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Clinical Investigation

CLINICAL INVESTIGATION

Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE)

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Abstract

Background: Neonates and infants requiring anaesthesia are at risk of physiological instability and complications, but triggers for peri-anaesthetic interventions and associations with subsequent outcome are unknown.
Methods: This prospective, observational study recruited patients up to 60 weeks' postmenstrual age undergoing anaesthesia for surgical or diagnostic procedures from 165 centres in 31 European countries between March 2016 and January 2017. The primary aim was to identify thresholds of pre-determined physiological variables that triggered a medical intervention. The secondary aims were to evaluate morbidities, mortality at 30 and 90 days, or both, and associations with critical events.
Results: Infants (n=5609) born at mean (standard deviation [SD]) 36.2 (4.4) weeks postmenstrual age (35.7% preterm) underwent 6542 procedures within 63 (48) days of birth. Critical event(s) requiring intervention occurred in 35.2% of cases, mainly hypotension (>30% decrease in blood pressure) or reduced oxygenation (SpO_2 <85%). Postmenstrual age influenced the incidence and thresholds for intervention. Risk of critical events was increased by prior neonatal medical conditions, congenital anomalies, or both (relative risk [RR]=1.16; 95% confidence interval [CI], 1.04–1.28) and in those

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requiring preoperative intensive support (RR=1.27; 95% CI, 1.15–1.41). Additional complications occurred in 16.3% of patients by 30 days, and overall 90-day mortality was 3.2% (95% CI, 2.7–3.7%). Co-occurrence of intraoperative hypotension, hypoxaemia, and anaemia was associated with increased risk of morbidity (RR=3.56; 95% CI, 1.64–7.71) and mortality (RR=19.80; 95% CI, 5.87–66.7).

Conclusions: Variability in physiological thresholds that triggered an intervention, and the impact of poor tissue oxygenation on patient's outcome, highlight the need for more standardised perioperative management guidelines for neonates and infants.

Clinical trial registration: NCT02350348.

Keywords: critical events; neonates; outcome; patient safety; quality

Editor's key points

- Neonates and infants have limited physiological reserve, and are at greater risk of complications with general anaesthesia.
- Premature neonates are at highest risk.
- This study quantifies the important physiological aberrations and their risk factors.
- A high degree of training and skill are required for safe delivery of anaesthesia for neonates and infants.

The incidence of premature birth is increasing worldwide,[1] and complex surgical interventions to manage complications or congenital anomalies are performed at early ages. Although neonatal surgery, especially in preterm babies, is associated with adverse neurodevelopmental outcomes[2] and the incidence of perioperative complications and mortality is higher than in older children,[3–7] the specific impact of anaesthesia technique and management has not been fully characterised. Alterations in perioperative physiological parameters (hypotension/hypertension, hypoxaemia/hyperoxia, hypocapnia/hypercapnia, and hypoglycaemia/hyperglycaemia) may be significant factors affecting early and late neurodevelopmental and health outcomes.[8–13] Despite efforts to define ranges of physiological normality during anaesthesia,[14,15] there is still limited information on the thresholds of clinical parameters that should trigger a therapeutic intervention during neonatal anaesthesia, and these may vary with postnatal age. Robust data from large series that describe current practice and identify associations with subsequent outcome are urgently needed to inform guidelines for clinical perioperative management.

We conducted a large prospective multicentre observational study (NECTARINE; NEonate and Children audiT of Anaesthesia pRactice IN Europe) to collect intraoperative management and perioperative outcome data for neonates and young infants requiring anaesthesia. The primary aim was to identify the thresholds of predetermined physiological parameters that were considered indicative of critical events occurring during and up to 120 min after anaesthesia. The secondary aims were to evaluate: (1) morbidity at 30 days, (2) mortality at 30 and 90 days after surgery, and (3) associations between critical events during anaesthetic care and the measured outcomes at 30 and 90 days.

Methods

Study design

NECTARINE is a European multicentre, prospective, observational cohort study. A standardised protocol and Case Report Form (CRF) was developed with consensus within the Steering Committee. A call-for-centres was sent to members of the European Society of Anaesthesiology (ESA), European Society for Paediatric Anaesthesiology (ESPA), and the study was endorsed by national paediatric anaesthesia associations. Each country was represented by a national coordinator, and all participating centres obtained ethical approval in accordance with local or national requirements (approval forms available online: www.esahq.org/CTN/Nectarine). Subjects were recruited during a 3-month period at each site, with overall recruitment between March 1, 2016 and January 31, 2017. The trial was registered (ClinicalTrials.gov NCT02350348), and a statistical analysis plan was posted online (https://www.esahq.org/research/clinical-trial-network/completed-trials/nectarine/). Data are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org).

Participants

All neonates and infants up to 60 weeks' postmenstrual age (PMA; gestational age at birth plus chronological age)[16] undergoing anaesthesia for surgical and non-surgical procedures, in the operating room (OR), ICU, or diagnostic suite, were eligible for inclusion. Parental consent was obtained in all elective cases, or within 48 h of inclusion for those requiring urgent or emergency procedures. Information related to the patient's medical history, pre-anaesthesia assessment, baseline physiological parameters, indication for non-surgical or surgical procedure, and anaesthesia management were collected.

Data collected from the history included:

1. *Previous neonatal medical condition and congenital anomalies* (defined as history of: respiratory support or apnoea; cardiovascular support or extra-corporeal membrane oxygenation; neurological impairment or intraventricular haemorrhage; previous patent ductus arteriosus or surgery; and congenital anomalies)

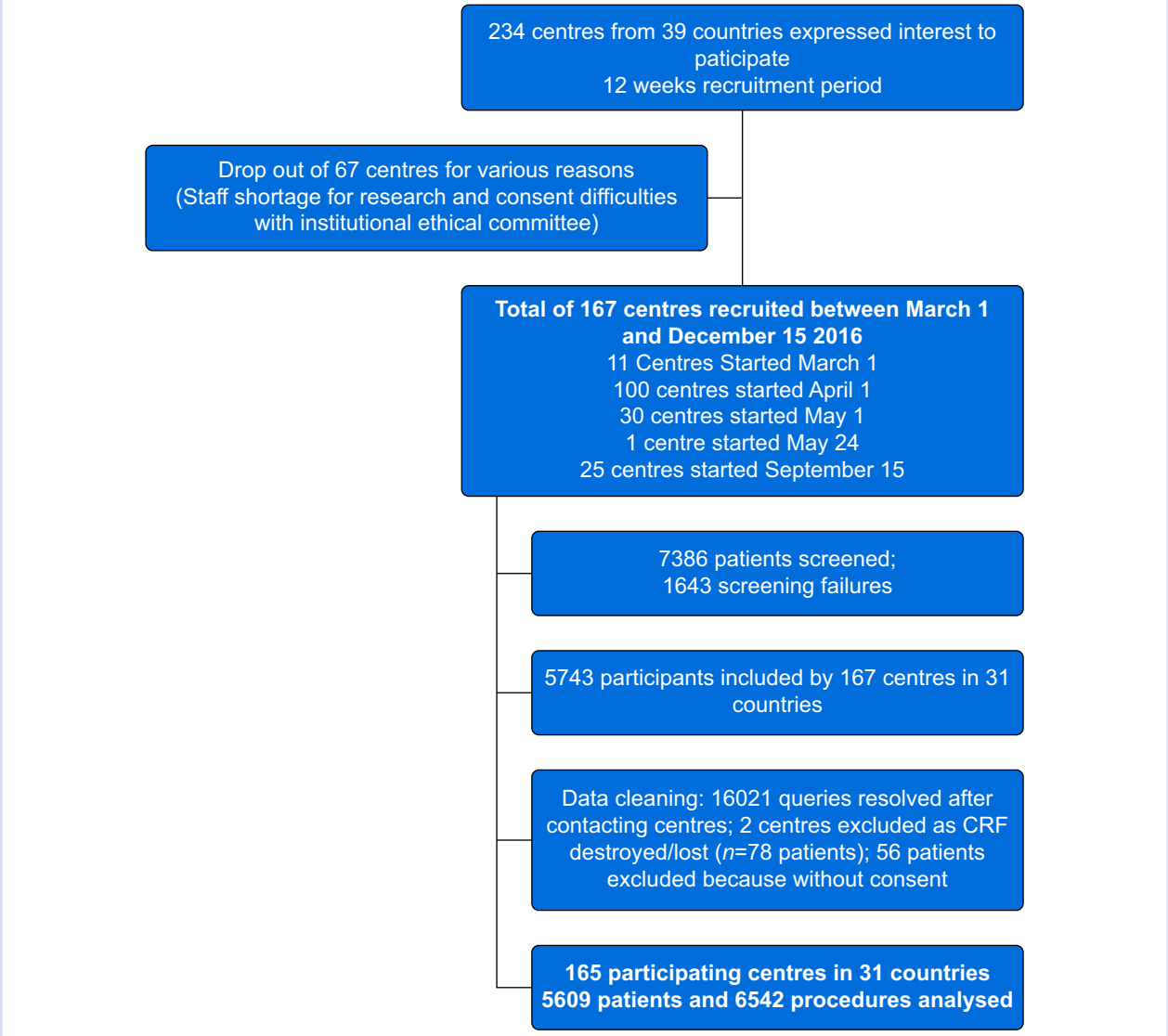

Fig 1. Flow chart of the study. CRF, Case Report Form; NECTARINE, NEonate and Children audiT of Anaesthesia pRactice IN Europe.

