

Cardiorespiratory parameters in newborns during sedation with chloral hydrate

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ABSTRACT

We commonly use chloral hydrate sedation in newborns, though its cardiorespiratory side effects have not yet been fully investigated. Our study aimed to analyze the impact of chloral hydrate on cardiorespiratory parameters in term newborns. We performed a prospective, pre-post single-arm interventional study in 42 term, respiratorily and hemodynamically stable newborns. Oxygen saturation (SpO₂), end-tidal CO₂ (ETCO₂), the apnea-hypopnea index and the respiratory and heart rates were recorded by polygraphy, starting 0.5-1 hour before oral administration of chloral hydrate at a dose of 40 mg/kg and ceasing 4 hours post-administration. After administration of chloral hydrate, the mean basal SpO₂ dropped by 2.0% (from 97.1% to 95.1%; p<0.001) and the mean basal ETCO₂ increased by 3.9 mmHg (25.6 to 29.5 mmHg; p<0.001). We found a significant decrease in the minimal SpO₂ values (p<0.001) and an increase in the percentage of time spent with SpO₂ <95% and <90% (p<0.001). The mean increase in the estimated apnea-hypopnea index was 3.5 events per hour (p<0.001). The mean respiratory and heart rates were significantly lower 150 min after the administration of chloral hydrate when compared with pre-sedation values (51/min and 127/min versus 61/min and 138/min respectively; p<0.001). A considerable number of patients exhibited changes in cardiorespiratory parameters that differed considerably from the normal ranges. In conclusion, SpO₂, ETCO₂, the estimated apnea-hypopnea index and the respiratory and heart rates changed after the administration of chloral hydrate. They remained within normal limits in most newborns, but the inter-individual variability was high in the studied population.

Key words: chloral hydrate, newborn, oximetry, respiration, sedative.

Chloral hydrate is frequently used for light sedation of newborns to facilitate painless diagnostic procedures that require the patients to be motionless, such as various radiological and neurophysiological tests.¹⁻⁵ The recommended dose of chloral hydrate for newborns and infants is 25-50 mg/kg.⁶ The sedative effects of chloral hydrate become clinically apparent approximately 20 minutes after oral or rectal administration⁷⁻⁹ and last between 90^{7,8} and 165¹⁰ minutes, although they may be prolonged, especially in preterm infants.²

In some previous pediatric studies, it has been suggested that chloral hydrate sedation in

infants and children is effective and safe, with a relatively low risk of severe respiratory and hemodynamic adverse effects.^{1,3,4,8,9} On the other hand, some have reported severe complications of chloral hydrate sedation in children and even death.¹¹ Chloral hydrate may, like many other sedatives, affect respiratory and cardiovascular function and pose a risk of respiratory depression and hypoxia.¹²⁻¹⁴ This is especially important in newborns, who have unstable breathing patterns due to the immature control center, and in whom the elimination of chloral hydrate may be prolonged.^{6,15} It has been implied that the risk of hemoglobin desaturation during chloral hydrate sedation is relatively high in newborns¹⁶ and studies have shown that younger age is a risk factor for sedation-related adverse effects.^{3,17} Still, little data exist on the cardiorespiratory side effects of chloral hydrate in newborns. Previous studies have mainly

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Received 17th December 2017; revised 12th May 2018;
accepted 20th July 2018

included older infants and children^{3,5,8,9}, relied on intermittent measuring of vital signs^{3,4,8,9} or were mostly retrospective, focusing only on clinically apparent adverse events.^{1,4,16}

To further clarify the impact of chloral hydrate on cardiorespiratory function in term newborns, we analyzed continuously recorded cardiorespiratory parameters, including arterial oxygen saturation (SpO₂), end-tidal CO₂ (ETCO₂), the apnea-hypopnea index and the respiratory and heart rates, before and after the administration of oral chloral hydrate at a dose of 40 mg/kg.

Material and Methods

Patients

A prospective, pre-post intervention study on a single group of patients, where each newborn served as his or her own control, was conducted between May 2015 and June 2016 at the Department of Neonatology, Division of Pediatrics, University Medical Center Ljubljana, Slovenia. Ethical approval was obtained from the National Medical Ethics Committee on May 26, 2015 (number 40/05/15).

The inclusion criteria were: postmenstrual age at least 37 weeks, chronological age less than 4 weeks and the need for sedation with chloral hydrate for auditory brainstem response (ABR) audiometry. We excluded newborns receiving drugs that have known interactions with chloral hydrate (furosemide, phenytoin, flumazenil and amiodarone) and newborns with congenital cyanotic heart disease, liver failure, renal insufficiency and signs of infection or respiratory compromise.

Parents of all newborns signed an informed consent form prior to their enrollment in the study.

Methods

Polygraphic recordings of cardiorespiratory parameters were started half an hour to one

hour prior to the administration of a single dose of oral chloral hydrate of 40 mg/kg. A second dose was never given. Half an hour later, the ABR test was performed, during which the recording remained uninterrupted and was continued until 4 hours after the administration of chloral hydrate. During the monitoring, newborns were under constant supervision.

