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ORIGINAL ARTICLE

Towards integrative neuromonitoring of the surgical newborn

A systematic review

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BACKGROUND The altered neurodevelopment of children operated on during the neonatal period might be due to peri-operative changes in the homeostasis of brain perfusion. Monitoring of vital signs is a standard of care, but it does not usually include monitoring of the brain.

OBJECTIVES To evaluate methods of monitoring the brain that might be of value. We also wanted to clarify if there are specific risk factors that result in peri-operative changes and how this might be evaluated.

DESIGN Systematic review.

DATA SOURCES A structured literature search was performed in MEDLINE in Ovid, Embase, Cochrane CENTRAL, Web of Science and Google Scholar.

ELIGIBILITY CRITERIA Studies in neonates who received peri-operative neuromonitoring were eligible for inclusion; studies on neurosurgical procedures or cardiac surgery with cardiopulmonary bypass and/or deep hypothermia cardiac arrest were excluded.

RESULTS Nineteen of the 24 included studies, totalling 374 infants, reported the use of near-infrared spectroscopy. Baseline values of cerebral oxygenation greatly varied (mean 53 to 91%) and consequently, no coherent results were found. Two studies found a correlation between cerebral oxygenation and mean arterial blood pressure. Five studies, with in total 388 infants, used (amplitude-integrated) electroencephalography to study peri-operative brain activity. Overall, the brain activity decreased during anaesthesia and epileptic activity was more frequent in the peri-operative phase. The association between intra-operative cerebral saturation or activity and neuro-imaging abnormalities and/or neurodevelopmental outcome was investigated in six studies, but no association was found.

CONCLUSION Neuromonitoring with the techniques currently used will neither help our understanding of the altered neonatal pathophysiology, nor enable early detection of deviation from the norm. The modalities lack specificity and are not related to clinical (long-term) outcome or prognosis. Accordingly, we were unable to draw up a monitoring guideline.

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Introduction

The past decades have seen improved outcomes following the operative and nonoperative treatment and care for the surgical newborn with congenital anomalies.[1] Survival rates have increased due to changes in resuscitation time, pre-operative optimisation of homeostasis and subsequently better surgical timing and approach.[2,3] Yet, the few studies that have investigated the long-term outcomes of neonatal surgery show impaired neurodevelopment.[4–7] Causes of impairment are largely unknown, but a previous study has suggested a crucial role for the complex interactions between cerebral oxygenation, activity and perfusion in the peri-operative period.[8]

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Monitoring of vital signs as a surrogate for end-organ perfusion is the standard of care, but it does not usually include monitoring of the brain. The exception to this is neonatal cardiac surgery with cardiopulmonary bypass, where peri-operative neuromonitoring is advocated in view of the high risk of brain injury and the existence of abnormal cerebral flow antenatally in some complex cardiac anomalies.[9,10] No valid indications for neuromonitoring of the noncardiac surgical newborn are reported. However, a recent study has reported a high incidence, 58% in full-term born infants, of anatomical signs of brain injury on MRI after noncardiac neonatal surgery.[11] Hence, surgical newborns may be prone to peri-operative brain injury, although it is not clear from previous research whether these injuries occur in the pre-operative, intra-operative or postoperative period. Yet, after birth, the biggest changes in neonatal physiology might have occurred in the intra-operative period.

The brain can be monitored during surgery and anaesthesia by means of various techniques, such as near-infrared spectroscopy (NIRS), (amplitude-integrated) electro-encephalography (aEEG) or cerebral Doppler ultrasound (CDU). Measurements with these techniques alongside continuous measurement of vital signs can provide insight into the altered physiology of the surgical newborn and their brains in the peri-operative period. However, a systematic evaluation of indications and treatment algorithms for neuromonitoring is lacking. The aim was to evaluate methods of monitoring the brain that might be of value. We also wanted to clarify whether there are specific risk factors that result in peri-operative change and how this might be evaluated.

Methods

Eligibility criteria

We performed a structured literature search to identify clinical studies using peri-operative neuromonitoring in neonates, defined as children under 90 days of life or postmenstrual age less than 52 weeks. The search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[12,13] The studies needed to be original and published in a peer-reviewed journal. Limits were set on human and English-language studies. Studies were excluded if the article did not match the inclusion criteria; if the article was a case report; if the surgical procedure was neurosurgery or cardiac surgery with cardiopulmonary bypass and/or deep hypothermia cardiac arrest; or if the article did not contain original patient data.

Information sources

The search strategy included expanded Medical Subjects Headings terms and predefined search terms (see Appendix 1, Supplementary Digital File, http://links.lww.com/EJA/A307). On 11 December 2018, an electronic literature search was performed in MEDLINE in Ovid (PubMed), Embase, Cochrane CENTRAL, Web of Science and Google Scholar.

Search

The following search terms were used for Medline Ovid: (General Surgery/OR exp 'Surgical Procedures, Operative'/OR (surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*).ab,ti.) AND (electroencephalography monitoring/OR neuromonitoring/OR near infrared spectroscopy/OR cerebral oximeter/OR electroencephalogram/OR brain function/OR (EEG OR aEEG* OR NIRS OR ((near*-infrared*) ADJ (spectro*)) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) ADJ3 (monitor*)) OR ((cerebr* OR brain*) ADJ3 (oximeter* OR oxygenat*)) OR electroencephalogram*).ab,ti.) AND (infant/OR neonatology/OR neonatal intensive care unit/OR pediatric surgery/OR (infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU).ab,ti.) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.lg. NOT (exp animals/NOT humans/). The full search is added as an appendix.