2. *Preoperative intensive support* (defined as the following immediately before surgery: respiratory support with invasive or noninvasive ventilation; cardiovascular support with inotropes or cardiac devices; admission from intensive care; and/or ASA physical status $\geq$3)
3. *Current co-morbidities* (defined as respiratory, cardiovascular, neurological, metabolic disease)

Perioperative physiological data were collected into standardised fields within the CRF immediately before, during anaesthesia, and in the postoperative period until the patient was discharged from the post-anaesthesia care unit (maximum 120 min). Additional follow-up was performed at 30 and 90 days, dated from the last anaesthesia episode if patients required multiple anaesthesia within the 3-month period of recruitment. Follow-up was conducted via a face-to-face interview, through medical records (if the patient was still in the hospital), or via a standardised telephone interview with a parent/carer if the patient was discharged. CRF data were entered anonymously into a secure internet-based electronic case record form (OpenClinica, Boston, MA, USA).

Variables

To identify the thresholds of physiological parameters that were considered by the anaesthesia team to indicate a critical event and led to a medical intervention, treatment, or both, eight predetermined critical events were defined, and the interventions to treat them were reported on each CRF (Supplementary Appendix). Parameter thresholds and related corrective interventions included:

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Table 1 Study population characteristics. Percentages express the incidence in the whole study population. Data are presented as mean (standard deviation) and median (range). *Missing values for weight (2, 4, 8, and 45, respectively). †Missing values for APGAR score at 5 min (99, 149, 301, and 1342, respectively). ‡Several congenital abnormalities could be associated. NA, not available.

Gestational age at birth, *n* (%)	<28 weeks *n*=460 (8.2)	28–32 weeks *n*=555 (9.9)	33–36 weeks *n*=985 (17.6)	>37 weeks *n*=3609 (64.3)	Total *n*=5609 (100)
Gestational age (weeks)	25.29 (1.35)	30.14 (1.47)	34.84 (1.08)	38.85 (1.09)	36.17 (4.42)
	25 (5)	30 (4)	35 (3)	39 (5)	38 (20)
Weight at birth (g)*	795 (219)	1398 (472)	2361 (567)	3286 (525)	2730 (984)
	775 (1740)	1340 (3360)	2325 (4015)	3280 (4400)	2960 (4650)
Sex: male/female, *n* (%)	284/176	390/165	657/328	2339/1270	3670/1939
	(61.7/38.3)	(70.3/29.7)	(66.7/33.3)	(64.8/35.2)	(65.4/34.6)
Mode of delivery, *n* (%)	162/277/21	131/384/40	398/517/70	2181/1075/353	2872/2253/484
Vaginal/Caesarean/NA	(35.2/60.2/4.6)	(23.6/69.2/7.2)	(40.4/52.5/7.1)	(60.4/29.8/9.8)	(51.2/40.2/8.6)
APGAR at 5 min†	6.9 (2.0)	7.7 (1.9)	8.7 (1.7)	9.3 (1.3)	8.8 (1.7)
	7 (10)	8 (9)	9 (10)	10 (10)	9 (10)
Congenital anomalies,‡ *n* (%)	88 (19.1)	175 (31.5)	485 (49.2)	1708 (47.3)	2456 (43.8)
Congenital heart disease	53	71	113	477	714
Metabolic disorder	3	8	15	58	84
Chromosomopathy	3	8	34	86	131
Other	37	113	388	1257	1795
Number of procedures	588	645	1162	4147	6542

1. SpO_2, Pa_{O_2}, or both (intervention to improve oxygenation)
2. End-tidal carbon dioxide ($ETCO_2$), arterial/venous blood CO_2 (intervention to improve alveolar ventilation), or both
3. Systolic or mean arterial blood pressure
4. Heart rate, ECG rhythm disturbances, or both, resulting in cardiovascular instability
5. Absolute values or relative changes in cerebral oxygenation when near-infrared spectroscopy (NIRS) was part of clinical monitoring
6. Blood glucose, plasma sodium (Na^+), or both
7. Haemoglobin values (need transfusion of packed red cells)
8. Core body temperature values (correction for hypo/hyperthermia)

A description of the intervention(s), the time of occurrence, and the immediate outcome of the event were also recorded. Thirty day morbidity data included new-onset neurological, respiratory, cardiovascular, renal, hepatic and surgical complications, and any re-admission to an ICU. Mortality data were collected at 30 and 90 days follow-up.

Of note, data on difficult airway management were also collected and will be the subject of a separate report.

Statistical analysis

The expected percentage of severe perioperative critical events in this age group was approximately 11%.[4] Considering the minimum number of patients required for a logistic regression analysis with more than one covariate in the model, and assuming a drop-out rate of 15%,[17] we estimated 4941 patients were required in order to obtain 462 critical events.

Patient categorical data are summarised as absolute frequencies and percentages. Quantitative variables are summarised as means and standard deviations (SD) or median and range or first quartile (Q1) and third quartile (Q3). The incidence of the primary endpoint (number of interventions or critical events) is reported as percentage and 95% binomial exact confidence intervals (CIs). Critical events and interventions were categorised by groups according to the study definitions.

All tests were two-sided, and a *P* value <0.05 was considered as statistically significant. Univariable and multivariable Poisson regression models with a robust error variance and age and sex adjustment were fitted to identify the potential risk factors associated with the endpoints. Multiple correspondence analysis was used to detect associations between categorical variables, and the clinically relevant correlated binary or dichotomised categorical variables were collapsed into one variable using the OR logical operator.[18] Clinically relevant continuous variables were included in the multivariable model. Adjusted relative risks (RR_{adj}) with their 95% CIs were calculated and reported for the Poisson regression model.

Multivariable analyses were carried out via generalised linear mixed models using the Poisson distribution for the outcomes, the log link function, and a robust error variance structure while controlling for cardiac surgery and multiple procedures as confounders and taking the participating centre as a random factor.

Statistical analyses were performed within R V4.0.2 (R Core Team [2020]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria) with the sandwich, lme4, lmerTest,

Table 2 Primary outcome with baseline values of measured parameters, number (%) of unplanned interventions and thresholds values that triggered an intervention. Data are presented in terms of number of procedures and based on postmenstrual age at inclusion in the study. Data are presented as mean (standard deviation [SD]) and number (%) when appropriate. *Trigger value for any intervention (volume, medication, or both). No trigger was based on diastolic pressure. †Percentages expressed for relative changes from baseline values obtained in infants where intervention was performed. ‡Percentage of interventions for desaturation when the trigger was at SpO_2 levels of 90%, 85%, and 80% respectively. ¶Values reported when arterial blood gas analysis was obtained. §Percentages are based on the number of cases in which near-infrared spectroscopy (NIRS) was available (9, 11, 52, 176, 106, 179, and 533, respectively).

