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Chest compressions and epinephrine during resuscitation of infants born at the border of viability: Yes, no or maybe?

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Neonatology, in large part due to its population of babies born at the edge of viability, is rife with bioethical issues. This unique population is at high risk of mortality and considerable neurodevelopmental morbidity. One contentious, ongoing debate concerns whether these extremely low birth weight infants born at the border of viability should, if required by the Neonatal Resuscitation Program guidelines, receive chest compressions and epinephrine as part of their delivery room resuscitation. The present article, through a case presentation and discussion based on the ethical framework of principlism, provides readers with a thoughtful approach to the controversial issue of the provision of chest compressions and epinephrine as part of resuscitation for extremely low birth weight infants born at the border of viability.

Key Words: Bioethics; Cardiopulmonary; Epinephrine; Extremely low birth weight; Infant; Resuscitation

Neonatology provides multiple profound and interesting cases to examine bioethical issues and principles. Extremely low birth weight (ELBW) premature infants, defined as those with a birth weight of lower than 1000 g, comprise a significant proportion of the patient population. Some of these infants are born at less than 25 weeks' gestation – a gestational age that is generally considered to be at the border of viability. When born in this gestational age range, at least 50% of infants will either die or have considerable neurodevelopmental impairment. The decision regarding whether to resuscitate such babies is an ongoing debate. Many centres do resuscitate these infants, which raises a secondary question: if the medical team provides respiratory resuscitation (including intubation), should they give chest compressions (CC) and epinephrine when it is required, as per the Neonatal Resuscitation Program (NRP) guidelines? The present review will, through a case presentation and discussion based around the ethical framework of principlism, provide readers with a thoughtful approach to the controversial issue of the provision of CC and epinephrine as part of resuscitation for ELBW infants born at the border of viability. Principlism was chosen as the bioethical framework with which to examine this question because most clinicians are more familiar with it than other ethical frameworks.

CASE PRESENTATION

Mrs Dawn (see Disclaimer), a 23-year-old woman in her first pregnancy, presented to her local medical centre at a gestation of

L'administration de compressions thoraciques et d'adrénaline pendant la réanimation chez les nourrissons nés à la limite de la viabilité : Oui, non ou peut-être?

La néonatalogie, en grande partie à cause de sa population de bébés nés à la limite de la viabilité, regorge d'enjeux bioéthiques. Cette population unique est très vulnérable à la mortalité et à une morbidité neurodéveloppementale considérable. Une question litigieuse et continue consiste à se demander si ces nourrissons d'extrême petit poids de naissance nés à la limite de la viabilité devraient, si les lignes directrices du Programme de réanimation néonatale l'indiquent, recevoir des compressions thoraciques et de l'adrénaline dans le cadre de leur réanimation en salle d'accouchement. Au moyen d'une présentation de cas et d'un exposé fondé sur la structure éthique du principlisme, le présent article offre au lecteur une démarche réfléchie à l'égard de la question controversée d'administrer des compressions thoraciques et de l'adrénaline dans le cadre de la réanimation de nourrissons d'extrême petit poids de naissance nés à la limite de la viabilité.

24 weeks plus one day with premature rupture of membranes. Given the concerns about possible premature delivery, Mrs Dawn was given a dose of antenatal steroids and transferred by air to the nearest tertiary care centre.

The paediatrics team consulted with Mrs Dawn and her husband; they were told that the statistics reported a 65% chance of death or significant neurodevelopmental impairment if the baby survived after being born at this gestational age (1). Given these statistics, the parents were informed of the treatment options, which included either an active attempt to resuscitate their baby or the provision of palliative care with the understanding that they would be able to hold their baby until it passed away in a short period of time. Resuscitation was described as only respiratory support including intubation and ventilation. There was no offer of CC or epinephrine during resuscitation at this gestational age because it was considered futile by the neonatal team. The parents decided that they would provide palliative care.

At a gestational age of 24 weeks plus six days, the paediatrics team came to revisit the issues relating to a baby being born at 25 weeks' gestation. The statistics now suggested a 40% chance of death or significant neurodevelopmental impairment if the baby was born at this gestational age (1). The parents were told that the standard of care for babies born at this gestational age and beyond was full resuscitation. The parents were surprised by this information and stated that they had been given the impression that

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palliation was still an option and they had made the decision to wait until 26 weeks' gestation to consider resuscitation.

The neonatal consultant then became involved in the discussion. The use of CC and epinephrine was mentioned as something that could be provided but, if required, was generally a bad sign for the baby's outcome. The parents believed that they had made the right decision at 24 weeks and that it should remain the same at 25 weeks, even in the face of improved statistics.

After much discussion, it was decided that the current decision for palliation would stand because the gestational age of the fetus was still 24 weeks plus six days. The discussion was to be continued the next morning with the parents, the consultant, the medical director of neonatal services and the hospital legal counsel.

That evening, Mrs Dawn experienced sudden cramping and then saw that the baby's foot was presenting. She and her husband began to fluctuate between saying "Do everything and help the baby", "No, this isn't supposed to happen, the baby's too young, we don't want the baby resuscitated", and "We don't know what to do". In the face of parental indecision, the neonatal fellow in attendance said the paediatric team would initiate resuscitation if the baby was born with a heart rate. No discussion occurred about whether "everything" included CC and epinephrine.