Study selection

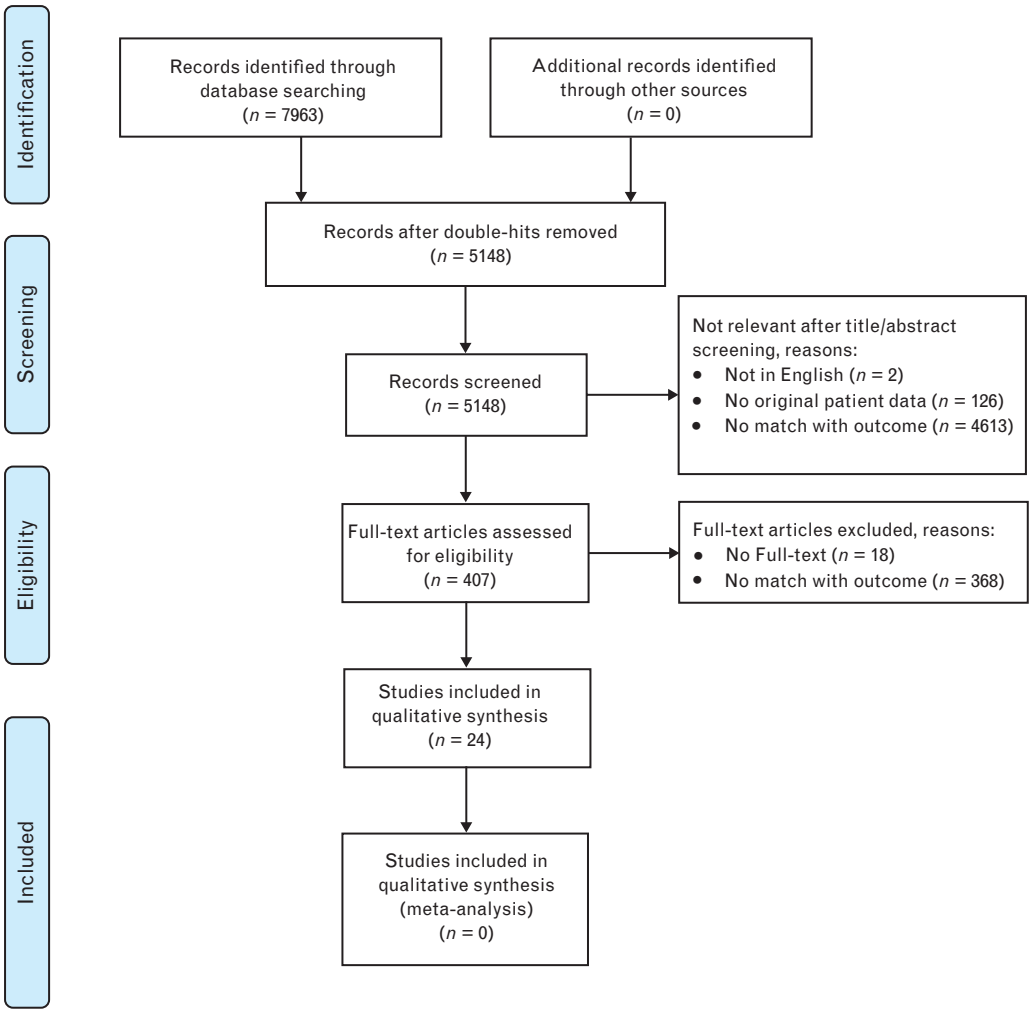
After removing the duplicates, two authors (SC and CvH) independently screened the titles and abstracts of the remaining citations on relevance, and reviewed the full texts of eligible articles on inclusion criteria (Fig. 1). All studies were scored for methodology (Appendix 2, Supplementary Digital File, http://links.lww.com/EJA/A307). The following data were extracted: study design, sample size, study patient characteristics, modality, device and period of neuromonitoring, results of neuromonitoring, outcome and, if applicable, the follow-up data.

Results

Structured literature search

The systematic search retrieved 7963 records (Fig. 1), of which 24 articles met the inclusion criteria. All studies had a prospective observational design and were scored for methodology (Appendix 2, http://links.lww.com/EJA/A307). The median [range] sample size was 16 [5 to 226] and the total number of children studied was 762 (Tables 1 and 2). Nineteen studies used NIRS.[14–32] Fourteen of these measured only cerebral oxygenation and five combined cerebral oxygenation with cerebral blood flow (CBF) or cerebral autoregulation (Table 1). Five studies used aEEG – in four to measure cerebral activity[33–36] and in one, a large cohort study, to detect epileptic activity only (Table 2).[37]

Fig. 1



PRISMA flow diagram of article selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Clinical outcome was reported in five studies. Postoperative neuro-imaging was performed in three of these studies.[20,30,35] In one of these the findings of the neuro-imaging were combined with neurodevelopmental outcome at the age of 2 years.[30] The two other studies reported the outcome of neurodevelopment (Table 3).[26,29]

Near-infrared spectroscopy: cerebral oxygen saturation

Nineteen of the 24 included studies made use of NIRS (Table 1). All but one monitored the patients over time, most commonly starting before surgery and continuing until the end of surgery (Table 4). The reported mean and median baseline NIRS values range widely (Table 4). Of the four studies that investigated the effect of ligation of (haemodynamically significant) patent ductus arteriosus (hsPDA) on cerebral oxygenation conflict, one reported no significant changes after ligation, one a significant decline, and two a significant increase in cerebral oxygenation after ligation (Table 4).[16–19] The other studies concern different types of surgical approach. Four studies investigated NIRS during open abdominal surgery; one during laparoscopic surgery, and two during thoracoscopic surgery. Two studies did not specify the surgical approach. In these studies, measurements at different peri-operative moments were compared with each other, without coherent results (Table 4). Five studies showed a significant decrease in cerebral oxygenation; four a significant increase; and eight no significant change.