Postmenstrual age at inclusion	<28 weeks (*n*=68)	28–31 weeks (*n*=115)	32–36 weeks (*n*=507)	37–40 weeks (*n*=1309)	41–44 weeks (*n*=1406)	45–60 weeks (*n*=3137)	Entire cohort (*n*=6542)
Days post birth at inclusion (days)	12.6 (7.1)	18.9 (13.4)	21.6 (26.4)	24.1 (29.8)	44.3 (29.9)	98.1 (38.7)	63.5 (48)
Weight at inclusion (kg)	0.8 (0.2)	1.3 (0.5)	2.2 (0.6)	3.1 (0.6)	3.7 (0.7)	5.2 (1.3)	4.1 (1.5)
Systolic blood pressure (mm Hg)							
Baseline before induction	51.4 (13.7)	60.4 (15.7)	65.7 (14.1)	73.2 (14.5)	80.1 (16.4)	85.4 (15.9)	78.1 (17.3)
Baseline after induction	49.9 (10.0)	60.5 (10.3)	59.0 (13.4)	65.1 (14.4)	69.8 (16.7)	77.7 (15.3)	72.7 (16.6)
Number of interventions	15 (22.1%)	25 (21.7%)	91 (17.9%)	196 (15.0%)	155 (11.0%)	191 (6.1%)	673 (10.3%)
Number of drug administrations	8 (11.8%)	16 (13.9%)	51 (10.1%)	112 (8.6%)	74 (5.3%)	109 (3.5%)	370 (5.7%)
Trigger value*	39.2 (10.2)	38 (9.5)	41.6 (8.3)	44.7 (8.5)	46.9 (9.2)	50.8 (10.2)	46.2 (9.9)
Percentage change from baseline†	22.7 (22.2)	29.6 (14.9)	28.8 (16.9)	29.6 (18.9)	31.3 (19.5)	30.5 (15.9)	30.0 (17.9)
Mean blood pressure (mm Hg)							
Baseline before induction	35.7 (10.7)	43.0 (12.8)	48.6 (11.6)	52.6 (12.5)	56.5 (14.2)	59.0 (13.9)	54.8 (14.2)
Baseline after induction	35.3 (9.2)	38.5 (5.8)	41.7 (10.5)	46.8 (12.2)	47.6 (14.1)	53.1 (12.7)	50.1 (13.3)
Number of interventions	21 (30.9%)	23 (20.0%)	77 (15.2%)	153 (11.7%)	102 (7.3%)	182 (5.8%)	558 (8.5%)
Number of drug administrations	15 (22.1%)	16 (13.9%)	56 (11.0%)	103 (7.9%)	74 (5.3%)	109 (3.5%)	373 (5.7%)
Trigger value*	25.2 (5.4)	27.9 (4.9)	30.9 (5.7)	32.9 (5.9)	32.2 (6.2)	35.3 (6.4)	32.7 (6.5)
Percentage change from baseline†	21.0 (20.6)	23.9 (19.4)	24.3 (18.5)	30.2 (19.3)	33.1 (21.5)	30.3 (18.1)	29.3 (19.5)
Heart rate							
Baseline (beats min^{-1})	154 (19)	156 (18)	146 (19)	143 (19)	146 (19)	140 (19)	143 (19)
Number of interventions	3 (4.4%)	7 (6.1%)	15 (3.0%)	44 (3.4%)	31 (2.2%)	45 (1.4%)	145 (2.2%)
Trigger value for low heart rate	92 (11)	82 (19)	76 (29)	85 (17)	81 (15)	79 (24)	81 (21)
Trigger value for high heart rate	180 (–)	150 (–)	170 (–)	183 (36)	198 (45)	169 (38)	181 (38)
Oxygen saturation							
Baseline (%)	93 (7)	95 (5)	97 (5)	97 (5)	98 (4)	98 (4)	98 (4)
Number of interventions	22 (32.4%)	41 (35.7%)	99 (19.5%)	204 (15.6%)	180 (12.8%)	284 (9.1%)	830 (12.7%)
Trigger values based on SpO_2‡	31.8/36.4/31.8	26.8/17.1/56.1	43.4/22.2/34.3	39.2/20.1/40.7	40/20/40	43.7/15.1/41.2	40.6/18.9/40.5
Trigger value based on Pa_{O_2}	(–)	4 (–)	6.6 (1.9)	6.2 (1.4)	5.9 (1.9)	6.9 (5)	6.3 (1.6)
Partial pressure in CO_2¶							
Baseline (kPa)	6.1 (1.2)	6.3 (1.7)	6.1 (1.7)	5.7 (1.5)	5.8 (1.5)	5.6 (1.4)	5.8 (1.5)
Number of interventions	7 (10.3%)	20 (17.4%)	58 (11.4%)	151 (11.5%)	95 (6.8%)	191 (6.1%)	522 (8.0%)
Trigger value based on low $Paco_2$	3.9 (–)	2.5 (–)	3.7 (1.1)	3.7 (0.7)	3.2 (–)	3.8 (1.0)	3.6 (0.8)
Trigger value based on high $Paco_2$	10.3 (2.5)	11.0 (4.6)	9.0 (1.8)	9.1 (2.6)	8.1 (1.4)	8.0 (1.8)	8.7 (2.3)
Trigger value based on low $ETCO_2$	3.0 (0.0)	2.5 (1.3)	3.0 (1.1)	3.4 (0.7)	3.2 (1.0)	3.3 (1.0)	3.3 (0.9)
Trigger value based on high $ETCO_2$	8.0 (–)	8.0 (1.9)	8.0 (1.5)	8.2 (3.4)	7.8 (1.6)	7.7 (1.4)	7.9 (2.1)
Haemoglobin =							
Baseline (g dl^{-1})	11.6 (2.6)	12.3 (2.8)	13.6 (3.4)	14.0 (3.4)	12.2 (2.8)	11.1 (2.0)	12.3 (3.0)
Number of interventions	16 (23.5%)	19 (16.5%)	32 (6.3%)	91 (7.0%)	53 (3.8%)	123 (3.9%)	334 (5.1%)
Trigger value	9.1 (2.1)	9.3 (1.6)	8.9 (1.7)	9.2 (1.9)	7.9 (1.6)	8.1 (1.3)	8.6 (1.7)
Percentage change from baseline 2	3.3 (21)	10.8 (12.2)	21.8 (18.5)	19.2 (18.4)	19.4 (20.2)	17.1 (16.3)	17.4 (18.1)
Metabolic							
Baseline se. sodium (mEq L^{-1})	137.2 (7.4)	136.1 (5.5)	137.3 (4.5)	138.1 (4.0)	137.7 (3.5)	137.5 (3.6)	137.6 (4.0)
Baseline se. glucose (mmol L^{-1})	8.6 (4.9)	6.1 (2.2)	5.6 (2.5)	5.6 (2.4)	5.6 (1.8)	5.8 (1.7)	5.7 (2.1)
Number of interventions	4 (5.9%)	6 (5.2%)	35 (6.9%)	55 (4.2%)	39 (2.8%)	43 (1.4%)	182 (2.8%)

Continued

Table 2 Continued

Postmenstrual age at inclusion	<28 weeks (n=68)	28–31 weeks (n=115)	32–36 weeks (n=507)	37–40 weeks (n=1309)	41–44 weeks (n=1406)	45–60 weeks (n=3137)	Entire cohort (n=6542)
Trigger value for hypoglycaemia	3 (–)	2.1 (1.2)	2.9 (0.7)	2.8 (0.8)	2.8 (0.7)	2.8 (0.8)	2.8 (0.8)
Trigger value for hyperglycaemia	12 (–)	10.7 (1.0)	15.1 (9.4)	12.7 (3.0)	15.6 (6.7)	16.3 (9.2)	14.6 (7.1)
Near-infrared spectroscopy							
Baseline (%)	73.3 (13.9)	66.5 (7.2)	80.9 (11.7)	72.9 (14.2)	73.3 (15)	69.1 (16)	72.3 (15)
Number of interventions[§]	6 (66.7%)	3 (27.3%)	14 (26.9%)	47 (26.7%)	25 (23.6%)	52 (29.1%)	147 (27.6%)
Trigger value	51.2 (84.4)	47.0 (15.6)	42.4 (18.7)	42.8 (15.6)	45.4 (12.0)	46.9 (11.4)	45.2 (13.4)
Percentage change from baseline 2	14.6 (11.5)	30.9 (14.2)	29.3 (16.8)	32.6 (19.1)	31.2 (15.9)	29.6 (15.2)	30.4 (16.7)
Temperature (°C)							
Baseline	36.3 (1.0)	36.5 (0.7)	36.4 (0.7)	36.4 (0.6)	36.5 (0.6)	36.6 (0.6)	36.5 (0.6)
Number of interventions	7 (10.3%)	12 (10.4%)	47 (9.3%)	82 (6.3%)	48 (3.4%)	97 (3.1%)	293 (4.5%)
Trigger value for hypothermia[†]	34.7 (1.0)	34.6 (0.7)	34.9 (0.9)	34.2 (1.7)	34.4 (1.4)	34.6 (1.6)	34.5 (1.5)
Trigger value for hyperthermia[†]	(–)	38.0 (0.0)	38 (–)	38.2 (0.6)	38 (0.0)	38.2 (0.4)	38.1 (0.4)
Total number of interventions in response to a critical event	48 (70.6%)	80 (69.6%)	263 (51.9%)	588 (44.9%)	478 (34%)	849 (27.1%)	2306 (35.2%)

merDeriv, pROC, FactoMineR, factoextra, and ggplot2 packages.[19,20]

Results

Participants

Peri-anaesthetic data were obtained from 6542 procedures in 5609 patients [65.4% male], with 651 children requiring more than one anaesthetic during the 3-month inclusion period. After clarification or queries regarding missing data, the final dataset from 165 participating centres in 31 countries (Fig. 1) was exported for analysis in October 2019. Recruited patients represented 75.9% of all eligible neonates and infants admitted during the 3-month inclusion period for each centre.