Sadly, the baby died before delivery due to prolonged cervical entrapment of the head; a decision about resuscitation and the use of CC or epinephrine was, therefore, not required. It is, nevertheless, an important question to consider.

DISCUSSION

If delivery room resuscitation is provided for an ELBW infant at the edge of viability, should CC and epinephrine be a mandatory part of the resuscitation as outlined in the NRP guidelines? As with many ethical issues, there is no simple or universally applicable answer to this question. Insufficient research has been published to answer the question. However, by considering key bioethical principles in conjunction with an examination of the practical issues surrounding administration of CC and epinephrine, as well as a review of the more recently published clinical outcomes, we hope to provide health care practitioners (HCPs) with insight into the controversy surrounding the provision of CC and epinephrine to ELBW infants. We propose a solution to this controversy based on ethical considerations.

The NRP guidelines (2) were initially published before the routine survival of ELBW infants (3). Although at first consideration these infants may appear to simply be 'miniature' versions of full-term infants, they are anything but; they are a unique population with dramatically heightened risks of death and severe morbidities (4). These risks are most significant for infants born at the edge of viability. Appropriate delivery room resuscitation contributes significantly to improving these outcomes, as demonstrated by the decreased death and morbidity rates observed with ELBW infants born in tertiary care hospitals compared with those born elsewhere (5). Given the risks associated with the resuscitation of ELBW infants, it is recognized that there will be differences in how and when NRP guidelines are used. What benefits a full-term neonate by promoting survival with little chance of neurodevelopmental impairment, may actually result in harm to an ELBW infant (eg, survival with severe neurodevelopmental disability [6]). There have been discussions about modifying the NRP guidelines surrounding the use of CC and/or epinephrine for ELBW babies, but the amount and/or quality of evidence supporting any modifications in this population is underwhelming. The risk-to-benefit ratio for these interventions in the resuscitation of ELBW infants remains a debatable subject.

The absence of clear data suggesting usefulness in conjunction with the presence of possible harms creates a situation of equipoise. These are situations in which HCPs often experience moral distress surrounding decision making. If these situations are not adequately resolved with thoughtful process, the HCPs can be left with significant residue. It is in times such as these that ethical frameworks help us make a well-considered decision about an appropriate course of treatment. The ethical framework of principlism, as coined by Beauchamp and Childress (7), is one with which most HCPs are familiar. Its use in the present review will help HCPs consider their approach to the provision of CC and/or epinephrine to ELBW infants born at the edge of viability. Principlism's constituent parts include respect for autonomy, non-maleficence, beneficence and justice (7).

Beneficence is defined as "a group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs" (7). If an intervention provides no benefit, it should not even be considered; if there are benefits, they must be weighed against the risks before instituting the intervention. Given that the vast majority of neonates, including premature ones, with a heart rate of less than 60 beats/min respond favourably to 30 s of effective positive pressure ventilation (PPV) (2,8), its beneficence is obvious. Unfortunately, effective PPV is not always easily accomplished in ELBW infants due to increased difficulties with suctioning, positioning, equipment selection (8,9), intubation (10) and positive end-expiratory pressure use (8,11). Even when PPV is achieved, the traditional chest rise may not be observed despite adequate tidal volumes (12). Given these difficulties with establishing and assessing effective PPV and, moreover, the fact that even effective PPV will not uniformly improve the heart rate, some ELBW infants will remain bradycardic for more than 30 s. If CC are initiated as per NRP guidelines, this intervention may be life saving by sustaining cardiac output and circulating blood to the vital organs (2). Animal models of adult cardiac arrest suggest that CC alone provides better neurological outcomes than CC and PPV (13). Although the applicability of this and other data (14) to neonates can certainly be questioned, it does suggest that CC support cardiac output. At the same time, CC may cause harm by hindering the provision of what the baby needs most – continued, effective PPV. If CC fail to improve the neonate's clinical condition, the addition of epinephrine may result in the return of spontaneous circulation (based on animal studies) due, in part, to its enhancement of the coronary artery perfusion pressure (15). The actual benefit to human patients is more difficult to surmise due to the understandable ethical barriers to prospective or laboratory-based human research on the subject.

The principle of nonmaleficence is defined as "[the] norm of avoiding the causation of harm" (7). Due to the absence of a clear benefit with the use of CC and epinephrine, the principle of non-maleficence must be considered. It has been hypothesized that CC causes atelectasis (16) and may, therefore, have a negative impact on the establishment of effective PPV. In addition, CC may cause rib fractures and pneumothoracics during aggressive resuscitative attempts (17-19). The few studies investigating these outcomes are limited by small sample sizes and primarily rely on autopsy specimens for diagnosis. The results are equivocal but do not suggest an increase in severe complications. The appropriate use and dosing of epinephrine remain unclear and largely unstudied, and are primarily extrapolated from the adult literature. The possibility of direct harmful effects, such as intraventricular hemorrhage and decreased survival with high doses, due to this drug exists (15). Epinephrine, when given for persistent bradycardia despite CC and PPV, may

help increase the heart rate and improve cardiac output but, when it is given via an endotracheal tube (common for first dose[s] in an extensive resuscitation), the appropriate dose and its efficacy are uncertain (20). It has the potential to obstruct the airway with resulting lung collapse and transient loss of effective PPV. The risk of accidental extubation may also increase due to endotracheal tube manipulations, further compromising PPV (21). These concerns exist for all neonates requiring extensive resuscitation and are, therefore, not unique to the ELBW population.