Near-infrared spectroscopy: correlations with other physiological variables

In the five studies that reported a decrease of cerebral oxygenation, three reported no significant changes in blood pressure (BP)[15,16,27] and two did not report BP values.[24,28] In the four studies that reported an increase in

Table 1 Overview of included studies reporting about near-infrared spectroscopy as intra-operative neuromonitoring technique

Demographics								Measurement			Results		
Reference	*n*	Device	Pathologies	Surgery	Age at surgery (days)	GA (weeks)	BW (kg)	Cerebral oxygenation	Cerebral blood flow	Cerebral autoregulation	Comparison over time	Neuro-imaging	Neuro-development
Fortune *et al.*[14]	49	NIRO-300	Acute abdomen	NR	Neonatal age, not specified	26.8 to 40.0[a]	1100 to 4000[a]	X					
Dotta *et al.*[15]	25	NIRO-300	CDH	Laparotomy	3.5 ± 2.5 [2 to 14][a]	37.8 ± 1.8	3057 ± 354	X			X		
Zaramella *et al.*[16]	16	NIRO-300 + CDU	PDA	Ligation	7 to 29[a]	27.3[b] [24 to 34][a]	1036[b] [680 to 1740][a]	X	X		X		
Hüning *et al.*[17]	10	NIRO-300	PDA	Ligation	14[c] [2 to 22]	24[c] [23 to 27][a]	748[c] [590 to 1070][a]		X		X		
Vanderhaegen *et al.*[18]	10	INVOS	PDA	Ligation	33 ± 30.9 [6 to 88][a]	27 ± 2.64 [24 to 32][a]	987.5 ± 391 [555 to 1855][a]	X			X		
Chock *et al.*[19]	12	INVOS	PDA	Ligation	16 ± 9	26 ± 1	841 ± 159	X			X		
Chock *et al.*[20]	10	INVOS	PDA	Ligation	NR	26 ± 1	830 ± 170		X	X	X	x	
Conforti *et al.*[21]	13	INVOS	OA	Laparotomy	NR	33 to 41 + 5[a]	1170 to 3740[a]	X			X		
Michelet *et al.*[22]	60	INVOS	Emergency thoracic or abdominal surgery, CVC insertion, urological procedures, imperforate hymen, pharyngeal teratoma and endoscopy	NR	22 ± 22	37 ± 4	NR	X			X		
Tytgat *et al.*[23]	12	INVOS	HPS	Laparoscopy	38[c] [15 to 62][a]	39[c] [36 to 41][a]	3500[c] [2400 to 4400][a]	X			X		
Conforti *et al.*[24]	13	INVOS	CDH	Laparotomy	3[c] [2 to 9][d]	38[c] [35 to 40][d]	3055[c] [2660 to 3620][d]	X			X		
Koch *et al.*[25]	21	NIRO-300	CDH, OA, intestinal atresia, omphalocele, PDA, HPS, circumcision, oophorectomy	NR	12.8 ± 10.1	35.7 ± 5.4	2878 ± 1002	X			X		
Razlevice *et al.*[26]	43	INVOS	General, thoracic or urologic surgery for congenital anomalies or disease	NR	6[c] [0 to 70][a]	38[c] [5 to 41][a]	3400[c] [800 to 5000][a]	X			X		X
Tytgat *et al.*[27]	15	INVOS	OA	Thoracoscopy	2[c] [1 to 7][a]	39[c] [36 to 42][a]	2962[c] [2155 to 4490][a]	X			X		
Beck *et al.*[28]	19	INVOS	Gastroschisis, omphalocele, CDH, OA, NEC, neonatal bowel obstruction, abdominal tumour	NR	7 ± 15	36 ± 4.7	2770 ± 941	X	X		X		
Costerus *et al.*[29]	10	INVOS	CDH, OA	Thoracoscopy	1.3 to 4.5[a]	34 to 40.2[a]	1941 to 3338[a]	X			X		X
Stolwijk *et al.*[30]	5	INVOS	LGOA	Thoracoscopy	4[c] [2 to 53][a]	35 + 3[c] [33 + 4 to 39 + 6][a]	1580 to 2825	X			X	X	X
Nissen *et al.*[31]	12	INVOS	HPS	NR	43[c] [20 to 74][a]	38[c] [35 to 40][a]	3105[c] [2380 to 4000][a]	X			X		
Kuik *et al.*[32]	19	INVOS	NEC, SIP	Laparotomy	9[c] [7 to 12][c]	27.6[c] [26.6 to 31.0][d]	1090[c] [924 to 1430][d]	X		X	X		

CDH, congenital diaphragmatic hernia; CVC, central venous catheter; HPS, hypertrophic pyloric stenosis; LGOA, long gap oesophageal atresia; NEC, necrotising enterocolitis; NR, not reported; OA, oesophageal atresia; PDA, patent ductus arteriosus; SIP, spontaneous intestinal perforation. Values are given as mean ± SD. [a]Range. [b]Mean. [c]Median. [d]IQR.

