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New Series

Management of neonatal emergencies: current evidence from Cochrane/other systematic reviews
Clinical Question 1: Room air vs. 100% oxygen for neonatal resuscitation

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Question 1:.....

This is the first of the series on Cochrane systematic reviews planned for the Journal.Data comparing room air with 100% oxygen for neonatal resuscitation in a systematic manner have been scant.This review on a common management scenario by ShankarJ and Jhuma S translates best evidence into best care.It analyses several important findings and merits consideration of its implications for practice.The Editorial Board looks forward for such relevant submissions.

CASE SCENARIO

You have been called to the emergency OT to help resuscitate a term infant to be born by vacuum extraction. The obstetrician informs you that the fetus has significant bradycardia and might need resuscitation.

You ensure that all necessary equipments are in order and oxygen is available. You attach oxygen to the self-inflating bag when your colleague who has been trained abroad questions the need for 100% oxygen to resuscitate an asphyxiated neonate.

You don't remember reading about room air resuscitation in your residency! You are now confronted with the following questions:

1. How can one *think of* using room air for resuscitating an asphyxiated neonate? Is it not a 'standard practice' to use 100% oxygen for neonatal resuscitation?

2. Are there any studies available that have compared use of room air and oxygen in this setting?

3. If available, do the results favor room air or oxygen?

4. Is there any need to change my practice?

You inform him that you will answer his query after reviewing the available literature.

CLINICAL QUESTION

Is room air better than 100% oxygen for resuscitating an asphyxiated neonate?

Background

When a newborn baby is being resuscitated in the delivery room, almost all attending pediatrician/neonatologists would resort to using 100% oxygen as a reflex – either as free-flow or along with bag and mask ventilation. With the increasing knowledge of the adverse effects of oxygen induced free radicals in both experimental animals[1] as well as humans[2], the

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routine practice of using 100% oxygen is being questioned in the last two decades or so. The fact that most infants who require resuscitation have normal lungs and hence are more susceptible to oxidant injury following use of high oxygen concentration lends credence to this view. The controversy has lead to a spate of studies in the last few years. In this article, we have tried to review the evidence available till date and tried to answer some of the queries that lurk us with regard to use of room air for resuscitating an asphyxiated neonate.

Evidence

As of today, there are three systematic reviews (including a Cochrane review) available in this regard:

1. Cochrane review: The review by Tan et al in the year 2005 includes five studies that enrolled a total of 1302 infants.[3] Pooled analysis of the four trials reporting effect on mortality showed a signiûcant reduction in the rate of death at latest follow-up in the group resuscitated with room air (typical relative risk [RR]: 0.71, 95% confidence interval [CI]: 0.54 to 0.94; number needed to treat [NNT]: 20, 95% CI: 12 to 100). There were no signiûcant differences between the groups with respect to rates of grade 2 or 3 hypoxic ischaemic encephalopathy (HIE). One of the four trials also reported a statistically signiûcant difference in median 5 minute Apgar scores, favoring the group allocated to room air.

2. Only one of the included trials followed up survivors until 18-24 months. It found no signiûcant differences in rates of adverse neurodevelopmental outcomes including cerebral palsy (RR: 1.34, 95% CI: 0.55 to 3.24) between the two groups; however, the proportion of eligible patients lost to follow-up was as high as 30%.[4] The authors concluded that there is insufficient evidence at present on which to recommend a policy of using room air over 100% oxygen, or vice versa, for newborn resuscitation.[1]

3. Other systematic reviews: (a) The review by Saugstad et al in year 2005 included five studies (four of which were included in the Cochrane review as well) that enrolled about 1700 infants.[5] The authors found a significant reduction in neonatal mortality in the room air group (odds ratio [OR]: 0.57, 95% CI: 0.42 to 0.78). On subgroup analysis, the reduction in mortality was found to be significant in both term (n=1502; OR: 0.59, 95%CI: 0.4 to 0.87) and preterm (n=235; OR: 0.51, 95% CI: 0.28 to 0.90) neonates.

