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EDITORIAL

Assessing anaesthesia practice in the vulnerable age group: NECTARINE

A European prospective multicentre observational study

Nicola Disma, Brigitte Leva, Julia Dowell, Francis Veyckemans and Walid Habre

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It is well established that perioperative complications and life-threatening events occur more frequently and are more severe in the neonatal population.^{1–5} Several factors contribute to this increased risk such as the particular physiology of neonates, the immaturity of organs and systems, the frequency of coexisting multiple comorbidities (such as extreme prematurity, congenital malformations, congenital heart disease and others) and the incomplete understanding of the pharmacology of the routinely used anaesthetics drugs.^{6,7} Furthermore, the ranges of normal physiological parameters for term and preterm babies under general and/or regional anaesthesia are not validated. There is a lack of consensus in the literature with regard to the definition of hypotension/hypertension, bradycardia/tachycardia, hypocarbia/hypercarbia, anaemia, among others, in neonates and small infants undergoing anaesthesia. Consequently, there is no evidence for establishing a threshold at which a specific intervention for treating deviations in physiological parameters should be performed to prevent a poor outcome.^{8,9}

Recently, the concept of differentiating hypotension between three different entities (normative, physiological and operational) has been introduced.¹⁰ Operational hypotension is reported to be the blood pressure level at which anaesthesiologists should intervene. Ideally, a similar concept of operational thresholds could be applicable to high and low values of routinely monitored physiological parameters at which an intervention is recommended. Certainly, physiological parameters are surrogate measures of adequate organ perfusion. Thus, another option is to monitor the end-organ perfusion such

as measuring the regional oxygen saturation (rSO₂), by applying near-infrared spectroscopy.¹¹ But, here again, we are lacking clear evidence about the thresholds that may trigger intervention on several physiological parameters that may impact upon such values [blood pressure, carbon dioxide (CO₂), oxygenation, haemoglobin level, among others].

In the last decade, there is increased awareness of the potential neurotoxicity of anaesthetic drugs administered to this vulnerable population and the consequent long-term cognitive effects.¹² To date, most of the supporting evidence comes from animal studies performed on different models at different ages and often without any surgery (and thus with no associated inflammation). Some human clinical epidemiological or cohort studies have also been published, but with conflicting results. However, epidemiological studies cannot resolve the question as to whether anaesthesia may affect long-term cognitive development, as several concomitant confounding factors (i.e. surgery, inflammation, pain, among others) cannot be excluded.¹³ Moreover, the data collection process was not designed at the time of anaesthesia exposure to detect later specific neurodevelopmental variations from normal. As a consequence, the way forward for clinical research on neurotoxicity is to perform prospective cohort or randomised controlled trials and three projects are currently in progress: GAS, PANDA and MASK. These three studies will potentially provide some evidence as to whether anaesthesia may affect cognitive outcome, particularly when administered to neonates and infants.¹⁴ One should keep in mind, however, that such studies are tremendously expensive, time-consuming for the follow-up phase and are greatly influenced by the effects of social and environmental factors.

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In an attempt to understand the operational threshold in neonates and infants less than 60 weeks of postmenstrual age, a newborn Clinical Trial Network study named NECTARINE was selected by the European Society of Anaesthesiology (ESA) Research Committee in 2014. This prospective, observational, multicentre cohort study is completely devoted to this vulnerable population and aims to determine the current interventions used during the anaesthetic management of neonates and infants undergoing elective, emergency or urgent, diagnostic and surgical procedures. This new project is aimed at covering the aforementioned gaps in knowledge in neonatal anaesthesia, providing information on current clinical practice across Europe and the occurrence of treatments and/or interventions performed in response to a critical event during anaesthesia. The incidence of immediate postanaesthetic unplanned events will also be reported if they were linked with the intraoperative course of anaesthesia. In addition, and as secondary endpoints, children will be followed up for 30 and 90 days after anaesthesia for in- and out-of-hospital morbidity and mortality. The study is registered at www.clinicaltrials.gov (NCT02350348).

Consequently, the following research questions will be answered by this study. What is the incidence of significant perioperative medical interventions and/or treatments? What factors and/or clinical conditions have triggered an intervention? Are there specific factors that can predict the need for different forms of intervention? What is the morbidity and mortality at 30 and 90 days after neonatal/infant anaesthesia in Europe? What is the current clinical practice of anaesthesia in neonates and infants across Europe?

The primary endpoint is the incidence of perianaesthetic interventions and medical treatments performed by the anaesthesia team in response to a potentially life-threatening critical event or to correct major changes in physiological parameters during anaesthetic management. These interventions have been grouped according to the condition(s) to which they will respond:

- (1) difficult airway management;
- (2) poor peripheral oxygen saturation (SpO_2) and/or arterial oxygen saturation (SaO_2);
- (3) end-tidal CO_2 (and/or arterial or venous CO_2) derangement;
- (4) hypo/hyperglycaemia, and/or hypo/hypernatraemia;
- (5) cardiovascular instability;
- (6) hypo/hyperthermia;
- (7) poor brain oxygenation as measured by near-infrared spectroscopy (whenever available); and
- (8) low haemoglobin level.

For secondary endpoints, patients will be followed up for incidence of several adverse events immediately after anaesthesia: unplanned PICU/NICU admission;

unplanned delayed tracheal extubation; need for extracorporeal membrane oxygenation (ECMO); need for chest left open; unplanned hospital admission (if originally scheduled as outpatient) and morbidity and mortality 30 and 90 days after anaesthesia. In the event of multiple anaesthetic procedures during the study inclusion period, the follow-up will be performed 30 and 90 days after the last anaesthetic, to have a unique outcome for each patient.

The sample size calculation was based on the primary endpoint and the minimum number of events (462 interventions for critical events during anaesthesia management) required to analyse the data through multivariate regression analysis models for the identification of the potential predictors of poor outcomes. Thus, 5000 patients need to be enrolled over a predetermined recruitment period of 12 consecutive weeks for all participating centres throughout Europe over the course of 2016, on a 24/7 basis, including weekends.

The NECTARINE study will recruit as many participating institutions (private or public, academic, regional or referral centre) as possible across the European countries represented at the ESA Council. One of the major challenges that NECTARINE will face is the variability in the requirements for informed consent throughout Europe.^{15,16} To address the research question, this study needs to be as inclusive as possible. However, Institutional Review Boards (IRB) and Institutional Ethical Committees (IEC) have different requirements regarding parental information and consent form process. Some institutions would agree to waive the consent form considering that no alterations to participants' usual routine care and no research-related interventions are foreseen. In contrast, other centres would demand a signed consent form from the parents/guardians. In any event, NECTARINE will be submitted to the local or National IRB/IEC for review.

NECTARINE is a promising research project as several national societies and associations for paediatric anaesthesia have endorsed this ESA-led Clinical Trial Network in collaboration with the European Society for Paediatric Anaesthesiology. Moreover, data obtained from the NECTARINE study will be novel, as the literature is scarce with regard to information on anaesthesia management in this vulnerable population group, on the morbidity and mortality across Europe and the predicting factors of poor outcome. The results of the study may provide some evidence on what can be considered the operational threshold for physiological parameters in neonates and infants and move neonatal anaesthesia to evidence-based practice rather than expert-opinion management.

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