At birth, mean (SD) gestational age was 36.17 (4.42) weeks and weight 2730 (984) g. Preterm birth was common (35.7%) and included 460 patients born extremely preterm (<28 weeks' GA; 795 [219] g; Table 1). Congenital anomalies were reported in 2456 (43.8%) children, with congenital heart disease being the most frequent (n=714) (Supplementary Table A). Patients were enrolled on average 63.5 (48) days after birth, at a median PMA 57 weeks (Q1–Q3, 22–97) and weight of 4 (3–5.1) kg (Table 2). Additional details are available in the Supplementary material (Tables A–E, Fig. 1).

Procedures

Surgical procedures (n=5200) often related to abdominal surgery for gastrointestinal indications (n=3215; 61.8%) with inguinal hernia repair the most common procedure overall (n=1408). Cardiac surgery (n=439, 8.4%) comprised the second highest group. Anaesthesia for non-surgical procedures (n=1341) included imaging (MRI, n=340), intravenous access (n=251), bronchoscopy (n=153), and additional diagnostic procedures (see Supplementary Appendix Table B).

Anaesthetic technique included general anaesthesia (96.7%, n=6324), combined with regional analgesia in 29.6% (n=1935), or regional anaesthesia alone in 216 patients (3.3%). Airway management comprised tracheal intubation (n=4683, 71.6%), supraglottic airway device (n=722, 11%), and a face-mask or nasal prongs (n=827, 12.6%). Additional intraoperative monitoring included an invasive arterial line (n=898, 13.7%), NIRS (n=533, 8%), or both. After the procedure, 43.9% (n=2867) of patients were admitted to a paediatric (PICU) or neonatal (NICU) intensive care unit, 9% (n=587) to a high dependency unit, and 45.7% (n=2986) to a general ward. Unplanned admission to the PICU/NICU was reported in 3.3% (n=94).

Primary outcome

The overall incidence of critical events requiring an intervention was 35.3% (95% CI, 34.1–36.4). Interventions were required for all eight pre-determined critical events, but there was significant variability in the frequency of events and the range of physiological parameters that triggered an intervention (Table 2).

Episodes of cardiovascular instability triggered 60.7% of all interventions, and were most commonly related to hypotension (almost 50%). Mean (SD) values that triggered an intervention were 46.2 (9.9) and 32.7 (6.5) mm Hg for systolic and mean blood pressure, respectively (30% decrease from baseline). As physiological parameters change significantly throughout postnatal development,[21,22] data were also stratified into six age groups. Baseline and trigger blood pressure values were lower in

younger infants, but at all ages there was significant variability in both baseline and trigger values (Table 2). In infants monitored with NIRS (n=302), an acute decrease in blood pressure was accompanied by a change in rSO_2 in 36% of cases. Despite medical interventions, low blood pressure persisted in 79 (8%) infants, of which 16 were <32 weeks PMA at the time of surgery. There were eight cases (four with congenital heart disease) of intraoperative cardiac arrest requiring cardiopulmonary resuscitation (incidence=0.12%; 95% CI 0.053–0.241), and no intraoperative deaths.

Hypoxaemia triggered 36% of all interventions, with 60% of these related to SpO_2 <85%. Episodes of hypoxaemia predominantly occurred during maintenance (55%) rather than at induction (26%) or emergence (15%). Despite intervention, persistent decreases (3.5% of cases) or further deterioration in oxygenation (1.2% of cases) was reported. In infants monitored with NIRS, hypoxaemia was accompanied by a change in cerebral saturation that was considered significant by the anaesthesiologist in 45.7% (54 of 118) of cases. Interventions based primarily on NIRS values were uncommon and occurred when NIRS value decreased by almost 30% from baseline. Changes in ventilation were more commonly triggered by hypercapnia than hypocapnia (2.3% *vs* 0.8% of all interventions), but persistent difficult ventilation was noted in 7.1% of all cases.

Red blood cell transfusion, triggered by haemoglobin values of 8.6 (1.7) g dl^{-1}, comprised 5.1% of interventions, and was required in a higher proportion of infants <32 weeks' PMA (19.1% *vs* 4.7% of cases at older ages). Interventions for blood glucose (n=43, 2.8%) and temperature (n=97, 4.5%) were less common, with comparable trigger values across all age groups. Hypothermia was associated with cardiovascular instability in eight patients and coagulopathy in five.

Critical events occurred in a higher proportion of very young patients (70% of infants <32 weeks PMA at the time of surgery) (Fig. 2). Events occurred predominantly during maintenance of anaesthesia (80%), with instability at induction in 10.5% and at both induction and maintenance in 7%.

Secondary outcomes

Risk factors associated with critical events requiring intervention include: previous neonatal medical condition and congenital anomalies (RR=1.17; 95% CI, 1.05–1.30); preoperative intensive support (RR=1.27; 95% CI, 1.15–1.41); and current co-morbidities (RR=1.15; 95% CI, 1.05–1.26) (Table 3). Multivariable analysis also confirmed an increased risk of intervention associated with longer duration of surgery (RR=1.22; 95% CI, 1.18–1.26), whereas there was no statistical association with anaesthesia management (general, regional, or both; choice of airway; seniority of team) (RR=1.51; 95% CI, 0.99–2.31) (Table 3).

Morbidity data at 30 days were available for 93.3% of cases. One or more complications occurred in 16.3% (n=850; incidence=0.17; 95% CI, 0.16–0.18) of the cohort, with respiratory (n=457), surgical (n=329), and/or cardiovascular (n=315) complications being the most common (Supplementary Table C). A number of children were still hospitalised (7.8%, n=407) and 4.9% (n=257) were still requiring management in intensive care. Ninety-day data were available for 75% of the cohort (n=4184), at which time 5.3% of patients remained in hospital (Supplementary Table D).

Overall mortality was 3.2% (95% CI, 2.7–3.7%). The incidence at 30 days was 2% (95% CI, 1.6%–2.4%), and that between 30 and 90 days was 0.7% (95% CI, 0.5–1.1%) (31 of 4184 available

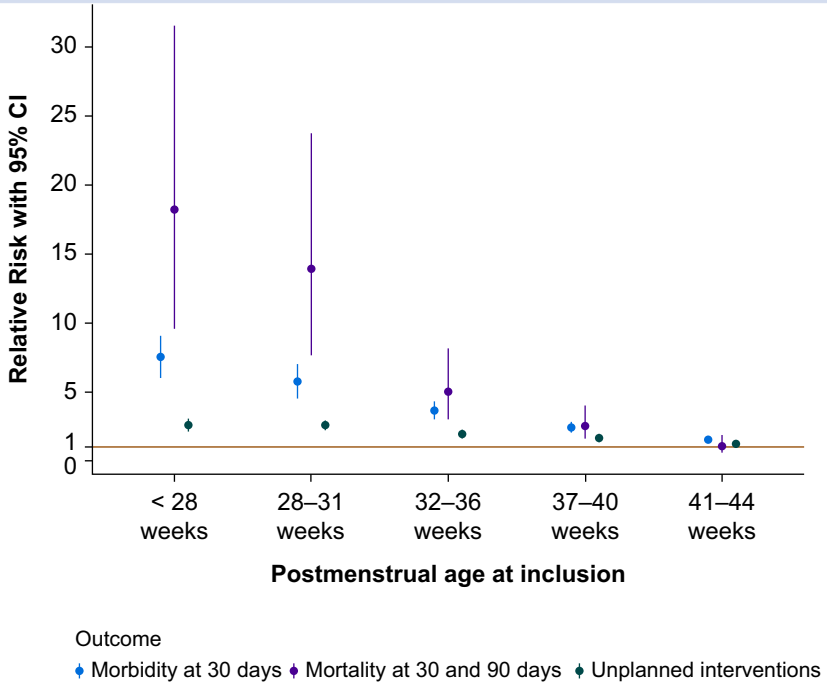

Fig 2. Relative risk and 95% confidence intervals (CI) for the three outcomes: interventions, morbidity, and mortality, stratified by postmenstrual age (PMA) at inclusion. PMA 45–60 weeks is considered the reference category (red line).

