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REVIEW PAPER

Controversies in neonatal resuscitation

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Abstract

Despite recent advances in perinatal medicine and in the art of neonatal resuscitation, resuscitation strategy and treatment methods in the delivery room should be individualized depending on the unique characteristics of the neonate. The constantly increasing evidence has resulted in significant treatment controversies, which need to be resolved with further clinical and experimental research.

Keywords

Controversies, neonates, resuscitation

History

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Background

Despite recent advances in perinatal medicine, about 4000 infants annually require extensive resuscitation [1]. Although resuscitation of the neonate at birth has been the subject of long discussions and debates among neonatologists, and research projects are constantly increasing, the principles of delivery room care did not change much until the end of the 90 s. After the establishment of the first guidelines on newborn resuscitation in 1999, the blooming of adult and animal research efforts resulted in the substantial modification of these recommendations [2]. However, despite the major changes in the way that newly born infants are managed in the delivery room, significant controversies exist after in-depth reviewing of the accumulated evidence.

Respiratory support in the delivery room

Although maintenance of the upper airway patency remains the cornerstone of adequate airway management at birth, the recommended airway opening maneuvers have not been adequately evaluated in neonates. In a mini-review of human studies, the authors concluded that jaw thrust appears to be more effective in achieving a patent upper airway and may help to reduce airway obstruction in mask ventilation, while the additional application of chin lift may reduce leak [3].

But, even in case of state-of-the-art ventilation, what should be the optimal concentration of the administered oxygen in the delivery room? Birth asphyxia is characterized by periods of hypoxia during which anaerobic metabolism increases. Although supplemental oxygen administration may rapidly improve tissue oxygen delivery, re-oxygenation with 100% O_2 enhances the production of reactive oxygen and nitrogen species which damage the reperfused tissues [4]. On the other hand, beginning the resuscitation efforts with low oxygen concentrations, it may extend the hypoxemic period with devastating consequences in survival and brain function. All these make the initial oxygen concentration a major controversy in neonatal resuscitation. In a recent meta-analysis re-evaluating the evidence regarding the oxygen concentration, it was reported that the literature is insufficient to make any statement regarding the superiority of oxygen or room air as the initial gas mixture for neonatal resuscitation [5]. In a meta-analysis of depressed neonates resuscitated with room-air or 100% oxygen, the authors reported that there is a significant reduction in the risk of neonatal mortality and a trend towards a reduction in the risk of severe hypoxic ischemic encephalopathy in neonates resuscitated with 21% oxygen [6]. Although the growing evidence supports the benefits of room-air and the risks of 100% oxygen used for neonatal resuscitation, there are substantial concerns about the effectiveness of room-air as compared with 100% oxygen in the return of spontaneous circulation and is unethical to propose a randomized blinded clinical trial [7]. Interestingly, 4 prospective randomized studies showed that resuscitation of extremely low gestational age neonates with minimal oxygen concentration is safe and effective [8–11]. This finding, and the increasing evidence regarding the harmful effects of hyperoxia support the concept of ‘‘titration of individual oxygen needs’’ in the delivery room.

Positive end-expiratory pressure in the delivery room

Spontaneously breathing preterm neonates with respiratory distress may be supported with continuous positive end-expiratory pressure (CPAP) [12]. Although the advantages of

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CPAP were first mentioned about 30 years ago, evidence supporting its early use in very low birth weight (VLBW) neonates has increased over the last years, during which animal and human research has shown that CPAP is less injurious to the lungs than mechanical ventilation [13,14].

Several clinical trials have shown that CPAP reduces the need for mechanical ventilation and surfactant administration. Aly et al. investigated the potential harmful effects of early intubation and examined whether unsuccessful early nasal CPAP attempts might subject infants to any unforeseen morbidity; they reported that the success of early nasal CPAP improved with increased gestational ages and with staff experience over time, concluding that an individualized approach should be considered for respiratory support of VLBW neonates [15]. Jobe et al. induced preterm labor in antenatally glucocorticoid-treated sheep carrying twins at 133 d gestation and reported that CPAP results in lower indicators of acute lung injury than mechanical ventilation, during the first 2 h of life [16]. In a randomized trial of early bubble continuous positive airway pressure for VLBW, CPAP resulted in a more benign evolution of respiratory distress syndrome and lower surfactant and mechanical ventilation requirements [17]. Other studies has shown that newborns receiving early CPAP require less surfactant, fewer days of mechanical ventilation, and less postnatal steroid use [18–21]. Amari et al. showed that more than 80% of newborns with birth weigh 900 g or over, did not require mechanical ventilation when CPAP was used; however, in newborns less than 700 g the treatment success was only 25%. The authors concluded that although several variables available near birth are strongly associated with early CPAP failure, they proved weak predictors of failure [22].