Table 2 Overview of included studies reporting the amplitude-integrated electro-encephalography as an intra-operative neuromonitoring technique

Demographic								Measurement			Results		
Reference	*n*	Device	Pathologies	Type of surgery	Age at surgery (days)	GA (weeks)	Birth weight (kg)	Cerebral activity	Epileptic activity	Sleep depth	Comparison over time	Neuro-imaging	Neuro-development
Kohelet *et al.*[37]	226	EEG, NR	NEC, PDA	Ligation or laparotomy	NR	>24	Very low birthweight		X				
Kasdorf *et al.*[33]	17	Olympic CFM 6000 Infant aEEG Cerebral Function Monitor	PDA	Ligation	24 ± 13 [8 to 55][a]	26.6 ± 3.4 [22.6 to 35.1][a]	867 ± 337 [538 to 1735][a]	X			X		
Leslie *et al.*[34]	17	Cerebral Function Monitor aEEG	PDA	Ligation	27 [14 to 42][a]	25 [23 to 27][a]	680 [500 to 1140][a]	X			X		
Stolwijk *et al.*[35]	111	BrainZ Monitor aEEG	OA, abdominal wall defects, intestinal atresia/volvulus, anorectal malformation, urogenital malformation	NR	2 [0 to 32][a]	38.28 [28 to 42][a]	NR	X	X	X	X	X	
Cornelissen *et al.*[36]	17	Waveguard EEG cap & EMU40EX; Natus Medical Incorporated	Elective surgery	NR	2.9 [2.6 to 3.5][b] months	NR	NR	X					

NEC, necrotising enterocolitis; NR, not reported; OA, oesophageal atresia; PDA, patent ductus arteriosus. Values are given as mean ± SD. [a] Median [range]. [b] [IQR].

Table 3 Results of neuro-imaging and neurodevelopmental outcome

Demographics			Neuroimaging			Neurodevelopmental outcome			
Reference	*N*	Device	Timing/Age	Type	Results	Test	Timing/Age	Results	Correlation
Razlevice *et al.*[26]	43	INVOS, NIRS	NP	NP	NP	Clinically documented neurological function by paediatric neurologist	In-hospital follow-up (range 14 days to 6 months)	Desaturated group: declined in 3 patients	NR
								Normal group: in normal range	NR
Costerus *et al.*[29]	10	INVOS, NIRS	NP	NP	NP	BSID-II, MDI, PDI	24 months	All in normal range	NR
Stolwijk *et al.*[30]	5	INVOS, NIRS	Preoperative	Ultrasound	2 patients with a small thalamic infarction	Griffith Mental Development Scales and BSID-III	24 months	All in normal range	No signs of altered peri-operative cerebral perfusion in the two patients
			Postoperative	MRI					
Chock *et al.*[20]	10	INVOS, NIRS	Baseline	Ultrasound and MRI	25% increased abnormalities compared with baseline[a]	NP	NP	NP	No correlation with cerebral autoregulation
			Before discharge or hospital transfer						
Stolwijk *et al.*[30]	111	BrainZ Monitor aEEG	Preoperative	Ultrasound	10% intracranial lesions	NP	NP	NP	No correlation with aEEG background patterns
			Postoperative	MRI	58% parenchymal lesions and 37% nonparenchymal injury				

NP, not performed; NR, not reported. [a] abnormalities not specified. BSID-II or III, Bayley's Scales of Infant Development; MDI, mental developmental index; PDI, psychomotor developmental index.

Table 4 Studies using near-infrared spectroscopy and reporting the changes in rSO_2

Reference	Type of surgery	NIRS device	Type of sensor	Baseline values (%)	Comparison between different time points		Significant change rSO2	Significant change MABP
Dotta *et al.*[15]	Laparotomy	NIRO-300	50 mm interoptode separation	NR	Begin surgery	End surgery	↓	NS
Zaramella *et al.*[16]	Ligation PDA	NIRO-300	NR	61.6 (3.8)	Before ligation	After ligation	↓	NS
Hüning *et al.*[17]	Ligation PDA	NIRO-300	50 mm interoptode separation	53 ± 15	Changes during closure		NS	NS
Vanderhaegen *et al.*[18]	Ligation PDA	INVOS	40 mm interoptode separation (large)	NR	Before ligation	After ligation	↑	NS
Chock *et al.*[19]	Ligation PDA	INVOS	Neonatal sensor	63 ± 13	Before ligation	After ligation	↑	NR
Conforti *et al.*[21]	Laparotomy	INVOS	Paediatric sensor	NR	Before surgery	During versus after surgery	NS	NR
Michelet *et al.*[22]	NR	INVOS	NR	78 ± 10	NR	NR	NR	NR
Tytgat *et al.*[23]	Laparoscopy	INVOS	Small adult sensor	68 ± 14	Before insufflation	During and after cessation	NS	↑
Conforti *et al.*[24]	Laparotomy	INVOS	Paediatric sensor	HFO 81 [70 to 98] CMV 82 [76 to 91]	Before surgery	During surgery	↓	NR
Tytgat *et al.*[27]	Thoracoscopy	INVOS	Small adult sensor	77 ± 10	After induction	After CO_2 insufflation	↓	NS
Beck *et al.*[28]	NR	INVOS	Neonatal sensor	79.11 ± 9.92	Changes during surgery		NS	NR
					0 h postoperative	24 h postoperative	NS	NR
Costerus *et al.*[29]	Thoracoscopy	INVOS	Neonatal sensor	CDH 82[a] OA 91[a]	Before surgery	During surgery	NS NS	↓ 30 min after insufflation & ↑ after 90 & 120 min insufflation NS
Nissen *et al.*[31]	NR	INVOS	Neonatal sensor	72.84 ± 4.60	Before surgery	After surgery	↑	NR
Kuik *et al.*[32]	Laparotomy	INVOS	Neonatal sensor	NR	Before surgery	During surgery	NS	NS
					During surgery	After surgery	↑	NS

