International Child Health Review Collaboration

What is the management of apnoea in birth asphyxia?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: What is the management of apnoea in birth asphyxia?

The **WHO Pocketbook of Hospital Care for Children** recommends that apnoea after birth asphyxia should be managed with oxygen by nasal catheter and resuscitation by bag and mask. (Pocketbook chapter 3.5, page 47).

Introduction:

Birth asphyxia is a global problem. Each year worldwide 4 million children die in the neonatal period. [1] It is estimated 23% of these deaths are due to birth asphyxia.[1] 99% of these deaths occur in low and middle income countries.[1] Birth asphyxia has a wide spectrum of severity but the most severely affected infants have high rates of mortality and/or significant neurodisability. Discussions regarding birth asphyxia have been hampered by the lack of a clear definition of the condition. However in broad terms it refers to infants thought to have suffered some hypoxic, ischaemic insult either antenatally, perinatally or in the immediate post natal period that leads to a depressed condition at birth requiring resuscitation. Apnoea may occur initially or later in the course as a complication of the ensuing encephalopathy and multi-organ dysfunction. The management of the initial apnoea in resource rich countries has focused on the use of basic resuscitation using bag-mask ventilation, oxygen and subsequent ventilation. All elements of resuscitation equipment and particularly oxygen may not be available in the resource poor setting and resuscitation with air has been studied. The management of apnoea after the initial resuscitation period in the asphyxiated neonate has been little studied. This review will examine the available evidence for the management of apnoea in birth asphyxia.

Methodology

The Cochrane Database of Systematic Reviews was searched. This revealed two systematic reviews. One referred to the use of naloxone for preventing morbidity and mortality in newborn infants of greater than 34 weeks gestation with suspected perinatal asphyxia. The second reviewed the use of air versus oxygen for the resuscitation of infants at birth.

The clinical search strategy used was that of Haynes et al "Clinical Queries" in PubMed. The words birth asphyxia AND apnoea or hypoxic ischaemic encephalopathy AND apnoea were entered. Both broad and narrow searches were conducted. Filters for therapy were employed. Sixty articles were found. Articles were excluded if they did not concern the clinical question being posed or if they concerned animal studies. This left four articles. Three of these concerned the use of room air versus 100% oxygen in the resuscitation of asphyxiated neonates and were all included in the Cochrane review.

One single study was found that evaluated the impact of a neonatal resuscitation programme on the incidence, management and outcome of birth asphyxia within the setting of 14 teaching hospitals in India. An additional randomised control trial (Vento et al, 2001) was included that was not revealed in the search strategy but has been extensively referenced in the air versus oxygen resuscitation debate.

No studies were found concerning the management of late or secondary apnoea in

asphyxiated infants beyond the initial period of resuscitation.

Results

Of the two Cochrane reviews on this topic the meta-analysis of the use of naloxone in treating infants > 34 weeks gestation with suspected perinatal asphyxia revealed only one eligible blinded, randomised, placebo controlled trial. The basis of this trial was animal model evidence suggesting the release of endogenous opioids in response to asphyxia may worsen neonatal depression. If this hypothesis holds true then the use of the opioid antagonist naloxone may theoretically decrease post-asphyxial neuronal injury. This trial did not look specifically at management of apnoea in this setting and included infants who met the criteria of a 1 minute Apgar score of < or equal to 6 which may not be the best criteria for perinatal asphyxia. The outcomes assessed in this trial were respiratory rate and heart rate up to 24 hours of age, time to establish spontaneous respirations and passive and active muscle tone up to 24 hours. There was no data available on the pre-specified outcomes proposed by the Cochrane review panel. It was not clear whether term and preterm infants were included in this trial but infants of mothers who had received narcotics within four hours of delivery or a general anaesthetic were excluded. The conclusion of this review was that at present there is insufficient data in human neonates to evaluate the safety or efficacy of naloxone in the setting of perinatal asphyxia. It is also important to acknowledge that results from animal studies have been conflicting with some showing naloxone exacerbating brain injury.