The practical issues of delivering CC and epinephrine during the resuscitation of ELBW infants and the exploration of benefits versus harms, as outlined above, lead one to consider the effectiveness or, alternatively, the futility of providing CC and epinephrine in this unique population. Futility of medical care was recently reviewed (22). If a treatment benefits neither the physical nor overall well-being of a patient, then the treatment, even if desired by the patient or family, is futile and not medically indicated. Several studies (23-25) since 1999, each retrospective and small in sample size, have investigated the outcomes of ELBW infants who received CC and/or epinephrine in the delivery room. Studies before 1999 generally supported the argument that outcomes were worse for preterm infants who required CC and/or epinephrine.

While no study has exclusively evaluated infants born at the extremes of viability (ie, less than 25 weeks), several focused on ELBW infants and can provide useful information. Sanchez-Torres et al (23) reported no difference in survival and non-neurological morbidity between infants weighing less than 996 g who did and did not receive CC, but those who received CC had three times ($P < 0.01$) the rate of general neurological morbidity (defined as a combined outcome of grade III intraventricular hemorrhages, periventricular hemorrhagic infarctions and/or periventricular cystic leukomalacia). While important short-term outcomes, these surrogate outcomes do not uniformly predict long-term outcomes. Finer et al (24) noted an increase in mortality and morbidity in infants weighing less than 1000 g receiving CC compared with controls, but pointed out that even in the CC group, the majority survived and showed no evidence of severe intraventricular hemorrhages. In another article, Finer et al (25) discovered that infants weighing less than 750 g who received CC or CC and epinephrine could have an intact survival as assessed by neurodevelopmental outcomes at more than nine months. They noted that the intact survival rate in the group that received CC or CC and epinephrine was not significantly different from the matched control group who did not require CC. Jankov et al (26) also reported a case series in which 16 infants weighing less than 750 g received CC or CC and epinephrine, and noted that eight of the nine survivors were free of significant neurodevelopmental disabilities at two years of age or older.

Although there are definite limitations to the studies cited and it is clear more research is required, the literature suggests that infants at the edge of viability who receive CC and/or epinephrine can survive and have comparable long-term outcomes to age-matched controls who did not require these measures. Given the potential benefits and lack of definitive harms, this treatment does not satisfy the criteria for medical futility. The remaining ethical principles of respect for autonomy and justice must be considered.

In western medical culture, respect for patient autonomy (in this case, parental authority) holds significant importance. Our legal and ethical obligations are to ensure that parents know the aforementioned information when deciding on a resuscitation plan for their ELBW infant. Emerging research has explored different types of physician-patient relationships (27,28) and parental decision making (29,30). The importance of parental participation in the decision-making process was universally identified.

The difference between parental and HCP viewpoints must be acknowledged and discussed (31,32). Parents should be informed by their HCP about all reasonable options for resuscitation including palliative care, ventilatory support, CC and epinephrine. In the absence of obvious incapacity or clear harms, parental decisions should be respected.

Justice is defined as "a group of [normative values] for fairly distributing benefits, risks and costs" (7). In the context of this discussion, it can be summarized as the ethical requirement to treat equal cases equally. If CC and epinephrine are offered to larger, more mature babies with the same benefits, limitations and outcomes, it should be offered to infants at the extremes of prematurity. In addition, on a systemic level, if parents are offered a choice about the provision of CC and epinephrine during resuscitation at some centres, then parents giving birth in similar circumstances at other centres should have the same options. Invoking this principle of distributive justice ensures these cases are treated equivalently on a national and international level.

CLINICAL IMPLICATIONS

Is there presently a clear answer to the original question about the appropriateness of using CC and epinephrine in the delivery room resuscitation of infants at the extremes of prematurity? The medical literature acknowledges the beneficence of resuscitation, and the lack of specific and predictable harms caused by the use of CC and epinephrine in this population. It confirms that infants at the extremes of prematurity requiring these measures can survive with a neurodevelopmental outcome comparable with age-matched survivors who do not require CC or epinephrine. Tertiary care neonatal units in Canada offer parents resuscitation of their infants when born at the extremes of prematurity. Analysis of this clinical situation using the ethical framework of principlism strongly supports offering CC and epinephrine as part of the routine resuscitation plan for infants born at the extremes of prematurity.

FUTURE DIRECTIONS

A survey of Canadian (and international) neonatologists' practices regarding this controversial issue would be of great value, and increase our knowledge base and understanding of the current use of CC and epinephrine; such a survey is currently in early development, with distribution planned in the coming months.

DISCLAIMER: This case is not based on any one specific real-life case and, as such, there is no identifying patient information.

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