Hesham et al. in a randomized, open label, controlled trial reported a better approach for weaning preterm infants from nasal CPAP with or without transitioning to nasal cannula and found that weaning preterm infants from nasal continuous CPAP to nasal cannula is associated with increased exposure to oxygen and longer duration of respiratory support [23]. Of note, CPAP has several advantages in contrast to passive oxygen administration as it keeps the alveoli open, improves the functional residual capacity, reduces the work of breathing, reduces the levels of pulmonary superoxide and inflammatory mediators, and stimulate the growth of the lung [16,24].

Although there is strong evidence to support the use of CPAP in the treatment of babies with respiratory distress, a prospective controlled trial is certainly required to determine if extremely premature spontaneously breathing infants are better served by initial management with CPAP or mechanical ventilation. Also, it would be of major interest to determine whether premature neonates should be supported initially with CPAP following delivery, or after the neonate has been extubated following prophylactic surfactant administration. Furthermore, little is known about which strategies or CPAP devices should be used or how to manage patients using CPAP. In conclusion, despite the large body of information regarding the beneficial effects of CPAP, data are insufficient at this time to support or refute its use during neonatal resuscitation. Further research is necessary for the full clarification of the role of CPAP in neonatal resuscitation.

Temperature regulation

Approximately 25% of VLBW neonates with gestational age less than 26 weeks have a temperature lower than 35 °C on admission to the neonatal intensive care unit [25]. Warmth is a fundamental requirement of the newborn and especially of the preterm, but the dangers of hyperthermia should not be neglected. Traditionally, all neonates should be placed under a radiant heater, dried and covered with warmed towels with a hat covering the head in order to prevent them from becoming cold [26]. However, hypothermia remains common and is associated with increased mortality among extremely preterm neonates [27]. Therefore, despite recent advantages in neonatal resuscitation, the best method of achieving thermoneutrality remains the subject of ongoing research.

Today, food-grade polyethylene bags are recommended for thermoregulation of extremely preterm neonates [2]. The recommendation was based on randomized trials demonstrating that preterm neonates placed in food-grade polyethylene bags without drying them had higher mean temperature on admission to the neonatal intensive care unit compared with neonates that were only dried and wrapped with towels [28]. Although there is a large body of evidence supporting the wrapping of newborns with gestational age of less than 28 weeks' gestation in polythene wraps or bags at birth without drying to reduce heat loss [29,30], a recent Cochrane review reported that plastic bags and wraps reduce heat loss in preterm neonates but do not reduce mortality [31].

Exothermic sodium acetate gel mattresses are also used as an additional heat source in an attempt to prevent hypothermia. Singh et al. reported that the use of these mattresses for neonates with gestational age less than 30 weeks was associated with a significantly greater proportion of neonates admitted to the neonatal unit with a temperature in the euthermic range, although there was also an increased risk of hyperthermia [32]. In a study comparing the admission temperature of neonates treated with polyethylene bags alone, to that of neonates treated with exothermic mattresses in addition to bags in the delivery room, it was reported that the use of exothermic mattresses in addition to polyethylene bags, particularly in younger, smaller ones, may result in increased risk for hypothermia and hyperthermia on admission [33]. Moreover, another study showed that plastic bags are less effective for neonates below 28 weeks' gestation compared with more mature neonates, while the use of gel mattresses was associated with an increased rate of hyperthermia (>37 °C) [34].