The second Cochrane review is a meta-analysis of the trials evaluating resuscitation of newborns using room air. All randomised or quasi randomised studies comparing the use of room air or any other concentration of oxygen versus 100% oxygen for the resuscitation of the depressed neonate at birth were evaluated. Only five relevant studies were identified with a total of 1302 enrolled infants. Outcome measures examined included mortality and subsequent neurological disability. Pooled analysis of four trials reporting the effect on death showed a significant reduction in the rate of death in the group resuscitated with room air (typical RR 0.71 (0.54,0.94), typical RD – 0.05 (-0.08, -0.01), NNT 20 (12, 100)). There were no significant differences between groups with respect to the rate of Grade 2 or 3 hypoxic ischaemic encephalopathy. There were no significant differences in the three trials that reported on the 10 minute Apgar score. In the one trial that followed up a selected subgroup of survivors to 18-24 months there were no significant differences in the rates of neurodevelopmental disability (however the proportion of eligible patients who were assessed was less than 70%). Collating the data from all the reviewed studies it was evident that a clinical decision was made to use back up 100% oxygen in more than a quarter of infants initially resuscitated with air. The final conclusion of the Cochrane review was that there was insufficient evidence to recommend either room air over 100% oxygen or the contrary for the routine resuscitation of neonates although there did appear to be a reduction in mortality in the room air group and no evidence of harm has been demonstrated. If room air is chosen then 100% oxygen should also still be available. It is worth noting that the same review panel published this meta-analysis in the Lancet [3] and concluded in favour of using room air as the initial resuscitation gas in term and near term infants.

The papers revealed by the PubMed search included the RESAIR 2 study [4] cited in the Cochrane review. The RESAIR 2 trial was designed on the basis of previous evidence from animal studies and the pilot study conducted by Ramji et al [5] on newborns suggesting no harm and potential benefit from resuscitation with air. Ramji et al [6] conducted a further randomised study comparing resuscitation of 431 asphyxiated infants (>1000g) using air versus 100% oxygen in four Indian teaching hospitals. The heart rates at 1, 5 and 10 minutes, median 5 and 10 minute Apgar scores and median time to first breath were comparable in both groups. The median time to first cry and duration of resuscitation were significantly shorter in the group resuscitated with air ($p = 0.008$ and 0.000076 respectively). The number of babies with evidence of encephalopathy in the first week of life and the asphyxia related mortality was not significantly different between the two groups.

The RESAIR 2 trial was a multicentre trial (11 centres with infants mostly recruited from the developing world). The study was quasi randomised with allocation to room air or 100% oxygen based on date of birth. Perhaps the greatest weakness of the study is the lack of

blinding. The primary outcome measures were death within one week and/or presence of grade II or III hypoxic ischaemic encephalopathy. Secondary outcome measures were Apgar score at five minutes, heart rate at ninety seconds, time to first breath, time to first cry, duration of resuscitation, arterial blood gases and acid base status at ten and thirty minutes of age and abnormal neurological examination at four weeks of age. Only a proportion (<70%) of infants were assessed at 18-24 months of age for neurological outcome. The time to first breath and first cry were significantly shorter in the room air versus oxygen assisted group. Although there were no significant differences in the other outcomes including mortality and neurodevelopmental outcome no harm was demonstrated in the use of air. There were also a high number of "treatment failures" (25.7%) who were switched from air to 100% oxygen at ninety seconds if they remained bradycardic or centrally cyanosed. These were analysed by intention to treat. The proportion of infants in the oxygen group meeting this criteria at ninety seconds was not recorded.

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Deorarai et al [7] studied the impact of a neonatal resuscitation programme in fourteen Indian teaching hospitals. Two senior staff members from each institution attended a neonatal resuscitation certification course based on the AAP and AHA guidelines. They then returned to train staff at their respective hospitals. Data on asphyxia related morbidity and mortality was collected for three months prior and twelve months post this educational intervention. There was a statistically significant increase in the incidence of birth asphyxia after the programme thought to reflect increased recognition of the problem. There was also a statistically significant reduction in the use of chest compression and medications ($p < 0.001$) and an increase in the use of bag mask ventilation. The researchers concluded that this reflected a more rational approach to neonatal resuscitation with more effective and appropriate use of bag and mask ventilation leading to less need for chest compressions and resuscitation drugs. Overall neonatal mortality did not change but asphyxia related deaths declined significantly ($p <0.01$).
Vento et al [8] lent further support to the argument for resuscitation with air in 2001. They conducted a blinded, monocentric randomised controlled trial in Spain comparing the use of air versus 100% oxygen for the resuscitation of 40 term infants with clinical and biochemical evidence of moderate asphyxia. The time to establish regular respirations was significantly less in the room air group ($p<0.05$). This group also measured biochemical markers of oxidative

