



RESEARCH ARTICLE

Outcome following anaesthesia in infancy in the Nordic countries: Subgroup analysis of the NECTARINE study

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Abstract

Introduction: The neonate and children audit of anaesthesia practice in Europe (NECTARINE) prospective observational study reported an incidence of 35.2% of critical events requiring intervention during 6542 anaesthetics in 5609 infants up to 60 weeks postmenstrual age (PMA) from 165 centres in 31 European countries.

Methods: Sub-analysis of the cohort from the Nordic countries (8% of the entire cohort) was conducted. Secondary aims were to describe the Nordic countries' anaesthetic practices and compare morbidity and mortality with the overall European cohort.

Results: Eleven Nordic centres recruited 447 infants (66% males, 37.3% born pre-term and 45% had congenital anomalies) undergoing anaesthesia for 530 surgical or non-surgical procedures at 25–60 weeks PMA. Perioperative critical events triggered interventions in 228/530 (43%) cases. Hypotension (12.6%) or hypoxaemia (11.7%) were more common in younger patients and those with co-morbidities. Hypo/hypercapnia occurred in 1.5%/4.7% of cases. More than two attempts for intubation were required in 13 (2.9%) infants (max three attempts). Distribution of ASA-Physical Status Scores was similar to the total European cohort (40% was ASA > 2). A total of 236/530 (44.5%) patients were admitted to the postoperative intensive care unit. Thirty-day morbidity (complications in 87/447 = 19.5%) and mortality (8/447, 1.8%) did not differ from the overall European cohort. Hospital re-admissions were significant up to 90 days (98/447 = 21.9%).

Conclusions: In Nordic countries, anaesthesia in young infant children is resource-demanding, and perioperative critical events and co-morbidities are common. Thirty-day morbidity and mortality data in the Nordic countries did not differ from the overall European cohort.

KEYWORDS

adverse effects, anaesthesia, complications, infants, mortality, newborn, outcome, safety, surgery

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Editorial Comment

This is a descriptive analysis of neonatal anaesthesia of the neonate and children audit of anaesthesia practice in Europe cohort in the Nordic countries. Whilst anaesthesia in neonates and young children is resource-demanding, and perioperative critical events and co-morbidities are common, it is re-assuring that the 30-day morbidity and mortality data in the Nordic countries did not differ from the overall European cohort.

1 | INTRODUCTION

Due to their smaller size, organ immaturity and limited physiological reserves neonates and infants (particularly premature infants) undergoing anaesthesia are at a higher risk for perioperative complications and poorer outcomes than older children.^{1–5} Recently, the European prospective multicentre observational study, neonates and children audit of anaesthesia practice in Europe (NECTARINE) was published.^{6,7} The NECTARINE study collected intraoperative management and perioperative outcome data for neonates and infants undergoing anaesthesia.

The primary aim was to identify the threshold of predetermined physiological parameters (heart rate, blood pressure, haemoglobin, blood glucose, sodium, core body temperature, pCO₂, pO₂ and near-infrared spectroscopy [NIRS]) that were considered indicative of critical events occurring during and up to 120 min after anaesthesia. Secondary aims were: morbidity at 30 days, mortality at 30- and 90-days after anaesthesia, and associations between critical events during anaesthesia and outcomes at 30 and 90 days.

The NECTARINE study included 5609 infants from 165 centres in 31 European centres with a mean (standard deviation [SD]) postmenstrual age (PMA) of 36.2 (4.4) weeks (35.7% born preterm) who underwent 6542 procedures within 63 (48) days of birth. Overall, the incidence of critical events requiring intervention was as high as 35.2% comprising mainly hypotension (>30% fall in blood pressure) and low oxygenation (SpO₂ 85%). The risk of critical events was increased in patients with preexisting medical conditions, congenital anomalies (relative risk [RR] = 1.16; 95% confidence interval [CI], 1.04–1.28); and in those requiring preoperative intensive support (RR = 1.27; 95% CI, 1.15–1.41). The PMA influenced the incidence and thresholds for intervention. Ninety-day mortality was 3.2% (95% CI, 2.7%–3.7%), and intraoperative hypotension, hypoxaemia, and anaemia were associated with increased morbidity (RR = 3.56; 95% CI, 1.64–7.71) and mortality.

