Dexmedetomidine affects cerebral activity in preterm infants

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ABSTRACT

The use of dexmedetomidine (DEX) has been extended in preterm newborns, but the effects on cerebral activity and their relationship with haemodynamic changes has not been studied.

We retrospectively studied the effects of DEX administered to 10 preterm newborns, assessing amplitude-integrated EEG (aEEG) parameters, brain regional SO_2 ($brSO_2$), heart rate, non-invasive mean blood pressure (MBP), transcutaneous oxygen saturation (SpO_2), venous pCO2 and haemoglobin (Hb) values, in two 6-hour periods: one starting 6 hours before the beginning of DEX perfusion and the other 6 hours afterwards.

DEX infusion led to $brSO_2$ decrease not associated to heart rate, MBP, SpO_2, Hb or pCO2 variation, which suggests that $brSO_2$ decrease could be related to local vasoconstriction. DEX infusion led to prolongation of interburst interval and reduction of cycling. Such effects, not been described so far, should be considered in the assessment of aEEG traces after DEX administration to avoid misinterpretations regarding patient's prognosis. More studies are needed to assess the safety of DEX use in the newborn.

What is already known on this topic?

⇒ Dexmedetomidine is an effective sedative agent which is increasingly used in preterm newborns with no severe side effects reported so far.
⇒ However, there are no studies on the effects of dexmedetomidine on cerebral activity in preterm newborns.

What this study adds?

⇒ Dexmedetomidine infusion to preterm newborns decreases amplitude-integrated electroencephalogram activity and brain oxygenation.
⇒ Such effects should be considered to avoid misinterpretations regarding the patient's prognosis.

INTRODUCTION

Dexmedetomidine (DEX) is an effective alternative to benzodiazepines increasingly used to provide sedation in newborn babies because of the lack of short-term severe side effects other than moderate hypotensive effects.[1] Lately, its use has been extended to preterm newborns, with no reported severe side effects to date.[1] However, there are no studies on the effects of DEX on cerebral activity in preterm newborns, in contrast with other sedoanalgesic drugs[2] such as morphine and propofol. Awareness on the effects of sedative drugs on preterm newborn brain activity is important to avoid misinterpretations about the prognosis of those patients. The aim of this study was to determine how DEX affects cerebral activity in preterm infants and whether those effects would be related to DEX-induced haemodynamic changes.

METHODS

Informed consent exemption was approved due to the retrospective nature of the study.

All very low birthweight infants (VLBWI) born between January 2019 and May 2021 receiving DEX during their stay in our neonatal intensive care unit, were retrospectively studied collecting data from the medical charts and amplitude-integrated EEG (aEEG) (Olympic Brain Monitor, Natus, California, USA) recordings using neonatal sensors (Ambu Neuroline 715, Ambu, Denmark). DEX was selected as the first-line sedative except in four babies who needed deeper sedoanalgesia because of their clinical condition; in these latter babies fentanyl was selected as the first-line sedative and DEX was added when satisfactory sedation was not achieved with fentanyl alone. Two 6-hour periods were studied: one just before and the other starting 6 hours after DEX infusion (0.1–0.4 µg/kg/min). aEEG trace was assessed by a researcher blind to the corresponding period. The following parameters were recorded hourly: aEEG (lower limit amplitude in µV, interburst interval (IBI) and cycling (quantified after Burjdalov Score)); brain regional SO_2 ($brSO_2$) using near-infrared spectroscopy (INVOS 5100C, Medtronics, Colorado, USA) (percentage of baseline value) with neonatal sensors; non-invasive mean blood pressure (MBP) and heart rate, transcutaneous oxygen saturation (SpO_2) (Masimo Radical-7), venous pCO_2 and haemoglobin (Hb). Fractional tissue oxygen extraction (FTOE) was calculated using SpO_2 and $brSO_2$ values: $(SpO_2 - brSO_2)/SpO_2$.