CDH, congenital diaphragmatic hernia; CMV, conventional mechanical ventilation; HFO, high-frequency oscillation; NR, not reported; NS, not significant; OA, oesophageal atresia; PDA, patent ductus arteriosus. Values are given as mean ± SD, mean (SEM), mean. [a]median [IQR].

cerebral oxygenation, two studies found no significant changes in BP,[18,32] and the other two studies did not report BP values (Table 4).[19,31] Four studies aimed to find associations between cerebral oxygen desaturation and other peri-operative monitoring techniques.[22,25,26,28] One of these investigated the applicability of NIRS in neonates undergoing noncardiac surgery by comparing the event rate of hypoxia (defined as $SpO_2 < 90\%$) measured with the conventional peripheral pulse oximeter with the event rate of hypoxia measured with NIRS (defined as >20% decline from cerebral oxygen saturation (rSO_2) baseline or an absolute decline in rSO_2 less than 40%, lasting for a minimum of 3 min) and found that NIRS events occurred two to three times more often than hypoxia measured with the conventional peripheral pulse oximeter. During desaturation, the decline in SpO_2 was similar to that of rSO_2 in pattern and duration. Both SpO_2 and BP correlated positively with rSO_2.[25] Other studies found that cerebral oxygen desaturation (defined as delta $rSO_2 > 20\%$ from baseline) occurred in almost 20% of the patients and that a decrease in rSO_2 values was associated with a decrease in mean arterial BP.[26] Yet, another of these studies measured peri-operative rSO_2 in 60 infants less than 3 months of age with 960 data points and found cerebral desaturation (defined as delta $rSO_2 > 20\%$ from baseline) in 6.1% data points. The data suggest that a decrease in SBP of more than 20.5%, or a decrease in mean BP of more than 15.5%, is associated with a decrease in cerebral oxygenation of more than 10%. Furthermore, at the measurement points where delta rSO_2 was more than 20% from baseline, the mean ± SD absolute BP was lower, 62 ± 15 mmHg, than that at the normally saturated measurement points (71 ± 15 mmHg).[22] By contrast, the fourth study, with 19 neonates during a variety of surgical procedures, reported intra-operative desaturation (defined as delta $rSO_2 > 20\%$ from baseline) in six (6.7%) of the measurement points and did not find a correlation between mean arterial BP and cerebral rSO_2.[28] An overview of physiological variables correlated with NIRS are shown in Appendix 3, http://links.lww.com/EJA/A308.

Near-infrared spectroscopy: cerebral autoregulation

Two studies used NIRS to evaluate peri-operative cerebrovascular autoregulation.[20,32] Chock *et al.* compared the effect of different treatments for hsPDA on cerebral autoregulation. Autoregulation impairment was defined as an increase in the pressure passivity index. This is calculated by the concordance between the mean arterial BP (MABP) and rSO_2. Surgical ligation of the hsPDA was associated with an increased risk for impaired cerebral autoregulation in the first 6 h after ligation compared with neonates who had conservative treatment.[20] The other study concerned neonates undergoing abdominal surgery; impaired cerebral autoregulation was seen more frequently in the intra-operative period than in the pre and postoperative periods. Elevated P_aCO_2 as well as

elevated end-tidal sevoflurane levels negatively affected cerebral autoregulation.[32]

Near-infrared spectroscopy: cerebral blood flow/volume

One study investigated the effect of PDA ligation on the cerebral tissue oxygenation index with NIRS and the cerebral blood volume, and CBF velocity with CDU, in relation to changes in arterial pH.[16] Overall, the cerebral tissue oxygenation index declined after PDA ligation, while the cerebral blood volume remained the same. Furthermore, both a lower pH and an increase in arterial CO_2 were found to be associated with an increase in CBF. In another study, cerebral blood volume changes directly after surgical closure of PDA were measured with NIRS.[17] Total haemoglobin corresponded to cerebral blood volume and was calculated by the sum of oxygentated haemoglobin and deoxygenated haemoglobin. Cerebral oxygenation decreased in the first minutes after ligation (Table 4), although not significantly. Cerebral blood volume (mean ± SD) increased significantly in the first 2 min after ligation by 0.14 ± 0.12 ml per 100 g tissue and returned to baseline within 2 to 5 min.

Amplitude-integrated electro-encephalography: cerebral activity

Interpretation of the aEEG is based on pattern recognition of background activity.[38] One study in 111 neonates showed that overall the background pattern regressed two classes during surgery and anaesthesia compared with the pre-operative pattern.[35] Postoperatively, the trace returned to continuous normal voltage within 24 h in 86% of the preterm and 98% of the term neonates. A higher sevoflurane dose was significantly associated with more suppressed background patterns. Furthermore, epileptic activity during surgery was seen in four of the 111 neonates, in one directly after starting sevoflurane induction. Postoperatively, epileptic activity was observed in eight neonates.[35] Another study aimed to determine the incidence of seizures in 6525 very low birthweight infants and to identify perinatal and postnatal factors associated with the occurrence of these seizures. Seizures had occurred in 23/95 (24%) of the infants operated on for PDA versus 10% of the conservatively treated infants and in 21/131 (16%) of the infants operated on for necrotising enterocolitis versus 12% of the conservatively treated infants.[37] A third study, on age-related changes in EEG traces, showed that in neonates undergoing sevoflurane anaesthesia for elective surgery, slow-delta oscillations were present at all ages, but that theta and alpha oscillations emerged by approximately 4 months; seizures were not investigated.[39]