The practice of neonatal anaesthesia in Nordic countries may be more uniform than elsewhere in Europe in terms of centralisation, use of drugs, anaesthesia techniques and training.⁸ Furthermore, we have also had a unique training programme in paediatric anaesthesia and intensive care in the Nordic countries since 2003.⁹ Therefore, the Steering Committee of NECTARINE agreed to conduct a subanalysis of the Nordic cohort to investigate if there were any differences compared to the overall European cohort in both the primary and secondary outcomes.

2 | METHODS

The methodology of the NECTARINE study is described in detail in the original manuscript.⁶ In brief, all neonates and infants up to 60 weeks' postmenstrual age (PMA = gestational age at birth plus chronological age) undergoing anaesthesia for surgical and non-surgical procedures in the operating room, intensive care unit (ICU), or diagnostic suite were eligible for inclusion.

Subjects were recruited for a total of 3 months at each site between 1 March 2016 and 31 January 2017. Parental consent was obtained in all elective cases, or within 48 h of inclusion for those requiring urgent or emergency procedures. The trial was registered ([ClinicalTrials.gov](https://clinicaltrials.gov) NCT02350348), and a statistical analysis plan was posted online (<https://www.esahq.org/research/clinical-trial-network/completed-trials/nectarine/>). Data were reported following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org).

Previous neonatal medical condition and congenital anomalies, preoperative intensive support, ASA physical status, co-morbidities. Perioperative physiological data were collected into a standardised electronic case report form (eCRF) until the patient was discharged from the post-anaesthesia care unit (maximum 120 min). Follow-up was performed at 30 and 90 days via a face-to-face interview, through medical records, or via a standardised telephone interview with a parent/carer. CRF data were entered anonymously into a secure internet-based electronic case record form (OpenClinica, Boston, MA, USA).

Eight predetermined critical events were defined, and the interventions to treat them were reported on each CRF. These included: SpO₂, PaO₂, or both (intervention to improve oxygenation), end-tidal carbon dioxide (ETCO₂), arterial/venous blood CO₂ (intervention to improve ventilation), systolic or mean arterial blood pressure, heart rate, ECG rhythm disturbances (resulting in cardiovascular instability), absolute values or relative changes in cerebral oxygenation (when NIRS was part of clinical monitoring), blood glucose, plasma sodium (Na⁺), haemoglobin values (need for blood transfusion), 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. Follow-up data including mortality data were collected at 30 and 90 days follow-up. Additionally, data on difficult airway management were collected.

TABLE 1 Demography stratified by country.

	Denmark	Sweden	Norway	Finland	Total
N (%)	117 (26.2)	119 (26.6)	100 (22.4)	111 (24.8)	447 (100)
Gestational age (weeks)					
Mean (SD)	36.6 (4.1)	35.7 (5.7)	36.5 (3.9)	35.9 (4.8)	36.2 (4.7)
Median (range)	38 (17)	38 (20)	37.5 (16)	38 (18)	38 (20)
Weight at birth (g)					
Mean (SD)	2835.6 (903.9)	2787.5 (1199.2)	2869.6 (926.8)	2802.5 (1103.5)	2822.2 (1041.6)
Median (range)	3015 (4140)	3093.5 (4562)	3000 (4491)	3041 (4250)	3040 (4562)
Sex					
Male	76 (65)	77 (65)	71 (71)	71 (64)	295 (66)
Female	41 (35)	42 (35)	29 (29)	40 (36)	152 (34)
Mode of delivery					
Vaginal	68 (58)	58 (49)	60 (60)	70 (63)	256 (57)
Caesarean	46 (39)	54 (45)	33 (33)	37 (33)	170 (38)
NA	3 (3)	7 (6)	7 (7)	4 (4)	21 (5)
APGAR Score (5 min)					
Mean (SD)	9.3 (1.7)	8 (2.5)	8.5 (1.8)	8.2 (1.7)	8.6 (2)
Median (range)	10 (7)	9 (8)	9 (9)	9 (7)	9 (9)
Congenital anomalies					
Congenital heart disease	3	3	18	17	41
Metabolic disorder	3	0	4	2	9
Chromosomopathy	3	1	4	3	11
Other	47	45	34	35	161
Number of procedures	117	152	106	155	530

Note: Data are shown as number or number (percent) [N (%)] if not else indicated, Mean (SD = standard deviation), Median (range).