Exclusion criteria were severe intraventricular haemorrhage or periventricular leucomalacia or non-interpretable aEEG trace because of artefacts, but no newborn met such criteria.

Statistical analysis

Median (95% CI) of each parameter in each period of study was calculated. Since data were

Table 1 General data

Patient	GA	BW	Sex	Days of life when DEX	Clinical situation	Concomitant medication
1	27 (0)	930	Female	3	RDS: MV PHT CU Normal	Dobutamine Adrenalin Antibiotics Surfactant
2	23 (4)	600	Male	2	RDS: HFOV CU Normal	Dobutamine Antibiotics Surfactant
3	25 (6)	1061	Male	2	PDA with treatment, RDS: HFOV	Fentanyl Antibiotics Ibuprofen
4	25 (5)	750	Female	5	RDS: CPAP CU Normal	Dopamine Antibiotics
5	30 (3)	1000	Male	4	HFOV, PHT Pneumothorax—resolved CU Normal	Fentanyl Antibiotics Nitric oxide
6	28 (5)	990	Male	8	*S. epidermidis* sepsis: MV CU Normal	Dopamine Dobutamine Hydrocortisone Antibiotics Ranitidine
7	27 (0)	645	Male	8	HFOV PDA CU: IVH grade II left/grade I right	Fentanyl Ibuprofen
8	27 (0)	650	Male	30	BPD: HFOV Abdominal sepsis CU Normal	Antibiotics Acetaminofen Metamizole
9	26 (3)	715	Female	10	HFOV CU Normal	Antibiotics Acetaminofen Metamizole
10	27 (0)	1100	Male	11	RDS: HFOV PHT CU Normal	Fentanyl Dopamine Dobutamine Antibiotics Hydrocortisone

, ; BDP, Bronchopulmonary dysplasia ; BW, birth weight (grams); CU, cranial ultrasound; DEX, dexmedetomidine; GA, gestational age: weeks (days); HFOV, high frequency oscillatory ventilation; IVH, intraventricular haemorrhage); MV, mechanical ventilation; PDA, patent ductus arteriosus; PHT, pulmonary hypertension; RDS, respiratory distress syndrome.

not normally distributed (Shapiro-Wilkins test), changes before and after DEX infusion were studied using the Wilcoxon test. Correlations between parameters (Spearman's linear regression) and contingency 2×2 tables (Fisher's exact test) were also studied. A value of $p<0.05$ was considered statistically significant. Data were analysed using SPSS software (V.25.0; IBM, New York, USA).

RESULTS

Ten patients fulfilled the inclusion criteria over the study period. General data are summarised in table 1.

DEX infusion led to $brSO_2$ decrease (75 (68–80.5) vs 67.7 (58.5–77)%, W=−52, p=0.005) and FTOE increase (0.20 (0.11–0.27) vs 0.28 (0.19–0.37)%, W=64, p=0.002) but did not modify heart rate (160.8 (152.5–171.5) vs 153.6 (136.5–169)%, W=−24, p=0.24), MBP (39.6 (35–45) vs 39.5 (28–47)%, W=4, p=0.84), SpO_2 (93.5 (91.9–94.3) vs 93.0 (91.9–94.6)%, W=5, p=0.82), Hb (10.6 (9.7–13.3) vs 12.1 (10.2–13.4),W=5, p=0.81) or pCO_2 (42 (40–63) vs 51 (42–56), W=5, p=0.73).

DEX infusion did not modify the lower aEEG amplitude limit (W=−16, p=0.30; variance = 1.7 vs 3.3, coefficient of variation 0.34 vs 0.59 for basal and DEX, respectively) but led to prolongation of IBI (W=55, p=0.002; variance = 17.5 vs 29.73, coefficient of variation 0.30 vs 0.42 for basal and DEX, respectively) and reduction of cycling (W=−45, p=0.03; variance = 2.4 vs 1.6, coefficient of variation 0.90 vs 3.1 for basal and DEX, respectively) (figure 1). Cycling was present in seven babies before and in only one after DEX (p=0.01). $brSO_2$ did not correlate with IBI (R^2=0.01, F=0.08, p=0.78) or cycling (R^2=0.01, F=0.14, p=0.72).