Table 3 Relative risk and non-adjusted 95% confidence interval (CI) for the risk factors associated with any intervention in response to a critical event. Exposed and unexposed refer to the number of cases exposed and unexposed to the examined risk factor. For continuous variables the table shows the mean (standard deviation [SD]) when an intervention occurred or not. *Univariable robust Poisson regression controlling for postmenstrual age in weeks and sex. †Multivariable robust Poisson regression controlling for cardiac surgery and multiple procedures with the participating centre as a random factor (on procedures with combined or general anaesthesia), variables in the model: sex, chronological age at inclusion in weeks, weight at inclusion in kg, premature birth (<37 weeks) or low birth weight (<2500 g), medical history (congenital abnormality or history of respiratory support or intraventricular haemorrhage or patent ductus arteriosus or previous surgery), illness status at inclusion (presence of cardiovascular or respiratory support or admission from ICU or ASA status 3–5), comorbidities (presence of respiratory or cardiovascular or metabolic or renal problems), surgical plan (urgent/emergency or after hours or location of procedure: ICU), length of surgery (standardised), anaesthesia management (i.v. anaesthesia induction or inhalation anaesthesia management or presence of vasopressors or inotropes as part of anaesthesia management). Area under the curve=0.778. RA, regional anaesthesia; GA, general anaesthesia; SGA, supraglottic airway; CI, confidence interval; RR, relative risk.

Variable	Univariable*						Multivariable‡ (n=6072)				
	Exposed			Unexposed			RR	95% CI	P	RR	95% CI
	Total	Intervention	% or SD	Total	Intervention	%					
Sex (male *vs* female)	4225	1456	34.46	2316	850	36.70	0.962	0.900–1.028	0.050	1.065	1.000–1.135
Postmenstrual age, mean (SD)	43.20		7.39	46.18		(6.79)	0.963	0.958–0.967			
Chronological age at inclusion	7.86		7.08	9.69		(6.73)			0.297	0.997	0.990–1.003
Weight at birth, mean (SD)	2.55		1.03	2.80		(0.97)	0.938	0.906–0.970			
Weight at inclusion, mean (SD)	3.67		1.49	4.34		(1.49)	0.864	0.829–0.901	<0.001	0.904	0.875–0.935
Premature birth (<37 weeks' GA)	2395	983	41.04	4146	1323	31.91	1.056	0.982–1.136			
Premature birth or low birth weight	2391	1018	42.58	3681	1202	32.65			0.144	1.063	0.979–1.154
Congenital abnormality	3054	1274	41.72	3487	1032	29.60	1.387	1.300–1.480			
History of respiratory support	2526	1132	44.81	4014	1174	29.25	1.337	1.248–1.432			
History of intraventricular haemorrhage	462	203	43.94	6078	2102	34.58	1.057	0.945–1.182			
History of patent ductus arteriosus	1219	651	53.40	5321	1654	31.08	1.463	1.361–1.572			
History of previous surgery	1630	635	38.96	4911	1671	34.03	1.196	1.114–1.284			
Neonatal medical history and congenital anomalies	4246	1774	41.78	1826	446	24.42			0.003	1.167	1.052–1.295
Presence of cardiovascular support	319	210	65.83	3777	1082	28.65	1.787	1.614–1.978			
Presence of respiratory support	1065	596	55.96	5476	1710	31.23	1.446	1.338–1.564			
Admission from ICU	1812	926	51.10	4729	1380	29.18	1.454	1.350–1.566			
ASA status 3–5	2631	1280	48.65	3904	1023	26.20	1.640	1.528–1.761			
Preoperative intensive support	2923	1423	46.68	3149	797	25.31			<0.001	1.272	1.146–1.411
Presence of respiratory problems	1194	554	46.4	5340	1747	32.72	1.253	1.163–1.350			
Hypoxaemia at inclusion (<85%)	112	71	63.39	3775	1380	36.56	1.539	1.319–1.795			
Presence of cardiovascular problems	1404	746	53.15	5124	1554	30.33	1.561	1.459–1.669			
Presence of metabolic problems	666	357	53.60	5852	1934	33.05	1.372	1.263–1.491			
Presence of neurological problems	812	303	37.32	5678	1972	34.73	0.976	0.887–1.073			
Presence of renal problems	462	177	38.31	6047	2109	34.88	1.074	0.956–1.207			
Current co-morbidities	2598	1228	47.27	3474	992	28.55			0.002	1.152	1.052–1.261
Urgent/emergency *vs* elective	3137	1314	41.89	3403	992	29.15	1.180	1.097–1.268			
After hours/opening hours	488	205	42.01	6026	2085	34.60	1.033	0.926–1.152			
Location of procedure (ICU *vs* OR)	263	126	47.91	6278	2180	34.72	1.090	0.959–1.238			
Surgical plan	3018	1287	42.64	3054	933	30.55			0.087	1.070	0.990–1.157
Length of surgery, mean (SD)	99.74		(90.52)	55.92		(59.62)	1.003	1.002–1.003	<0.001	1.218	1.178–1.259
Minimally invasive surgery	458	189	41.27	4739	1806	38.11	1.133	1.010–1.269			
Gastrointestinal surgery	3215	1217	37.85	1984	778	39.21	0.904	0.843–0.970			
Thoracic surgery	58	36	62.07	5140	1959	38.11	1.587	1.287–1.957			
Cardiac surgery	439	267	60.82	4759	1728	36.31	1.539	1.410–1.679			
Neurosurgery	332	151	45.48	4865	1843	37.88	1.155	1.016–1.312			
Genitourinary surgery	350	108	30.86	4847	1886	38.91	0.857	0.731–1.004			

Continued

Table 3 Continued

Variable	Univariable*						Multivariable‡ (n=6072)			
	Exposed			Unexposed			RR	95% CI	P	RR	95% CI
	Total	Intervention	% or SD	Total	Intervention	%					
Ear, nose, and throat surgery	340	112	32.94	4857	1882	38.75	1.038	0.888–1.213			
Surgical *vs* non-surgical procedure	5195	1994	38.38	1345	312	23.20	1.570	1.416–1.741			
Anaesthesia induction (i.v. *vs* inhalation)	2518	1047	41.58	3802	1238	32.56	1.169	1.095–1.247			
Anaesthesia management (inhalation *vs* TIVA)	5452	2047	37.55	608	211	34.70	1.201	1.077–1.339			
Presence of vasopressors or inotropes as part of anaesthesia management	499	344	68.94	5813	1939	33.36	1.716	1.591–1.850			
Anaesthesia management	5975	2199	36.80	97	21	21.65			0.057	1.511	0.988–2.311
Team in charge (at least one senior)	5501	1949	35.43	1038	357	34.39	1.004	0.918–1.098			
Anaesthesia technique											
Regional alone *vs* general anaesthesia	216	18	8.33	4389	1670	38.05	0.217	0.140–0.337			
Combined RA–GA *vs* GA	1934	618	31.95	4389	1670	38.05	0.910	0.843–0.982			
Airway management											
Face mask *vs* tracheal intubation	728	67	9.20	4682	2056	43.91	0.227	0.181–0.286			
SGA *vs* tracheal intubation	722	136	18.84	4682	2056	43.91	0.485	0.415–0.567			

datasets). Thirty-day mortality in the subpopulation of neonates (*n*=1648 less than 28 days post birth) revealed a mortality rate of 4.1% (95% CI, 3.2–5.3%). Major causes of mortality included sepsis (*n*=38 of 136) and multiorgan failure (*n*=27) (see Supplementary Table C).

PMA at time of surgery had a major impact on both morbidity and mortality (Fig. 2). Requirement for preoperative intensive support was associated with the greatest increased risk of complications (RR=2.55; 95% CI, 2.02–3.23; Table 4) and mortality (RR=6.80; 95% CI, 3.08–15.04; Table 5). Current co-morbidities also had a negative impact on morbidity at 30 days and mortality. Surgical revision for postoperative bleeding was also associated with increased mortality (RR=7.71; 95% CI, 4.51–13.2; Table 5). Patient sex was not a significant risk factor for mortality (RR=1.14; 95% CI, 0.083–1.56).

Even in infants without potential confounders (multiple procedures, congenital abnormalities, and cardiac surgery), a composite adverse event with hypotension, hypoxaemia, and anaemia, indicative of impaired tissue oxygenation, significantly increased RR of morbidity (RR=3.56; 95% CI, 1.64–7.71) and mortality (RR=19.80; 95% CI, 5.87–66.7).