Parameter thresholds and related information related to the patient's medical history, pre-anaesthesia assessment, baseline physiological parameters, indication for non-surgical or the surgical procedure and anaesthesia management were collected.

2.1 | Statistics

A statistical analysis plan was published prior to commencing the NECTARINE study (<https://www.esaic.org/uploads/media/ESA/Files/Research/NECTARINE%20Statistical%20Analysis%20Plan%20V10.pdf>). This also includes information about missing data.

Data are presented as actual numbers (%) in the tables. In the text, the data are condensed to mean (SD) or median (95% CI) as appropriate. No statistical comparisons were performed because of the relatively small sample size and low incidence of critical events in the NECTARINE cohort from the Nordic countries.

3 | RESULTS

The Nordic NECTARINE dataset contained details about 447 infants (equally distributed among the Nordic countries: Denmark [$n = 117$],

Finland [$n = 111$], Norway [$n = 100$] and Sweden [$n = 119$]) comprising a total of 530 anaesthetics (Denmark [$n = 117$], Finland [$n = 155$], Norway [$n = 106$] and Sweden [$n = 152$]). The participating centres were: Denmark: Odense University Hospital and Copenhagen University Hospital, Rigshospitalet, Finland: Helsinki University Central Hospital, Kuopio University Hospital, Tampere University Hospital, and Turku University Hospital, Norway: Oslo University Hospitals (Rikshospitalet and Ullevål) and St. Olav's University Hospital, Trondheim, Sweden: Astrid Lindgren Children's Hospital, Stockholm, Queen Silvia Children's Hospital, Gothenburg, and Uppsala University Hospital, Uppsala.

For the Nordic cohort, the demographics were quite similar between the four countries except that more children with congenital heart diseases were included in the Norwegian and Finnish cohorts (Table 1). One-third of the entire cohort comprised prematurely born infants, with 10.3% being extremely premature infants. Demographics stratified according to gestational age at birth are shown in Table 2. The distributions of premature infants varied extensively among the Scandinavian countries with more extremely born premature infants in the Swedish cohort (Table S1).

Clinical and per-operative characteristics of the Nordic cohort are shown in Table 3. Anaesthesia was required for 371 surgeries and 76 non-surgical procedures. In the entire Nordic cohort, there were 83 episodes of repeated anaesthetics.

TABLE 2 Demography stratified by gestational age at birth.

	<28 weeks	28–32 weeks	33–36 weeks	>36 weeks	Total
N (%)	46 (10.3)	27 (6.0)	92 (20.6)	282 (63.1)	447 (100)
Gestational age (weeks)					
Mean (SD)	24.78 (1.5)	30.44 (1.6)	34.88 (1.1)	39.01 (1.2)	36.18 (4.7)
Median (range)	25 (5)	31 (4)	35 (3)	39 (5)	38 (20)
Weight at birth (g)					
Mean (SD)	732.89 (198.5)	1513.19 (625.6)	2439.92 (498.9)	3418.01 (555.6)	2822.19 (1041.6)
Median (range)	733 (850)	1420 (2675)	2383 (2595)	3423 (2985)	3040 (4562)
Sex					
Male	30 (65)	19 (70)	63 (68)	183 (65)	295 (66)
Female	16 (35)	8 (30)	29 (32)	99 (35)	152 (34)
Mode of delivery					
Vaginal	23 (50)	5 (19)	42 (46)	186 (66)	256 (57)
Caesarean	23 (50)	22 (81)	45 (49)	80 (28)	170 (38)
Information not available	0 (0)	0 (0)	5 (5)	16 (6)	21 (5)
APGAR Score (5 min)					
Mean (SD)	6 (2.4)	8.35 (1.6)	8.49 (1.9)	9.24 (1.3)	8.58 (2)
Median (range)	6 (9)	9 (5)	9 (8)	10 (8)	9 (9)
Congenital anomalies					
Congenital heart disease	0	2	7	32	41
Metabolic disorder	1	0	0	8	9
Chromosomopathy	0	0	4	7	11
Other	3	3	49	106	161
Number of procedures	68	36	107	319	530

Note: Data are shown as number or number (percent) [N (%)] if not else indicated, Mean (SD = standard deviation), Median (range).