DISCUSSION

In this study DEX infusion modified brain activity in VLBWI as assessed by aEEG, which led to the prolongation of IBI and the disappearance of cycling. These two parameters are of major prognostic value regarding neurological outcome in premature neonates.[3] Therefore, awareness about such an effect of DEX is important to avoid misinterpretations about the patient's clinical condition. Changes in the aEEG pattern and background have been reported in preterm neonates for propofol as well as benzodiazepines and opioids[2] but not for DEX to date.

DEX infusion neither induced bradycardia or hypotension nor SpO_2, pCO2 or Hb decrease in our patients. Therefore, DEX-induced decrease of $brSO_2$ and rise of FTOE could not be attributed to systemic hypotension, hypoxia, anaemia or hypocapnia as it could not be attributed to increased brain activity. It can be speculated, therefore, that DEX-induced $brSO_2$ decrease might reflect the vasoconstrictor effect reported for DEX in cerebral vessels.[4] In fact, sedative infusion usually leads to increased $brSO_2$ because of reduced brain activity.[5] Reduction of $brSO_2$

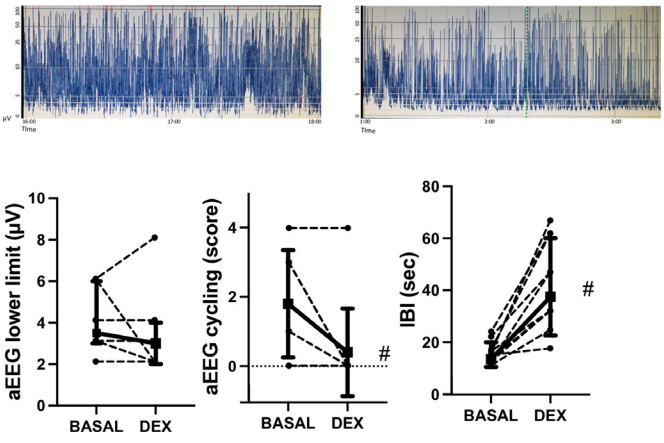

Figure 1 *Top:* Example of amplitude-integrated EEG (aEEG) record showing 3-hour long traces obtained just before and 4 hours after starting dexmetomidine (DEX) infusion in a preterm baby. The alternance in basal amplitude disappeared and the interburst interval (IBI) increased. *Bottom* Quantification of aEEG changes after dexmedetomidine infusion. Dashed lines represent the individual values of each infant; bold lines represent the median (IC 95%) at each time point. (#)=p<0.05 by Wilcoxon paired test.

is a noteworthy effect although it had no relationship with the prolongation of IBI or the disappearance of cycling.

The fact that such alterations of aEEG and $brSO_2$ were also observed in those newborns already receiving fentanyl supports the consistency of DEX effects on cerebral activity, although some additive effects of DEX and other sedatives cannot be ruled out in our study. However, since this is a small size retrospective study, larger prospective studies are warranted to confirm DEX effects on brain activity and cerebral blood flow and to analyse gestational age, sex and DEX dose influences on those effects.

In conclusion, DEX infusion to ELBWI led to decreased brain activity with prolonged IBI and cycling disappearance, and decreased $brSO_2$. Such effects should be considered to avoid misinterpretations regarding the patient's prognosis. More studies are needed to assess the safety of DEX use in the newborn.

Contributors CL conceptualised and designed the study, collected data, carried out the initial analyses and drafted the initial manuscript. SV and LA designed the data collection instruments, collected data and revised the manuscript. MO conceptualised and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

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