with IQ < 70 (37, 38). Cerebral palsy, cognitive impairments, and visual and hearing impairments at school entry were strongly associated with the degree of disability at 18 months of age. However, even children with apparently normal development sometimes showed cognitive difficulties upon starting school, where more complex skills were required (37, 38).

Discussion

The most serious outcome measure following perinatal asphyxia and cardiopulmonary resuscitation is the neonatal mortality rate, which is 10 % in high-income countries and 28 % in low-income countries. Up to 70 % of surviving infants develop hypoxic ischaemic encephalopathy of varying severity. The incidence of late effects varies between studies owing to the use of different definitions and inclusion criteria. Reported incidences vary markedly in high- and low-income countries.

Changes in treatment algorithms and the routine use of therapeutic hypothermia, especially when initiated within six hours of birth, have reduced the risk of death or severe disability in cases of hypoxic ischaemic encephalopathy. Therapeutic hypothermia reduces cellular damage, depending on how quickly the treatment is initiated after birth. Current guidelines state that therapeutic hypothermia should be initiated within six hours of birth. Neonates affected to a moderate degree (grade II) derive greater benefit from the treatment than those affected more severely (grade III) (6).

There remains a need for further optimisation of neuroprotective treatment. Adjunctive therapy with melatonin and erythropoietin has shown good results in clinical trials (32, 39).

Motor, cognitive and sensory developmental impairments at school entry (aged 6–7 years) are associated with functional level at 18 months of age. However, impairments in fine motor and cognitive skills are also sometimes revealed in apparently healthy children upon starting school, where more complex skills are required (36).

An awareness of the likely outcomes following cardiopulmonary resuscitation of an infant with perinatal asphyxia is an important prerequisite for being able to make informed decisions about whether to continue or discontinue resuscitation and treatment of the infant. This reinforces the need for major national and international follow-up studies.

MAIN MESSAGE

Neonatal mortality following cardiopulmonary resuscitation and perinatal asphyxia is 10 % in high-income countries and 28 % in low-income countries

Up to 70 % of survivors of severe perinatal asphyxia develop hypoxic ischaemic encephalopathy of varying severity

Therapeutic hypothermia and careful use of oxygen have reduced the risk of death and of motor, cognitive and sensory functional impairments

Functional impairments at school entry are strongly correlated with functional status in infancy

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Published: 29 May 2018. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.17.0358
Received 18.4.2017, first revision submitted 1.11.2017, accepted 28.2.2018.