Today, it remains unknown what does the use of polyethylene wrap/bag and exothermic mattress as compared to polyethylene wrap/bag only do, or how rapidly should a VLBW neonate with an initial temperature below 35 °C be rewarmed. Also, we do not know if the delivery room temperature affects the initial temperature of the baby or if raising the temperature has adverse maternal consequences [35]. In addition, maternal fever in labor, its treatment and its consequences on newborn temperature and thermoregulation

have to be elucidated. Again, until appropriately powered randomized trials reporting important outcomes become available, individualization of therapeutic modalities should be the rule; the temperature in delivery room should be maintained at least 26 °C for neonates of less than 28 weeks' gestation with careful monitoring of their temperature in order to avoid both hypothermia and hyperthermia [36].

Early vs. delayed cord clamping

Despite the fact that clamping and cutting the umbilical cord at birth is the oldest intervention in humans, the time at which the umbilical cord should be clamped remains unknown and clamping times vary significantly between studies [37].

Cord clumping can be managed by two distinct approaches; in the physiological management, the placenta is allowed to deliver spontaneously, while in the active management, oxytocin is administered, the cord is clumped, and the placenta is delivered by controlled traction [38]. Although it has been reported that routine 'active management' is superior to 'expectant management' with regards to blood loss and post-partum hemorrhage, there are no guidelines on this important issue and considerable differences concerning the management of stage of labor exist worldwide [39].

The European Resuscitation Council latest guidelines (2010) for neonatal resuscitation recommends delaying the umbilical cord clamping for at least 1 min in case of neonates not requiring resuscitation or premature neonates requiring stabilization. Contrarily, for neonates requiring resuscitation, resuscitative intervention remains the priority [40]. In a Cochrane meta-analysis, delayed cord clumping was defined as a delay of 30 s or more after birth [41]. A randomized controlled trial comparing delayed *versus* immediate cord clamping in term neonates reported that providing additional placental blood to the preterm neonate by delaying cord clamping for 30–120 s, rather than early clamping, seems to be associated with less need for transfusion, better circulatory stability, and less intraventricular hemorrhage [42]. In a single-center randomized controlled trial, delayed cord clamping, compared with early, did not have a significant effect on maternal postpartum hemorrhage or on the proportion of valid umbilical blood gas samples [43]. Moreover, De Paco et al. reported that a delay of 2 min before umbilical cord clamping does not significantly change acid-base and gas analysis results, with the exception of a higher mean umbilical artery pO_2 value in the delayed clamping group [44]. Andersson et al. investigated the effects of delayed umbilical cord clamping, compared with early clamping, on infant iron status at 4 months of age and found that delayed cord clamping, compared with early clamping, is a safe procedure which results in improved iron status and reduced prevalence of iron deficiency at 4 months of age [45], while Oh et al. reported that a higher hematocrit is achieved by delayed cord clumping in VLBW neonates, suggesting effective placental transfusion [46]. Aziz et al. reported that delayed cord clamping appears practical, safe, and applicable, and has minimal impact on immediate neonatal transition, with possible early neonatal benefits [47]. Indeed, delayed cord clamping seems to protect VLBW neonates from intraventricular hemorrhage, late-onset sepsis, and motor disability [37,48,49].

On the contrary, there is evidence that early cord clamping may be a potential iatrogenic cause for both the need for resuscitation and later outcome. Immediate cord clamping results in a 30% lower blood volume and up to a 50% lower red-cell volume for the neonate, predisposing to hypoxia, inflammation, and ischemic damage [50,51]. In the meta-analysis by Hutton and Hassan, the risk of developing polycythemia was slightly higher in neonates allocated to delayed cord clamping at both 7 h after birth and at 24 to 48 h after birth [37]. In another double-blind randomized-controlled study, Jahazi et al. reported that no neonate developed clinical manifestations of polycythemia at 2 h, 18 h, or 5 d after birth, but that 21.9% of the neonate from both delayed and immediate clamping group developed asymptomatic polycythemia at 2 h of life [52].

Furthermore, transient tachypnea of the newborn may be related to delayed cord clamping, although the data concerning this association are still inconclusive. Cernadas et al. reported a slight increase in respiratory rate in neonates that experienced delayed cord clamping [53], while McDonald and Middleton found that both the delayed and immediate clamping groups had a similar number of neonates admitted to any level of neonatal intensive care unit for respiratory distress [38].