Discussion

This European prospective multicentre study in a large cohort of infants requiring anaesthesia at less than 60 weeks' PMA identified a high incidence of perioperative critical events, particularly in preterm-born infants, that required intervention by the anaesthesia team. The need for preoperative intensive support, current co-morbidities, and length of surgery were associated with an increased incidence of critical events. RR of morbidity at 30 days was increased in patients who required perioperative interventions, and a composite adverse event (hypotension, hypoxaemia, and anaemia) that would impair tissue oxygenation had a major impact even in the absence of congenital anomalies or cardiac surgery. Overall mortality was primarily associated with a positive history for neonatal medical conditions and congenital anomalies. Morbidity and mortality were also highest when surgery was required before 28 weeks PMA. These data highlight both the unique risk factors and age-specific vulnerability of neonates and infants requiring anaesthesia for surgical and diagnostic interventions.

Intraoperative interventions

Postnatal differences in physiology between preterm and term-born neonates result in age-dependent differences in baseline parameters.[21,22] Although many factors may affect blood pressure, the baseline values reported here were higher than previously published for preterm and term neonates.[14,15,23,24] This confirms the challenge of defining reproducible and reliable normal values in this population. However, intervention thresholds for systolic blood pressure were low (<5th percentile values for awake age-matched groups[23,25]) despite current clinical practice guidance suggesting critically ill children may require higher systolic or mean blood pressure.[26]

A major finding of this study is that more than 60% of the interventions for hypoxaemia were triggered by a SpO_2 of less than 85%, regardless of age. Severe hypoxaemia was strongly associated with increased morbidity and mortality, which is consistent with the previously reported higher hazard ratio for morbidity and mortality in infants exposed to SpO_2 <90%.[27]

Table 4 Relative risk and non-adjusted 95% confidence interval (CI) for the risk factors associated with any morbidity occurring at 30 days follow-up. Exposed and unexposed refer to the number of cases exposed and unexposed to the examined risk factor. For continuous variables the table shows the mean and standard deviation when morbidity occurred or not. *Univariable robust Poisson regression controlling for corrected age in weeks and sex. †Multivariable robust Poisson regression controlling for cardiac surgery and multiple procedures with the participating centre as a random factor (on procedures with combined or general anaesthesia, last procedure per child), variables in the model: sex, chronological age at inclusion in weeks, weight at inclusion, premature birth (<37 weeks) or low birth weight (<2500 g), medical history (congenital abnormality or history of respiratory support or intraventricular haemorrhage or ECMO support or previous surgery), illness status at inclusion (presence of cardiovascular support or admission from ICU or ASA status 3–5), medical comorbidities (presence of respiratory or cardiovascular or metabolic or neurological or renal problems), surgical plan (urgent/emergency or after hours or location of procedure: ICU), length of surgery (standardised), anaesthesia management (general anaesthesia or i.v. anaesthesia induction or presence of vasopressors or inotropes as part of anaesthesia management), the occurrence of any unplanned intraoperative intervention, surgical revision for postoperative bleeding. Area under the curve=0.870. ‡Total volume in ml kg^{-1}. Data are mean (standard deviation [SD]). ECMO, extra-corporeal membrane oxygenation; GA, general anaesthesia; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; RA, regional anaesthesia; rSO_2, regional cerebral oxygen saturation; SGA, supraglottic airway.

Variable	Univariable*						Multivariable† (n=4632)				
	Exposed			Unexposed			RR	95% CI	P	RR	95% CI
	Total	Morbidity	% or SD	Total	Morbidity	%					
Sex (male *vs* female)	3277	523	15.96	1727	327	18.93	0.879	0.779–0.992	0.114	1.103	0.977–1.245
Postmenstrual age in weeks	42.06		7.88	46.44		(6.66)	0.929	0.920–0.938			
Chronological age at inclusion	7.42		7.48	9.83		(6.73)			0.763	1.001	0.993–1.010
Weight at birth, mean (SD)	2.41		1.07	2.81		(0.95)	0.865	0.809–0.925			
Weight at inclusion, mean (SD)	3.29		1.46	4.41		(1.46)	0.637	0.594–0.683	<0.001	0.845	0.794–0.900
Premature birth (<37 weeks' GA)	1752	413	23.57	3252	437	13.44	1.209	1.050–1.392			
Premature birth or low birth weight	1751	435	24.84	2881	388	13.47			0.455	1.060	0.910–1.234
APGAR score at 5 min (≤7 *vs* >7)	550	188	34.18	2769	459	16.58	1.647	1.418–1.913			
Congenital abnormality	2201	548	24.90	2803	302	10.77	2.202	1.943–2.495			
History of respiratory support	1780	563	31.63	3223	287	8.90	2.870	2.493–3.303			
History of intraventricular haemorrhage	301	105	34.88	4702	745	15.84	1.587	1.325–1.901			
History of ECMO support	33	23	69.70	4971	827	16.64	4.042	3.108–5.257			
History of previous surgery	1114	373	33.48	3890	477	12.26	2.988	2.669–3.344			
Neonatal medical history and congenital anomalies	3055	751	24.58	1577	72	4.57			0.001	1.560	1.188–2.048
Presence of cardiovascular support	181	114	62.98	3045	231	7.59	5.661	4.663–6.872			
Admission from ICU	1217	530	43.55	3787	320	8.45	4.401	3.784–5.118			
ASA physical status 3–5	1786	649	36.34	3215	200	6.22	4.912	4.187–5.762			
Preoperative intensive support	1996	700	35.07	2636	123	4.67			<0.001	2.552	2.019–3.226
Presence of respiratory problems	823	310	37.67	4174	539	12.91	2.354	2.073–2.674			
Presence of cardiovascular problems	979	393	40.14	4015	455	11.33	2.898	2.556–3.286			
Presence of metabolic problems	457	167	36.54	4534	676	14.91	1.769	1.527–2.049			
Presence of neurological problems	539	176	32.65	4435	661	14.90	1.834	1.585–2.123			
Presence of renal problems	336	97	28.87	4650	747	16.06	1.725	1.446–2.059			
Post-ductal oxygen saturation <85%	52	24	46.15	2901	536	18.48	2.176	1.593–2.972			
Current comorbidities	2071	639	30.85	2561	184	7.18			<0.001	1.517	1.274–1.805
Urgent/emergency *vs* elective	2239	567	25.32	2765	283	10.24	1.768	1.526–2.049			
After hours/opening hours	334	86	25.75	4656	757	16.26	1.180	0.974–1.431			
Location of procedure in ICU	142	76	53.52	4862	774	15.92	2.161	1.776–2.629			
Surgical plan	2146	561	26.14	2486	262	10.54			<0.001	1.318	1.141–1.523
Length of surgery, mean (SD)	103.2		92.9	61.9		(65.2)	1.003	1.002–1.004	<0.001	1.125	1.076–1.176