Another study investigated if aEEG could be useful to detect pain during hsPDA ligation in preterm neonates and investigated the relation between vital signs and aEEG during anaesthesia. There was no correlation between vital signs and aEEG voltage; aEEG was suppressed during surgery and remained suppressed during the 2-h postoperative monitoring; seizures were not investigated.[33]

The fifth study investigated aEEG during ligation of hsPDA under fentanyl and rocuronium. During the procedure, the aEEG lower border of the background pattern trace decreased and continuity decreased. Five of the 17 neonates already had a discontinuous background pattern pre-operatively and none demonstrated complete recovery of the lower margin 24 h postoperatively.[34]

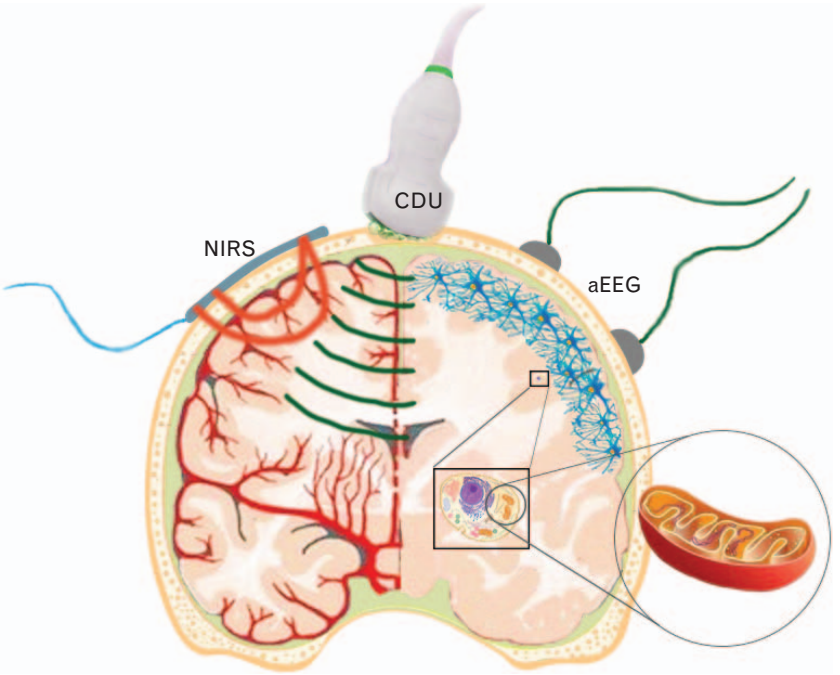
Neuro-imaging and neurodevelopmental outcome

Neuro-imaging and neurodevelopmental outcome were reported in six studies (Table 3). In one study with five children with long-gap oesophageal atresia, two of the children had postoperative intracranial abnormalities on MRI. Signs of changes resulting from altered cerebral perfusion (based on hypotension or hypocarbia) or cerebral oxygenation were absent in these two infants. All five children showed normal cognitive development and motor development at the age of 2 years (assessed with the Bayley Scales of Infant and Toddler Development, Third Edition and the Griffith Mental Development Scales).[30]

Two other studies examined peri-operative neuromonitoring in relation to neurodevelopment after neonatal surgery. One examined the relation between cerebral desaturation (defined as at least one delta $rSO_2 > 20\%$ from baseline) during anaesthesia and neurological function during clinical follow-up at 14 days and up to 6 months. Neurological function had deteriorated in three out of eight infants who had desaturated and in none of the 35 infants who had not desaturated. This deterioration might also be related to clinical factors other than peri-operative cerebral desaturation, since all three infants with deteriorated neurological function had received cardiopulmonary resuscitation after birth. Moreover, two of them were born prematurely and had not undergone pre-operative imaging. The absolute minimal rSO_2c value in the desaturation group was 66% [41.5 to 71%], versus 76.5% [60.5 to 90%] in the group without desaturation.[26] The other study reported NIRS values and neurodevelopmental outcome at the age of 2 years in seven infants after surgery for congenital diaphragmatic hernia and oesophageal atresia. Correlations between intra-operative rSO_2 and neurodevelopmental outcome were not investigated.[29]

Chock *et al.* performed MRI and/or cranial ultrasound in 40 infants after the diagnosis of PDA was made (baseline) and at discharge or hospital transfer, together with peri-operative cerebral autoregulation measurements calculated by the pressure passivity index with NIRS as mentioned above. Ten infants showed worsening neuro-imaging findings compared with baseline, of whom

Fig. 2



Broad outlines of the different neuromonitoring modalities and their shortcomings in providing information on a cellular level.

three were treated with indomethacin alone, four were surgically ligated after failed indomethacin closure, and three received primary surgical ligation. An association between impaired cerebral autoregulation and neuro-imaging abnormalities was not found. The neurodevelopmental outcome of these infants was not reported.[20]

Another study investigated peri-operative aEEG in relation to MRI in 111 various noncardiac surgical newborns. Pre-operatively, 10% of the neonates had brain injury on ultrasound scan; 58% of all neonates had parenchymal lesions and 37% had nonparenchymal injury on the postoperative MRI. An association between MRI-abnormalities and type of aEEG background patterns was not found.[35]