stress. These were significantly higher in the group resuscitated with 100% oxygen ($p < 0.01$). By 28 days these markers (GSH/GSSG ratio and SOD and catalase levels) in the room air group had returned to the same levels as nonasphyxiated controls but remained significantly higher in the oxygen group. At 28 days there were no differences in clinical and neurological condition between the control, room air and 100% oxygen groups. They concluded that there were no apparent disadvantages to resuscitation with room air and potentially significant advantages but recommended further studies.

Discussion

Birth asphyxia results in a period of primary neurological injury followed by a longer period of secondary injury caused by a number of deleterious physiological processes. One of these processes is the generation of oxygen free radicals. There has been mounting concern in recent years over the role that treatment with 100% oxygen may have in the generation of oxygen free radicals and subsequent reperfusion injury and the negative effect on cerebral blood flow. Resuscitation with room air is one of a raft of potentially neuroprotective strategies being investigated.

The greatest burden of perinatal asphyxia is in the developing world. Resource poor countries have the highest incidence, the highest mortality and the highest rates of morbidity following a perinatal asphyxial insult. A WHO survey [9] of resuscitation practices in 16 countries has revealed that often there is no basic resuscitation equipment available or it is in poor condition and health personnel are not properly trained in its use. In these same countries oxygen is often not readily available. This has provided further incentive for researchers to examine whether resuscitation of the newborn with room air is as effective as 100% oxygen and to look at national neonatal resuscitation programmes.

In the management of apnoea associated with birth asphyxia there is little doubt that some method of respiratory support is important. There is however a lack of data concerning the optimal method of administering respiratory support. Resource wealthy countries centres tend to use either an Ambu or Laerdal type bag and mask or alternatively a flow-driven anaesthetic-type bag which requires a pressurised gas supply and usually a manometer. There is also almost no data on which mask design is optimal. Even with the answers to these questions available the challenge in the resource poor setting is to establish what respiratory support device is practicable in terms of equipment supply and maintenance and ease of use by less skilled medical personnel.

Summary

There is a paucity of studies examining the optimum management of apnoea in birth asphyxia in both a resource poor and a resource rich setting. There has however been a recent focus on the utility of resuscitation of the depressed newborn with room air which has primarily emerged out of collaborative work done in the developing world. This data suggests no harm from resuscitation with room air and a possible survival advantage (grade A evidence). It must be emphasised that oxygen should also be available for "rescue" therapy should resuscitation with room air fail. Large scale studies looking at neurodevelopmental outcome are awaited. The pendulum does appear to have swung towards air as the optimum initial resuscitation gas in term neonates. There is currently insufficient data regarding preterm infants however it is likely that they may also benefit from resuscitation with less than 100% oxygen.

This review was unable to find any human studies examining the management of secondary apnoea in birth asphyxiated infants. There is currently insufficient evidence to recommend the routine use of naloxone in the primary resuscitation of depressed infants at birth. There does however appear to be a significant benefit from a staff training programme on neonatal resuscitation in reducing asphyxia related mortality in a developing country setting. India has been leading the way in implementing a National Resuscitation Programme based on the "train the trainer" approach. The impact of such a programme on the burden of long term morbidity in these survivors is yet to be studied. However given that most births in the world occur out of hospital and are attended by traditional birth attendants we must also consider the effectiveness of even simpler resuscitation strategies when bag and mask ventilation equipment is unavailable.
It must also be emphasised that birth asphyxiated infants are a heterogenous group and may have a

number of underlying conditions contributing to their depressed state at birth. There may be significant differences in preterm and term asphyxiated infants and management strategies may not be able to be extrapolated from one group to the next. It is clear that further research is needed in this area. Given the enormous contribution of birth asphyxia to global neonatal mortality and morbidity it must be a research imperative.

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