The anaesthesia team members comprised a senior anaesthesiologist in the majority of cases in all four countries, often accompanied by a junior anaesthesiologist, and a trainee doctor as well as 1–2 nurse anaesthetists.

The anaesthesia techniques included 300 (67.1%) cases for general anaesthesia (GA) alone and 142 (31.2%) for a combined GA and regional anaesthesia (RA) and 5 (1.1%) for RA alone.

Airway management comprised: an endotracheal tube (ET) in 351 (78.5%) cases, a supraglottic Airway (SGA) in 58 (13%) cases, a facemask in 27 (6.0%) cases, a nasal CPAP/non-invasive ventilation in 4 (0.9%) cases and a tracheostomy in 1 (0.2%) case.

Standard monitoring (ECG, non-invasive BP, SpO₂, capnography, anaesthetic agent and temperature) was used for all cases. An arterial line was used in 112 (25.1%) cases, a central venous catheter was used in 68 (15.2%), and NIRS was used in 82 (18.4%) cases, mainly in Denmark. However, no interventions were made solely based on a NIRS value.

3.1 | Incidence and type of critical events

The distribution of perioperative events requiring interventions is shown in Table 4 stratified according to age (PMA). A total of

228 interventions were made in the 530 anaesthetics (43%). Interventions were most commonly for cardiovascular instability (low blood pressure) and/or hypoxaemia (oxygen saturation). However, interventions were also related to changes in body temperature, haemoglobin, blood glucose, and/or sodium.

3.2 | Cardiovascular events

Perioperative cardiovascular instability (hypotension) requiring intervention was reported in 67 cases (11 systolic and 56 mean BP) (12.6%). These infants were often born at younger ages.

3.3 | Respiratory events

Interventions were required for hypoxaemia in 62 cases (11.7%), with trigger values of 90% SpO₂ in 24.2% of cases 85% in 21% of cases, and 80% in 54.8%, high pCO₂ in 25 cases (4.7%), low pCO₂ in eight cases (1.5%) with trigger values of 8–9 and 3.2–4.0 kPa, respectively. Hypoxaemia occurred both at induction (*n* = 21; 4.7%), during maintenance (28; 6.2%), and awakening (17 cases, 3.8%). Respiratory events most often occurred in the youngest infants.

TABLE 3 Clinical and per-operative characteristics of the Scandinavian cohort.

	Denmark	Sweden	Norway	Finland	Total
ASA score					
I (only applicable if >3 months)	10 (8.5)	20 (16.8)	3 (3)	3 (2.7)	36 (8.0)
II	81 (69.2)	53 (44.5)	50 (50)	48 (43.2)	232 (51.9)
III	18 (15.4)	34 (28.6)	34 (34)	34 (30.6)	120 (26.8)
IV	8 (6.8)	12 (10.1)	13 (13)	25 (22.5)	58 (13)
V	-	-	-	1 (0.9)	1 (0.2)
Type of procedures					
Surgical	95 (81.2)	99 (83.2)	86 (86)	91 (82)	371 (83)
Non-surgical procedures	22 (18.8)	20 (16.8)	14 (14)	20 (18)	76 (17)
Anaesthesia team members					
Senior anaesthesiologist	105 (23.2)	124 (27.4)	116 (25.7)	107 (23.7)	452 (34.8)
Junior anaesthesiologist	66 (43.1)	31 (20.3)	23 (15)	33 (21.6)	153 (11.8)
Anaesthesiologist in training	32 (22.1)	25 (17.2)	45 (31)	43 (29.7)	145 (11.2)
Anaesthetic nurse	119 (22.3)	153 (28.7)	136 (25.5)	126 (23.6)	534 (41.1)
ICU personal	2 (14.3)	1 (7.14)	4 (28.6)	7 (50)	14 (1.1)
Anaesthesia techniques					
General anaesthesia	80 (68.4)	76 (63.9)	80 (80)	64 (57.7)	300 (67.1)
Regional anaesthesia alone	3 (2.6)	2 (1.7)	-	-	5 (1.12)
Combined	34 (29.1)	41 (34.5)	20 (20)	47 (42.3)	142 (31.8)
Airway management					
Face mask	8 (6.8)	-	4 (4)	15 (13.5)	27 (6.04)
Supraglottic airway	21 (17.9)	26 (21.8)	2 (2)	9 (8.1)	58 (13)
Tracheostomy	-	1 (0.8)	-	-	1 (0.224)
Endotracheal tube	84 (71.8)	89 (74.8)	93 (93)	85 (76.6)	351 (78.5)
Nasal probe/CPAP/non-invasive ventilation	1 (0.8)	2 (1.7)	-	1 (0.9)	4 (0.9)
Monitoring					
Standard	117 (53.7)	119 (78.3)	100 (62.9)	110 (61.5)	446 (63)
Arterial	25 (11.5)	20 (13.2)	31 (19.5)	36 (20.1)	112 (15.8)
Central venous line	25 (11.5)	9 (5.9)	18 (11.3)	16 (8.9)	68 (9.6)
NIRS	51 (23.4)	4 (2.6)	10 (6.3)	17 (9.5)	82 (11.6)
NIRS					
Has any low rSO ₂ and/or drop in rSO ₂ occurred					
No	2 (1.71)	10 (8.40)	12 (12)	18 (16.2)	42 (9.40)
Yes	5 (4.27)	2 (1.68)	1 (1)	4 (3.60)	12 (2.68)
NIRS was not available	7 (6)	31 (26.1)	25 (25)	19 (17.1)	82 (18.3)
Total volume (ML/kg) given as boluses, Mean (SD)	32.4 (17.7)	29.4 (63.6)	27.2 (13.4)	22.4 (13.2)	27 (36.3)
Time of occurrence of hypoxemia					
Induction	1 (0.8)	10 (8.3)	3 (3)	7 (6.1)	21 (4.6)
Maintenance	1 (0.8)	11 (9.1)	5 (5)	11 (9.6)	28 (6.2)
Awakening	3 (2.6)	4 (3.3)	7 (7)	3 (2.6)	17 (3.8)
PACU	-	-	1 (1)	-	1 (0.2)