Continued

Table 4 Continued

Variable	Univariable*						Multivariable† (n=4632)				
	Exposed			Unexposed			RR	95% CI	P	RR	95% CI
	Total	Morbidity	% or SD	Total	Morbidity	%					
Minimally invasive surgery	362	43	11.88	3726	647	17.36	0.757	0.569–1.008			
Gastrointestinal surgery	2588	382	14.76	1502	309	20.57	0.635	0.557–0.725			
Thoracic surgery	49	16	32.65	4040	674	16.68	1.744	1.161–2.619			
Cardiac surgery	320	165	51.56	3769	525	13.93	3.076	2.652–3.568			
Neurosurgery	207	45	21.74	3882	645	16.62	1.223	0.936–1.600			
Genitourinary surgery	289	30	10.38	3800	660	17.37	0.693	0.490–0.978			
Ear, nose, and throat surgery	274	36	13.14	3815	654	17.14	1.130	0.828–1.542			
Non-surgical *vs* surgical procedure	916	160	17.47	4088	690	16.88	1.172	1.004–1.367			
Anaesthesia technique											
General anaesthesia *vs* combined RA–GA	3220	729	22.64	1595	115	7.21	2.746	2.275–3.315			
Regional alone *vs* combined RA–GA	188	6	3.19	1595	115	7.21	0.378	0.169–0.842			
Anaesthesia management TIVA *vs* inhalation	390	138	35.38	4235	684	16.15	1.831	1.576–2.127			
Presence of vasopressors or inotropes as part of anaesthesia management	304	159	52.30	4500	682	15.16	2.407	2.078–2.788			
Team in charge (at least one senior)	4195	737	17.57	808	113	13.99	1.213	1.018–1.446			
Airway management											
Face mask *vs* tracheal intubation	584	39	6.68	3516	743	21.13	0.378	0.277–0.516			
SGA *vs* tracheal intubation	596	38	6.38	3516	743	21.13	0.406	0.296–0.557			
Anaesthesia management	3226	726	22.50	1406	97	6.90			<0.001	1.451	1.193–1.765
Intervention for difficult airways	221	40	18.10	4780	808	16.90	1.084	0.817–1.439			
Intervention for poor oxygenation	604	178	29.47	4397	670	15.24	1.567	1.359–1.806			
Intervention for CO_2 level	378	128	33.86	4623	720	15.57	1.837	1.570–2.149			
Intervention for glucose or sodium	123	54	43.90	4878	794	16.28	2.032	1.632–2.530			
Intervention for cardiovascular instability	998	312	31.26	4004	537	13.41	1.842	1.626–2.086			
Unplanned therapy for BP	519	189	36.42	437	105	24.03	1.424	1.174–1.727			
Total volume given to normalise BP‡	36.15		53.28	25.95		(26.34)	1.004	1.003–1.005			
Duration of cardiovascular instability	31.95		130.5	14.83		(21.10)	1.001	1.000–1.001			
Intervention on heart rate	95	43	45.26	886	264	29.80	1.506	1.184–1.915			
Change in rSO_2 concomitant to BP	78	30	38.46	143	57	39.86	0.984	0.701–1.381			
Intervention on temperature	218	61	27.98	4782	787	16.46	1.300	1.046–1.616			
Decrease in regional cerebral oxygenation	110	41	37.27	3942	551	13.98	2.150	1.657–2.790			
Administration of packed red cells	228	104	45.61	4773	744	15.59	2.406	2.055–2.817			
Unplanned intraoperative interventions	1643	445	27.08	2989	378	12.65			0.004	1.195	1.0571.350
Unplanned admission to PICU/NICU	71	17	23.94	1916	682	35.59	0.706	0.463–1.076			
Surgical revision for postoperative bleeding	22	10	45.45	4982	840	16.86	2.840	1.863–4.332	0.356	1.237	0.787–1.942
Unplanned overnight admission	69	9	13.04	4934	840	17.02	0.870	0.465–1.627			
Postoperative care											

Table 5 Relative risk and non-adjusted 95% confidence interval (CI) for the risk factors associated with mortality at 30 and 90 days follow-up. Exposed and unexposed refer to the number of cases exposed and unexposed to the examined risk factor. For continuous variables the table shows the mean and standard deviation (SD) when mortality occurred or not. *Univariable robust Poisson regression controlling for corrected age in weeks and sex on the last procedure of each child. †Multivariable robust Poisson regression controlling for cardiac surgery and multiple procedures (on procedures with combined or general anaesthesia, last procedure per child), variables in the model: sex, chronological age at inclusion in weeks, weight at inclusion, premature birth (<37 weeks) or low birth weight (<2500 g), medical history (congenital abnormality or history of respiratory support or intraventricular haemorrhage or ECMO support or previous surgery), illness status at inclusion (presence of cardiovascular support or admission from ICU or ASA status 3–5), medical comorbidities (presence of respiratory or cardiovascular or metabolic or neurological or renal problems), surgical plan (urgent/emergency or after hours or location of procedure: ICU), length of surgery (standardised), anaesthesia management (general anaesthesia or i.v. anaesthesia induction or presence of vasopressors or inotropes as part of anaesthesia management), the occurrence of any unplanned intraoperative intervention, surgical revision for postoperative bleeding. Area under the curve=0.885. ‡Total volume in ml kg^{-1}. Data are mean (SD). ECMO, extra-corporeal membrane oxygenation; GA, general anaesthesia; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; RA, regional anaesthesia; rSO_2, regional cerebral oxygen saturation; SGA, supraglottic airway.

Variable	Univariable*						Multivariable† (*n*=3982)				
	Exposed			Unexposed			RR	95% CI	*P*	RR	95% CI
	Total	Mortality	%	Total	Mortality	%					
Sex (male *vs* female)	2803	80	2.85	1486	56	3.77	0.807	0.581–1.121	0.432	1.136	0.827–1.560
Postmenstrual age, mean (SD)	40.12		8.67	45.88		(6.98)	0.893	0.868–0.920			
Chronological age at inclusion	7.27		8.10	9.48		(6.86)			0.129	1.019	0.995–1.044
Weight at birth, mean (SD)	2.01		1.06	2.77		(0.97)	0.646	0.534–0.782			
Weight at inclusion, mean (SD)	2.80		1.42	4.28		(1.51)	0.464	0.382–0.564	0.001	0.739	0.622–0.879
Premature birth (<37 weeks' GA)	1504	84	5.59	2785	52	1.87	1.728	1.152–2.594			
Premature birth or low birth weight	1497	90	6.01	2485	45	1.81			0.146	1.378	0.894–2.123
APGAR score at 5 min (≤7 *vs* >7)	489	46	9.41	2441	65	2.66	2.557	1.705–3.837			
Congenital abnormality	1913	85	4.44	2376	51	2.15	1.958	1.405–2.727			
History of respiratory support	1517	104	6.86	2771	32	1.15	4.108	2.662–6.341			
History of intraventricular haemorrhage	267	27	10.11	4022	109	2.71	2.178	1.373–3.454			
History of ECMO support	30	8	26.67	4259	128	3.01	8.724	4.433–17.169			
History of previous surgery	957	58	6.06	3332	78	2.34	2.912	2.105–4.028			
Neonatal medical history and congenital anomalies	2645	127	4.80	1337	8	0.60			0.558	1.222	0.625–2.391
Presence of cardiovascular support	169	44	26.04	2628	18	0.68	23.531	12.678–43.676			
Admission from ICU	1046	109	10.42	3243	27	0.83	9.464	5.696–15.722			
ASA physical status 3–5	1556	127	8.16	2731	8	0.29	20.966	10.275–42.778			
Preoperative intensive support	1735	130	7.49	2247	5	0.22			<0.001	6.803	3.078–15.035
Presence of respiratory problems	703	68	9.67	3580	67	1.87	3.673	2.503–5.391			
Presence of cardiovascular problems	853	88	10.32	3430	48	1.40	5.350	3.647–7.848			
Presence of metabolic problems	389	56	14.40	3886	80	2.06	4.616	3.199–6.659			
Presence of neurological problems	471	42	8.92	3790	91	2.40	2.727	1.832–4.061			
Presence of renal problems	310	32	10.32	3958	102	2.58	3.727	2.615–5.314			
Post-ductal oxygen saturation <85%	48	10	20.83	2459	78	3.17	4.167	2.306–7.531			
Current co-morbidities	1792	120	6.70	2190	15	0.68			0.003	2.290	1.330–3.945
Urgent/emergency *vs* elective	1838	110	5.98	2451	26	1.06	3.494	2.164–5.640			
After hours/opening hours	289	16	5.54	3993	120	3.01	1.125	0.675–1.874			
Location of procedure in ICU	131	23	17.56	4158	113	2.72	3.279	1.908–5.633			
Surgical plan	1776	110	6.19	2206	25	1.13			0.002	2.087	1.324–3.290
Length of surgery, mean (SD)	105.2		110.6	66.9		(68.3)	1.004	1.002–1.005	0.315	1.061	0.946–1.189
Minimally invasive surgery	313	4	1.28	3182	98	3.08	0.523	0.199–1.375			
Gastrointestinal surgery	2182	60	2.75	1314	42	3.20	0.722	0.492–1.059			
Thoracic surgery	42	0	0	3453	102	2.95	–	–			