Although the available evidence favors the delayed clamping of the umbilical cord, there are no guidelines on this issue; therefore, the timing to cord clamping is a decision made by the individual provider based largely on personal preference [39]. Further research is warranted for the fully understanding of the effects of early and delayed cord clumping in fetal-to-neonatal transition and newborn resuscitation.

Post-resuscitation management

Although post-cardiac arrest syndrome has been adequately described in adults, there are significant gaps in knowledge in neonates with return of spontaneous circulation (ROSC). Today it is known that cardiovascular dysfunction occurs in the majority of asphyxiated neonates and is a major cause of neonatal morbidity and mortality. The newborn heart is especially vulnerable to oxidative stress and reperfusion injury due to immature antioxidant defense mechanisms and increased vulnerability to apoptosis [54]. Although novel strategies for myocardial protection aimed at reducing the generation of reactive oxygen species through controlled reoxygenation, boosting antioxidant defenses, and attenuating cellular injury *via* mitochondrial stabilization, vasopressor or inotropic support may be necessary post-ROSC. However, the use of these drugs may be harmful as they have been associated with various undesired effects.

Although catecholamine therapies, including epinephrine, have also been shown to have potential side effects in bowel perfusion and carbohydrate and lactate metabolism [55,56], in an animal study of asphyxiated newborn piglets, vasopressin treatment caused a dose-dependent increase of mean arterial pressure, while preserving cardiac function and cerebral and mesenteric hemodynamics following reoxygenation [57]. In addition, adding milrinone or levosimendan to dopamine may

improve systemic hemodynamics [58]. However, Esch et al. reported that although levosimendan improves cardiac output, it has no marked effects in carotid, superior mesenteric and renal perfusion [59]. Of note, Nachar et al. reported that low to medium doses of dopamine, epinephrine, dobutamine and norepinephrine increase blood pressure and systemic and regional blood flow in a drug-specific manner: at higher doses, dopamine, epinephrine, and norepinephrine but not dobutamine decrease systemic, renal, intestinal, and muscle blood flow, while cerebral blood flow remains unchanged. Epinephrine induced significant increases in muscle blood flow and serum glucose and lactate concentrations. The authors concluded that their findings reveal novel drug- and dose-specific differences in the hemodynamic response to escalating doses of vasoactive medications in the neonatal cardiovascular system [60]. In a prospective, randomized, blind cross-over newborn piglet study, epinephrine infusion during normoxia increased systemic pressure more than pulmonary arterial pressure at doses equal or more than 8 micrograms/kg/min and produced a more appropriate hemodynamic profile in the presence of hypoxic pulmonary hypertension than dopamine infusion [61]. Of note, high-dose dobutamine treatment resulted in platelet aggregation dysfunction in hypoxic-re-oxygenated newborn piglets [62]. Further investigations are needed to investigate the use of vasoactive/inotropic medications for the treatment of post-cardiac arrest myocardial dysfunction.

Neurologically intact survival is another major concern after newborn resuscitation. Besides hemodynamic optimization and respiratory support using controlled reoxygenation, newborn animal studies and pilot human studies, suggest that mild hypothermia following peripartum hypoxia-ischemia in neonates may reduce neurological sequelae without adverse effects. A recent Cochrane review notes that therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic ischaemic encephalopathy [63]. Cooling reduces mortality without increasing major disability in survivors, while the benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. The authors concluded that hypothermia should be applied in term and late preterm neonates with moderate-to-severe hypoxic ischaemic encephalopathy if identified before six hours of age. Also, in a meta-analysis of well-designed conducted randomized trials of therapeutic hypothermia in asphyxiated term and near-term newborns, a significant increase was reported in the number of neonates surviving without serious impairment [63]. Despite the available evidence, the time at which cooling should be started remains unknown and further trials are required to determine the appropriate time and techniques of cooling and their effect on outcome and survival.

Conclusions

Despite recent advances in gestational medicine and resuscitation of the newborn, resuscitation strategy and treatment methods in the delivery room should be individualized depending on the unique characteristics of the newborn. The constantly increasing evidence has resulted in significant treatment controversies which will be resolved with further clinical and experimental research.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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