Note: Data are shown as number or number (percent) [N (%)] if not else indicated, Mean (SD = standard deviation); Median (range).

TABLE 4 Primary outcomes and number (%) of unplanned interventions.

Postmenstrual age in weeks (N)	<28 (n = 9)	28-31 (n = 6)	32-36 (n = 38)	37-40 (n = 77)	41-44 (n = 88)	45-60 (n = 229)	All (n = 447)
Days post birth at inclusion	10.1 (6.2)	31.8 (15.8)	15.6 (25)	19.2 (26.3)	43.8 (34.8)	97.8 (39)	64.0 (39)
Weight at inclusion (kg)	0.7 (0.11)	1.2 (0.35)	2.4 (0.55)	3.2 (0.58)	4 (0.70)	5.5 (1.28)	4.4 (1.64)
Systolic blood pressure (mm Hg)							
Baseline before induction	55 (7.1)	46.7 (14.7)	60.1 (10.6)	67.9 (15.7)	84.1 (22.7)	83.3 (21.2)	72.1 (20.9)
Baseline after induction	47.7 (9.5)	67.7 (3.0)	54.7 (11.9)	65.3 (17.2)	66.8 (16.8)	79.1 (17.3)	72.7 (18.6)
Number of interventions	1 (11.1%)	0 (-)	1 (2.6%)	2 (2.6%)	3 (3.4%)	4 (1.7%)	11 (2.5%)
Number of drug administrations	-	-	-	-	-	-	-
Trigger value	32 (-)	-	35 (-)	35.5 (9.2)	41.3 (9.4)	57.2 (8.4)	44.6 (12.5)
Percentage change from baseline	34.7 (-)	-	30 (-)	27.5 (26.6)	26.5 (36.0)	38.7 (5.37)	32.2 (19.3)
Mean blood pressure (mm Hg)							
Baseline before induction	39 (8.5)	36.7 (9.3)	43.9 (8.1)	52.7 (14.1)	60.3 (18.4)	59.5 (17.1)	52.4 (15.9)
Baseline after induction	35.8 (11.6)	41 (7.8)	39.4 (8.7)	47.8 (12.9)	46.4 (13.1)	55.5 (14.4)	51.2 (14.6)
Number of interventions	6 (66.7%)	3 (50.0%)	10 (26.3%)	13 (16.9%)	7 (7.9%)	17 (7.4%)	56 (12.5%)
Number of drug administrations	2 (22.2%)	2 (33.3%)	4 (10.5%)	10 (13%)	6 (6.8%)	17 (7.4%)	41 (9.2%)
Trigger value	24.3 (3.4)	27.3 (3.51)	29.1 (4.5)	34.2 (4.7)	33.3 (5.2)	37.6 (8.2)	32.8 (7.2)
Percentage change from baseline	18.0 (12.6)	24.0 (16.2)	20.0 (16.0)	27.8 (13.1)	31.8 (16.4)	24.1 (19.2)	24.6 (16.0)
Heart rate							
Baseline (beats min ⁻¹)	162 (14.7)	147 (14.7)	149 (17.2)	142 (20.8)	155 (14.5)	142 (19.2)	146 (19.1)
Number of interventions	0 (-)	0 (-)	0 (-)	3 (3.9)	1 (1.1)	1 (0.4)	5 (1.1)
Trigger value for heart rate (beats min ⁻¹)	-	-	-	150 (70)	180 (-)	60 (-)	138 (67.2)
Oxygen saturation							
Baseline (%)	94.9 (3.40)	95.6 (4.16)	97.7 (3.36)	98.4 (2.34)	98.2 (4.08)	98.9 (2.16)	98.4 (2.95)