Discussion

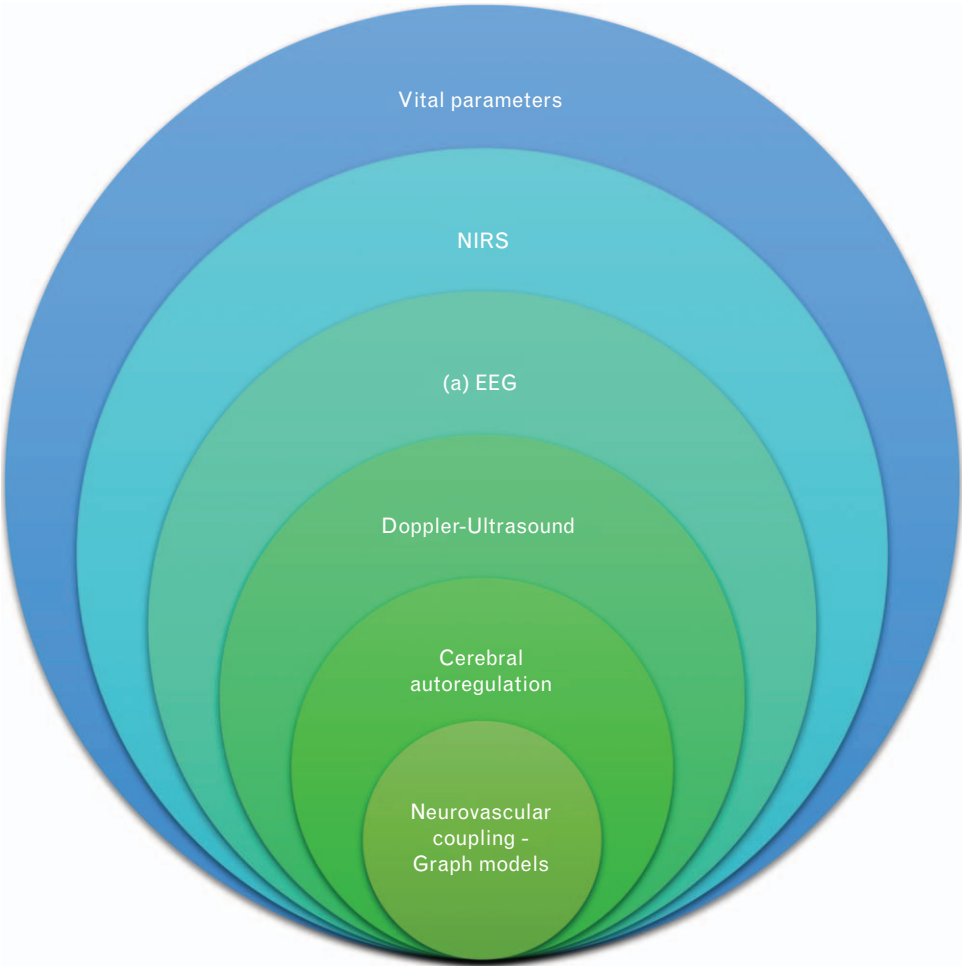
The current review included 24 articles reporting NIRS, aEEG and CDU employed for peri-operative neuromonitoring in infants less than 90 days of age undergoing surgery without cardiac bypass. Nineteen studies, with in total 374 infants, reported NIRS. These studies show a large heterogeneity in patient age, disease, surgical approaches, practical clinical use and measurement timing. Furthermore, baseline values of cerebral oxygenation and definitions of hypoxia greatly varied. Clear associations between changes in cerebral oxygenation and vital signs were not reported. Treatment algorithms for cerebral oxygenation were not found.

Five studies made use of the aEEG for studying peri-operative brain activity, 388 infants in total. Overall, brain activity decreased and epileptic activity occurred more frequently in the peri-operative phase. These studies also show a large heterogeneity in patient characteristics such as gestational age, birth weight and pathology.

Six studies investigated an association between intra-operative cerebral saturation or activity and neuro-imaging abnormalities and/or outcome. One reported impaired neurodevelopmental outcome after cerebral desaturation episodes.[26] A clear correlation with cerebral desaturation could not be established, however, as these infants had also received cardiopulmonary resuscitation. Another study showed that seizures are associated with a higher mortality rate in very-low-birth-weight neonates.[37] One study combined neuro-imaging findings with neurodevelopmental outcome and found no impaired neurodevelopment in infants with intracranial pathology at the age of 2 years.[30]

On the contrary, it was not possible to perform a statistical analysis on the correlation between neuromonitoring and outcome due to limited data. Overall, there is minimal clinical evidence for using a single neuromonitoring device during noncardiac surgery in neonates. Yet, a previous systematic review suggests that these neonates have an increased risk of delayed cognitive and motor development at the age of two.[5] It is important to stress that (possible) long-term morbidity of neonatal surgery

Fig. 3



Our proposal for 'integrative' neuromonitoring.

might not be seen before school-age. Motor function, concentration and attention deficits are reported from the age of 8 years and later as extensive neuropsychological evaluation is only feasible from that age.[40]