Continued

Table 5 Continued

Variable	Univariable*						Multivariable† (n=3982)				
	Exposed			Unexposed			RR	95% CI	P	RR	95% CI
	Total	Mortality	%	Total	Mortality	%					
Cardiac surgery	275	26	9.45	3219	76	2.36	2.669	1.610–4.424			
Neurosurgery	181	7	3.87	3313	95	2.87	1.245	0.583–2.660			
Genitourinary surgery	261	5	1.92	3233	97	3.00	0.854	0.352–2.072			
Ear, nose, and throat surgery	225	2	0.89	3269	100	3.06	0.576	0.139–2.387			
Non-surgical *vs* surgical procedure	795	34	4.28	3494	102	2.92	1.745	1.196–2.545			
Anaesthesia technique											
General anaesthesia *vs* combined RA–GA	2798	127	4.54	1334	9	0.67	5.252	2.666–10.350			
Regional alone *vs* combined RA–GA	157	0	0	1334	9	0.67	–	–			
Anaesthesia management TIVA *vs* inhalation	368	35	9.51	3577	93	2.60	2.701	1.816–4.018			
Presence of vasopressors or inotropes as part of anaesthesia management	282	55	19.50	3844	81	2.11	5.866	3.918–8.782			
Team in charge (at least one senior)	3608	123	3.41	680	13	1.91	1.686	0.962–2.954			
Airway management											
Face mask *vs* tracheal intubation	523	4	0.76	2941	122	4.15	0.252	0.093–0.680			
SGA *vs* tracheal intubation	545	4	0.73	2941	122	4.15	0.289	0.107–0.778			
Anaesthesia management	2816	128	4.55	1166	7	0.60			0.010	2.636	1.255–5.538
Intervention for difficult airways	182	3	1.65	4105	133	3.24	0.539	0.182–0.159			
Intervention for poor oxygenation	522	40	7.66	3764	96	2.55	2.121	1.467–3.066			
Intervention for CO_2 level	324	22	6.79	3963	114	2.88	1.846	1.180–2.889			
Intervention for glucose or sodium	102	7	6.86	4185	129	3.08	1.526	0.740–3.149			
Intervention for cardiovascular instability	883	59	6.68	3405	77	2.26	2.021	1.423–2.869			
Unplanned therapy for BP	467	46	9.85	382	11	2.88	3.030	1.592–5.767			
Total volume given to normalise BP‡	57.06		75.17	27.327		(33.39)	1.009	1.006–1.012			
Duration of cardiovascular instability	52.24		130.8	17.99		(72.87)	1.001	1.000–1.002			
Intervention on heart rate	87	9	10.34	789	50	6.34	1.619	0.858–3.053			
Change in rSO_2 concomitant to BP	76	11	14.47	125	6	4.80	3.199	1.247–8.205			
Intervention on temperature	184	14	7.61	4103	122	2.97	1.613	0.930–2.795			
Decrease in regional cerebral oxygenation	99	15	15.15	3354	72	2.15	4.890	2.745–8.711			
Administration of packed red cells	209	33	15.79	4078	103	2.53	4.517	3.087–6.610			
Unplanned intraoperative interventions	1413	82	5.80	2569	53	2.06			0.163	1.267	0.908–1.768
Unplanned admission to PICU/NICU	61	2	3.28	1654	122	7.38	0.503	0.126–1.998			
Surgical revision for postoperative bleeding	21	10	47.62	4268	126	2.95	17.804	10.848–29.220	<0.001	7.710	4.511–13.177
Unplanned overnight admission	62	2	3.23	4227	134	3.17	1.430	0.356–5.746			
Postoperative care											

Given the response time to hypoxaemia of most pulse oximeters, higher interventional thresholds in clinical practice could be considered. However, additional factors such as cyanotic cardiac disease and the risk of hyperoxia in preterm neonates[28] need to be considered when defining normative ranges and thresholds.

Interventions based on end-tidal CO_2 were relatively uncommon, suggesting that no major change in end-tidal CO_2 occurred, some low end-tidal values were considered artifactual, or that this parameter was considered less relevant than others. As both hypocapnia and hypercapnia have been associated with adverse cerebral outcomes,[29–31] more

attention to reliable measuring and interventions to maintain normocapnia are warranted.

Mild to moderate hypoglycaemia[12] was relatively uncommon, but blood glucose was measured in only 50% of the cohort. As even mild hypoglycaemia may impair neurodevelopmental outcome,[32] particularly when associated with hypoxaemia, hypotension, or both, more rigorous perioperative monitoring of blood glucose is suggested for this high-risk cohort.

Haemoglobin values demonstrated a less permissive attitude compared with current published transfusion triggers,[33] but also mirror higher thresholds for premature neonates than older infants.[34,35] In contrast, temperature that triggered an intervention for hypothermia was well below 36°C.

Risk factors for critical events

Although more prolonged surgery was associated with an increased need for interventions, there was no significant impact of surgical timing (emergency/elective, in/out of hours) or location (ICU or OR). However, pre-existing congenital anomalies and a medical history that included conditions particularly relevant to neonatal populations (e.g. patent ductus arteriosus or intraventricular haemorrhage) were associated with physiological instability, and highlight unique factors for inclusion in preoperative assessment in this patient population. In addition, the risk of age-specific complications (e.g. postoperative apnoea in preterm-born neonates[36]) needs to be considered when planning inpatient *vs* day-stay procedures. The high proportion of patients requiring preoperative intensive care, postoperative intensive care, or both, and associations between the need for preoperative intensive support and current co-morbidities with subsequent morbidity and mortality reflect both the vulnerability of neonates and infants, and the need for age-specific risk assessment tools and management protocols.[37]

Morbidity and mortality

The current data confirm the increased vulnerability of neonates for perioperative morbidity and mortality compared with older children.[3,4,38] Large variability in the incidence of post-anaesthesia mortality in infants younger than 1 yr has been noted in previous studies, several of which were retrospective.[39–43] In the present study, the 30-day mortality rate in the subpopulation of neonates was comparable with previous reports in this age group in two major tertiary institutions in Australia and The Netherlands (3.67% and 3.86%, respectively).[39,44] Factors associated with increased risk included the degree of physiological instability, need for intensive support, and current co-morbidities, and also, as previously reported,[45,46] out-of-hours surgery. In addition to higher mortality in the youngest age groups (anaesthesia before 32 weeks' PMA), the incidence of critical events and morbidity was also higher in the youngest patients. In extremely preterm-born neonates, surgery during initial hospitalisation increases the risk of adverse neurodevelopmental outcomes,[2,47] but the relative contribution of increased perioperative instability and critical events, *vs* factors throughout the intensive care stay, to 30-day morbidity and long-term outcome remains to be determined. Despite clear evidence for increased mortality and morbidity in males born preterm,[47] sex did not influence critical events or complications in this cohort.

Composite adverse events may be more relevant for reporting outcomes in paediatric anaesthesia.[48] We found strong evidence for increased morbidity and mortality in the presence of hypotension, hypoxaemia, and anaemia. The combination of these variables may significantly impair tissue oxygenation, and poor cerebral oxygenation has been mechanistically associated with adverse outcome in neonatal populations.[49,50] Interrupting this vicious cycle with earlier and more effective interventions might improve outcome. The incidence of perioperative cardiac arrest (12.2/10 000) was lower than that reported by the large American register 'Wake Up Safe' (27.3/10 000), which included infants up to 6 months of age.[6] Whether this reflects differences in management, anaesthesia care, or risk level across different populations remains to be determined.

Limitations

The present results represent the current practice and behaviour of anaesthesiologists managing neonates and infants for surgical and non-surgical procedures in centres that voluntarily participated in the study. Although potentially limiting generalisability, a large number of centres across multiple countries and healthcare systems in Europe were involved, and recruitment rates were high. Loss to follow-up at 90 days was relatively high (25%), but morbidity and mortality data at 30 days are highly representative of this specific population. Only interventions in response to a critical event were reported, whereas medical treatments provided for preventing their occurrence were not recorded. In addition, the incidence of potential critical events that were tolerated and not reported by some practitioners cannot be determined, as values were self-reported rather than obtained from a continuous electronic database. Therefore, although the quality of anaesthesia care provided for infants in Europe cannot be completely elucidated using our methodological approach, data for overall mortality reflect current practice. Analysis focused on potential associations of a single medical intervention with alterations in physiological parameters. However, as confounding or co-existing factors may have contributed, and this is an observational study rather than a controlled trial, the relative magnitudes of associations between outcomes and various potential risk factors should be interpreted with caution.

Summary and conclusion

Neonates requiring anaesthesia often have significant co-morbidities and physiological instability, and the incidence of critical perioperative events requiring intervention by the anaesthesia care team is high. Risk factors associated with increased morbidity and mortality should be considered when interpreting neurodevelopmental outcomes after surgery and anaesthesia in early life. Every effort should be made to develop and apply standardised levels of care in young infants undergoing anaesthesia. Future research should focus on prevention, rapid detection, and standardised management of acute and persistent deviations in physiological parameters.

Authors' contributions

Overall coordinating investigators: ND, WH, FV
Study design: ND, WH, FV, TGH, KB, LV, SW, TE
Literature search: ND, WH, FV

Data cleaning: ND, WH, FV, KV, PH
Data analysis: ND, WH, FV
Data interpretation: ND, WH, FV, KV, TGH, KB, LV, SW, TE
Coordination of team: ND, WH, FV
Study monitoring: TGH, KB, LV, SW, TE, PH
Statistics: KV
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Language editing: TGH, KB, LV, SW, TE
Writing of the manuscript: ND, WH, FV, KV
Review of the manuscript: TGH, KB, LV, SW, TE
Protocol writing: PH
Ethics approval coordination: PH
Final reports: PH

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Documents related to NECTARINE: https://www.esahq.org/research/clinical-trial-network/completed-trials/nectarine/

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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