Number of interventions	4 (44.4%)	2 (33.3%)	7 (18.4%)	12 (15.6%)	15 (17.0%)	22 (9.6%)	62 (13.9%)
Trigger values based on SpO ₂							
90%	25.0%	50.0%	28.6%	25.0%	20.0%	26.3%	24.2%
85%	0	0	28.6%	16.7%	26.7%	26.3%	21.0%
80%	75.0%	50.0%	42.9%	58.3%	53.3%	63.2%	54.8%
Trigger value based on PaO ₂	-	-	-	7 (-)	5 (-)	12 (0.9)	9 (3.6)
Partial pressure in CO ₂							
Baseline (kPa)							
Baseline (kPa)	46.8 (11.8)	48 (13.0)	48.3 (9.10)	44.4 (10.1)	47.6 (14.1)	46.8 (23.8)	46.8 (15.4)
Number of interventions							
Number of interventions	1 (11.1%)	0	3 (7.9%)	8 (10.4%)	5 (5.7%)	8 (3.5%)	25 (5.6%)
Trigger value based on PaCO ₂ (kPa)							
Trigger value based on PaCO ₂ (kPa)	12 (-)	-	9 (1.4)	8 (4.4)	12 (-)	8 (-)	9.25 (3)
Trigger value based on ET/CO ₂ (kPa)							
Trigger value based on ET/CO ₂ (kPa)	-	-	9 (-)	7.9 (2.1)	7.6 (2.9)	8.3 (0.8)	8 (1.9)

(Continues)

TABLE 4 (Continued)

Postmenstrual age in weeks (N)	<28 (n = 9)	28-31 (n = 6)	32-36 (n = 38)	37-40 (n = 77)	41-44 (n = 88)	45-60 (n = 229)	All (n = 447)
Haemoglobin							
Baseline (g dl ⁻¹)	12.5 (2.1)	12.1 (1.3)	14.4 (3.3)	14.3 (3.2)	13.2 (3.4)	11.0 (2.1)	12.8 (3.2)
Number of interventions	2 (22.2)	2 (33.3)	1 (2.6)	4 (5.2)	1 (1.1)	8 (3.5)	18 (4.0)
Trigger value	12.4 (0.8)	10.7 (0.6)	-	10.1 (1.3)	10 (-)	8.4 (1.9)	9.6 (1.9)
Percentage change from baseline	30.6 (43.3)	1.7 (2.5)	-	30.7 (25.8)	24.2 (-)	18.2 (22.4)	21 (23.4)
Metabolic							
Baseline serum sodium (mEq L ⁻¹)	140 (4.0)	134 (3.0)	138 (3.1)	139 (4.2)	137 (2.7)	138 (3.5)	138 (3.5)
Baseline serum glucose (mmol L ⁻¹)	8.6 (1.1)	5.4 (2.8)	5.1 (1.3)	5.4 (1.6)	5.5 (1.4)	6.1 (2.2)	5.7 (1.9)
Number of interventions	1 (11.1%)	1 (16.7%)	1 (2.6%)	2 (2.6%)	1 (1.1%)	1 (0.4%)	7 (1.6%)
Trigger value for hypoglycaemia (mMol/L)	-	1 (-)	3 (-)	3 (-)	3 (-)	-	2.5 (1)
Trigger value for hyponatremia (mMol/L)	-	-	-	-	-	129 (-)	129 (-)
Temperature (°C)							
Baseline	36.1 (1.1)	36.7 (0.7)	36.3 (0.6)	36.4 (0.6)	36.5 (0.5)	36.6 (0.6)	36.5 (0.60)
Number of interventions	2 (22.2%)	0 (-)	2 (5.2)	6 (8)	1 (1.1)	5 (2.2)	16 (3.6)
Value of trigger	35 (0)	-	35 (0)	34.5 (3.1)	34 (-)	36 (1.2)	35.1 (2)
Total number of interventions in response to a critical event	19	8	28	55	42	76	228