(b) In a more recent review by Rabi et al (2007)[6], seven controlled studies that enrolled 2011 infants were included. The results were in accord with that of the other two reviews: significant reduction in mortality in room air group at 1 week (OR: 0.70, 95%CI: 0.50 to 0.98) and at 1 month (OR: 0.63, 95%CI: 0.42 to 0.94) but no difference in the incidence of grade II or III HIE between the air and oxygen groups (OR: 0.86, 95%CI: 0.65 to 1.14).

To summarize, using room air for neonatal resuscitation as opposed to 100% oxygen

· Reduces neonatal and early neonatal mortality (until one week of life) in term neonates

· Possibly reduces neonatal mortality in preterm infants (Note: number of preterm infants enrolled in the trials is much less when compared to term neonates)

· Does not reduce the incidence of either short-term (HIE grade II or III) or long-term (cerebral palsy) adverse neurological outcomes

DISCUSSION

The available evidence seems to largely favor room air resuscitation in asphyxiated neonates. However, valid concerns remain with regard to the studies included in these reviews. They need to be addressed before a definite recommendation regarding room air resuscitation can be made.[7] The concerns include:

1. Methodological issues: The four largest studies included in the reviews were quasi-randomized and not blinded. Though the Cochrane review did not find any significant heterogeneity between the results from trials using different randomization methods, the possibility of selection bias (in quasi-randomized studies) cannot be completely ruled out. Similarly, lack of blinding - though unlikely to affect a 'hard' outcome like mortality - could result in different level of care

(either knowingly or unknowingly) in the two groups thus affecting the observed results.

2. Lack of proper and adequate long-term follow-up data: This is the major impediment in accepting the results of the systematic reviews as such. The follow-up data available comes from a single study, is incomplete, and points toward increased disability in surviving infants resuscitated with room air (albeit, not a statistically significant effect). Given that the particular study was not powered enough to detect a small difference in the incidence of long-term outcomes, one has to be really cautious in interpreting this data.

3. Use of room air with oxygen back-up: In most of the trials means that recommending *only* room air for neonatal resuscitation is not possible with the available evidence. Up to $1/4^{th}$ of infants randomized to room air in these studies were ultimately given 100% oxygen (usually after 90 seconds) because of the lack of clinical improvement. Hence, the question of abandoning oxygen in the delivery room simply does not arise.

4. Lack of adequate data in preterm infants: Though the studies have enrolled a sizeable proportion of preterm neonates, the number is still not enough to make any specific recommendation for this vulnerable group. Almost all studies have excluded extremely low birth weight infants (birth weight <1000 g). This is really unfortunate because preterm infants who are at higher risk of oxidant injury than term neonates could have benefited from using lower concentrations of oxygen for resuscitation.

5. Issue of 'all-or-none' phenomenon - the studies have looked at either 100% oxygen or room air for resuscitation while the answer could possibly lie somewhere in between the two extremes. Indeed, future trials should consider the use of oxygen blenders and pulse-oximeters in the labor room to titrate the oxygen concentration used according to pre-set limits of saturation.

In addition, the fact that majority of studies have emerged from essentially the same (three) centers brings into question the generalizabilty of their results. It must, however, be remembered that these trials have enrolled infants from many countries across the globe including the Indian subcontinent.

Given the concerns, we feel one cannot be dogmatic about using *only* room air for resuscitation at this point of time. Further studies with long term follow up as the primary outcome would be required before a definite recommendation with respect to use of room air alone can be made. Till such time, it might be prudent to follow the recommendation given by the American Heart Association and the American Academy of Pediatrics in the textbook of neonatal resuscitation (2005), "one can start resuscitation with room air in term asphyxiated neonates and have 100% oxygen as back up in case there is no improvement after 90 seconds".[8]

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