Neonatal physiology may be too complex to detect insufficient cerebral perfusion with one device only, but may be better understood when combining different modalities. Therefore, we searched for broader monitoring techniques and new ways of integrated data analysis. We suggest that 'integrative' neuromonitoring might be more beneficial, as visualised in Fig. 3. In this context, the term 'integrative' refers to multimodal neuromonitoring which combines multiple modalities for a better understanding of the pathophysiology. This starts with monitoring standard vital signs which provide information about particular organ systems and reflect end-organ perfusion, but lack specificity for brain perfusion.[41] To overcome this, NIRS is increasingly being used in neonatal ICUs. NIRS is based on the relative transparency of biological tissue to light. The technique is limited by interpatient and intrapatient variance because it depends on physiological variability, the NIRS device and the type of probe that is used for monitoring.[42–44] Previous research on liquid phantoms showed device-specific and sensor-specific hypoxic thresholds.[42] In that study, the NIRO large sensor was associated with a hypoxic threshold of 62%; the INVOS small adult sensor with a hypoxic threshold of 55%; and the INVOS neonatal sensor with a hypoxic threshold of 63%.[45] In this light, NIRS provides information about changes from an relative arbitrary zero-point, which means that it is only possible to monitor a trend at best.[45] In addition, cerebral oxygenation varies from 40 to 56% directly after birth and stabilises at 55 to 85% between 3 and 6 postnatal weeks.[43] Changes in cerebral perfusion due to fluctuations in MABP or end-tidal CO_2 and changes in saturation affect cerebral oxygenation, so it should be stressed that NIRS values can only be interpreted together with standard vital signs monitoring.[45,46] Anaesthesiologists should use

NIRS as a warning that a check is needed on everything else.

Adding NIRS, which mainly reflects changes in venous oxygenation,[47] enables the detection of changes in oxygen delivery to the brain and in oxygen consumption in the brain. These changes are generally quantified using fractional tissue oxygen extraction.[48]

Neuromonitoring with NIRS during sedation is complicated because of changes in oxygen consumption due to changes in cerebral metabolism.[49] Measurements of cerebral oxygenation are therefore often complemented with measurements of cerebral activity by means of aEEG.[49] The EEG is an electrophysiological technique for the recording of electrical activity arising from the brain.[50] EEG can be measured in its conventional format or in an amplitude integrated form (aEEG). At the neonatal ICU, aEEG is most commonly used in hypoxic ischaemic encephalopathy and therapeutic hypothermia. Hence, it may also be helpful in infants with encephalopathy of varying causes.[51,52] The infants presented in the work by McCann*et al.*[53] all developed new-onset postoperative epileptic seizures within 25 h of the administration of anaesthetics, and following relative small surgical procedures with an uneventful peri-operative course. In this light, peri-operative monitoring with the aEEG might be useful for early detection of (severe) postoperative encephalopathy and epileptic seizures. To identify the potential value of the aEEG in the operation threatre, a randomised controlled trial could be performed in which the anaesthesiologists is or is not blinded for the aEEG.

Cranial ultrasound with Doppler is still the only way to image and quantify real-time cerebral perfusion and flow velocity.[54] Mathematical approaches to measure the regulation of CBF are currently being developed.[55] Cerebral autoregulation is the most extensively studied regulation mechanism in neonates. At its core, cerebral autoregulation maintains a constant CBF in a wide range of cerebral perfusion pressures (CPP). Cerebral oxygenation measured by NIRS generally serves as a measure for CBF and MABP as a measure for CPP.[56] A marker for cerebral autoregulation can be obtained by combining CBF and CPP measurements. Note, however, that NIRS measurements are valid surrogates for CBF only in the absence of large variations in arterial saturation and under the assumption of a constant cerebral metabolism.[57] In addition to the partial pressures of arterial blood gases (CO_2 and O_2), the primary controllers of CBF are cerebral metabolism and the autonomic nervous system, which implies that CBF is mainly determined by neural activity.[58] An increase in neural activity results in a higher oxygen consumption, which, in turn, triggers an increase in CBF, to deliver more oxygen to the brain.[59] This regulation mechanism is commonly reffered to as *neurovascular coupling*.[58] General physiological markers of neurovascular coupling can be obtained by studying the interaction between NIRS and EEG measurements. Multimodal signal processing provides the tools to quantify interaction, coupling between different signals. In practice, signal coupling can be defined using numerous techniques. Popular simple examples include correlation, (wavelet) coherence and transfer function analysis.[60] A straightforward framework to integrate all of the different regulation mechanisms in one model can be constructed using signal interaction graphs.[61] From a clinical point of view, signal interaction graphs allow the capture of the dynamic coordinated interactions of organ systems. These interactions are essential to maintain homeastasis; distinct physiological states can be captured using these models. Examples include the differentiation between sleep and awake states, between consciousness and unconsciousness and the effect of particular medication.[62] More importantly, altered or disrupted organ communications could be detected that, when not managed, might lead to dysfunction of individual systems or to the collapse of the entire organism, such as fever, hypertension, coma or multiple organ failure.[63]

The presently used techniques for peri-operative neuromonitoring – NIRS, aEEG and CDU (Fig. 2) – lack specificity, standardised reporting and are not related to clinical (long-term) outcome or prognostics. We narrowed our literature search to neonates up to 90 days old. For this group, the results of this review indicate that neuromonitoring with any of these techniques will neither help to improve understanding of the altered neonatal pathophysiology, nor enable early detection of deviation from the norm. A meta-analysis could not be performed due to the absence of standardised reported results, preventing the drawing up of a clear monitoring guideline.

aEEG monitoring has proved to be useful in detecting epilepsy or status epilepticus, but there is no demonstrated additional value of NIRS or cerebral ultrasound with Doppler over standard monitoing of BP, end-tidal CO_2 and SpO_2. The value of these monitoring modalities in the neonate requires further prospective trials with relevant clinical outcomes.

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