Note: Data are shown as number or number (percent) [N (%)] if not else indicated, Mean (SD); Median (range).

TABLE 5 Morbidity data at 30- and 90-days post-anaesthesia.

	Denmark	Sweden	Norway	Finland	Total
Morbidity at day 30					
BRAIN/CNS complication? Yes	5 (4.3)	4 (3.4)	-	2 (1.8)	11 (2.5)
SURGICAL complication? Yes	10 (8.5)	7 (5.9)	4 (4)	4 (3.6)	25 (5.6)
RESPIRATORY complication Yes	7 (6)	17 (14.3)	2 (2)	4 (3.6)	30 (6.7)
CARDIO-VASCULAR? Yes	3 (2.6)	6 (5.0)	4 (4)	2 (1.8)	15 (3.4)
LIVER FAILURE? Yes	1 (0.8)	1 (0.8)	1 (1)	-	3 (0.7)
RENAL INSUFFICIENCY? Yes	3 (2.6)	-	-	-	3 (0.7)
Morbidity at day 90					
Any hospital re-admission until 90-day follow-up? Yes	39 (33.3)	22 (18.5)	18 (18)	19 (17.1)	98 (21.9)

Note: Data are shown as number (percent); N (%).

3.4 | Difficult airway

Overall, in 13 patients, more than two attempts were necessary for endotracheal intubation with an incidence of 2.9% varying between 0.85% (Denmark), 3.4% (Sweden), 4% (Norway) and 3.6% (Finland). All patients were intubated after three attempts or less.

3.5 | Morbidity, mortality, 30-day and 90-day follow-up

Thirty-day mortality in the Nordic Nectarine cohort was (1.8%); in Denmark (2.6%), Finland (0.9%), Norway (0%) and Sweden (3.4%). There were no mortalities at 90 days. Morbidity at 30 days was 87 (19.5%) and mainly surgical or respiratory and morbidity at 90 days was 98 (22%). Loss to follow-up at 30 days was 32 (7.2%) (1 from Denmark, 25 from Finland, 2 from Norway and 4 from Sweden). At 90 days, the loss to follow-up was 67 (15%) (4 from Denmark, 31 from Finland, 8 from Norway and 24 from Sweden). Until 90 days, there were 98 (21.9%) hospital readmissions for various causes.

4 | DISCUSSION

This secondary Nordic analysis of the European NECTARINE data showed that perioperative critical events occurred in 43% of the infant (before 60 weeks PMA), that is, 228 events during 530 anaesthetics. The participating centres were the major paediatric hospitals of the Nordic countries. Importantly, very few infants (if any) are anaesthetised outside these hospitals, for example, in private clinics.

The overall incidence (43%) was slightly higher than in the overall European cohort (35%) but similar in the predominance of events mainly triggered by cardiovascular and respiratory parameters. With the limitations of the Nordic cohort in mind (see later) 30-day mortality in the Nordic cohort (1.8%) was somewhat lower than in the overall European cohort (3.2%) as was the incidence of difficult intubations (2.9%) versus (5.8%). But it must be stressed that these

data should be interpreted with caution. Importantly, the NECTARINE study has drawn attention to the difficulties associated with endotracheal intubation in newborns and tiny infants,^{7,10} and recommendations for how to enhance the procedure's success in this particular population have been made.¹¹⁻¹³ A total of 236/530 children (44.5%) were admitted to the postoperative ICU.

The primary outcome of NECTARINE was unplanned interventions, whilst secondary outcomes included risk factors linked to crucial events requiring interventions, morbidity and mortality. We decided not to conduct statistical analyses to determine the risk factors for the secondary outcomes and only considered morbidity and mortality as secondary outcomes. There were some intriguing disparities between the Nordic nations as well as the total European cohort in both the primary and secondary outcomes (Tables 4 and 5). These results were probably primarily the result of case-mix, case-load and/or sessional variances. These results are also comparable to the recently published sub-analysis of the NECTARINE cohort from the United Kingdom.¹⁴

The sample size of the Nordic NECTARINE cohort ($n = 447$ infants and 530 anaesthetics) is too small for any meaningful comparison and firm conclusions to be made given the low incidences of critical events. Sometimes, a single complication would significantly alter the overall complication rate. The NECTARINE database contains a myriad of data, but it will make little sense to publish and/or describe all of these given the above.

The composition of the anaesthetic team was significant in this Nordic cohort. In the vast majority of cases (452/530, 85.3%), there was a senior anaesthesiologist (more than 5 years of experience in paediatric anaesthesia) present, often accompanied by a junior anaesthesiologist (less than 5-years' experience in paediatric anaesthesia) (153/447, 28.9%), and an anaesthetist-in-training (145/530, 11.2%) as well as 1-2 nurse anaesthetists.

The NECTARINE dataset from the Nordic countries represents the vast majority of all procedures in the participating centres during the 3-months inclusion period.

Significant clinical skills and knowledge are necessary when anaesthetising small infants. A 2-year training programme in the

Nordic countries in paediatric anaesthesia and intensive care has existed since 2003⁹ (for more information about the programme please visit: www.ssa.info/education/paediatric-anaesthesia). However, its impact on the outcome remains to be properly clarified. The 'Safe Anaesthesia for Every Child' (Safetots) initiative (www.safetots.org) which promotes safe perioperative paediatric practice has highlighted the challenges of paediatric and neonatal anaesthesia, and suggested where and how improvements can be made.⁴

4.1 | Strength and limitations

The current findings reflect how Nordic anaesthesiologists currently manage newborns and babies for both surgical and non-surgical procedures in the centres that willingly took part in the study. The study involved all of the main paediatric hospitals in the Nordic countries where a sizable number of young children are anaesthetised. The nature of voluntary participation and the snapshot method of recruitment may miss unusual and potentially dangerous practices and may introduce a reporting bias.

Only crucial event-related interventions were recorded; none of the medical care given to prevent them from happening was recorded. Additionally, because values were reported by the participants rather than taken from an ongoing computerised database, it was impossible to ascertain the frequency of potentially serious incidents that some practitioners tolerated but did not disclose.

This study concentrated on potential relationships between changes in physiological markers and a single medical intervention, but the relative magnitudes of relationships between outcomes and other possible risk variables should be interpreted with care.

The current findings were based on the processes and activities currently employed by anaesthesiologists to manage newborns and babies undergoing surgical and non-surgical procedures at the centres that voluntarily participated in this study. The morbidity and fatality data at 30 days are indicative of this particular group, even though there was a considerable loss to follow-up at 90 days (15%, $n = 67$).

The adoption of thorough, consistent definitions of the numerous significant critical events in paediatric anaesthesia was an important NECTARINE quality.

Our research focused on possible connections between alterations in physiological indicators and a specific therapeutic strategy. But because this is an observational study rather than a controlled trial, confounding or coexisting factors may have contributed to the relative magnitudes of associations between outcomes and other potential risk variables.

In conclusion, in the Nordic countries, anaesthesia in young infant children is resource-demanding, and perioperative critical events and co-morbidities are frequent. Data on morbidity and mortality at 30 days are comparable to those of the entire European group. Although some outcomes appear better in the Nordic nations than in the entire European cohort, this is most likely because of variations in case-load and case-mix.

AUTHOR CONTRIBUTIONS

TGH and AGC collected the Nordic data from the NECTARINE database and wrote the first draft of the manuscript. TGH, JV, WBB and AGC contributed to the analysis of data and writing of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Tom G. Hansen is an associate editor of the *Acta Anaesthesiologica Scandinavica*. Jenny Vieri, Wenche Bakken Børke and Albert Gyllencreutz Castellheim declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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