Cardiorespiratory parameters were recorded by an Embletta MPR PG, Natus Medical Incorporated polygraphy device. The respiratory effort was measured by respiratory inductance plethysmography (XactTrace Single Use Cut-to-Fit Embla RIP Belts), nasal airflow by nasal thermistor (Embla Breath Sensor Airflow Thermistor Preemie), SpO₂ and the heart rate by pulse oximetry (Nonin Xpod External OEM Pulse Oximeter) and ventilation by ETCO₂ (Microstream CapnoLine H Infant/ Neonate nasal cannulas and Comdek Portable Color Oxi-Capnography MD-850, calibrated to assure accuracy). The thermistor and nasal cannulas were positioned in a way that they did not obstruct the nares of the newborns, conforming to the manufacturer's instructions. The newborns were breathing room air and there was no supplemental oxygen given. The noninvasive side-stream capnometry through nasal cannulas has previously been proven to be an accurate method for estimating ETCO₂ in nonintubated newborns without pulmonary disease.¹⁸⁻²⁰

Data processing

Polygraphic recordings were displayed and analyzed using Embla RemLogic-E Sleep Diagnostic Software version 3.4.1, calibrated for newborns, infants and children.

Cardiorespiratory parameters were determined for every newborn and for each part of the study (before and after the administration of chloral hydrate). The primary outcomes were: 1) basal SpO₂ as a marker of oxygenation; and 2) basal ETCO₂ as a marker of ventilation. The secondary outcomes included: 1) percentage of time with SpO₂ <95%; 2) percentage of time

with $SpO_2 < 90\%$; 3) minimal SpO_2 ; 4) estimated apnea-hypopnea index; 5) respiratory rate; and 6) heart rate. Normal ranges for these cardiorespiratory parameters were defined according to the published centiles for healthy term newborns.²¹⁻²⁵

The Embla RemLogic-E Software allowed automatic calculation of the basal and minimal SpO_2 and the percentage of time spent in a specified SpO_2 zone or below a chosen threshold in selected parts of the recordings.

The basal $ETCO_2$ was estimated manually from the capnometry curve by comparing $ETCO_2$ values before and after the administration of chloral hydrate and determining the most accurate basal value for these two periods.

Apneas and hypopneas were scored manually, according to the American Academy of Sleep Medicine criteria.²⁶ We also categorized apneas as central, obstructive or mixed. The apnea-hypopnea index was defined as the number of apneas and hypopneas per hour of estimated total sleep time. Total sleep time was estimated by manually excluding all parts of the recordings with motion artifacts on account of arousals, movement or handling of newborns.

The respiratory and heart rates were counted in the period before the administration of chloral hydrate and then at 30-minute intervals during sedation. The average respiratory rate over the 30-minute period was counted by analyzing the breathing waveform, derived from the signal from the respiratory inductance plethysmography: we counted the number of breaths in 60 seconds, when the breathing was calm and the respiratory pattern stable. The mean heart rate was calculated automatically by the Embla RemLogic-E Software.

Statistical analysis

All calculations were performed using Microsoft Excel 2013 and IBM SPSS Statistics version 21. Data are presented either as the mean and standard deviation or the median and interquartile range, depending on the normality

of the distribution of observed variables.

For all of the observed variables, the difference between the value before and after the administration of chloral hydrate, as well as the relative change from the baseline pre-sedation value, were calculated for each individual patient. The differences were statistically analyzed using the two-tailed Student's t-test for paired data and the two-tailed Wilcoxon signed-rank test. The level of significance (alpha) of 0.05 was used. Because of multiple comparisons, this significance level was adjusted using the Bonferroni correction. Hence, each individual hypothesis was tested at $\alpha = 0.006$. Confidence intervals were adjusted accordingly.

Results

Out of 49 newborns enrolled in the study, seven newborns were excluded due to the poor quality of the recordings. Measurements of $ETCO_2$ were available for 27 newborns. The characteristics of the study population are presented in Table I. Adequate depth of sedation to perform the ABR testing was achieved in all newborns. After we stopped the recording of cardiorespiratory parameters, newborns were awake and back to their baseline alertness.

In most newborns, basal SpO_2 was lower and basal $ETCO_2$ was higher after the administration of chloral hydrate compared with pre-sedation values (Table II). The mean basal SpO_2 level dropped by 2.0% (from 97.1% to 95.1%) and the mean basal $ETCO_2$ increased by 3.9 mmHg (from 25.6 to 29.5 mmHg). The maximum decrease in basal oxygen saturation was 5%. The maximal $ETCO_2$ recorded during sedation, was 38 mmHg. We observed a >20 % increase in $ETCO_2$ in 9 of 27 newborns (33%).

The decrease in oxygenation was additionally manifested by a higher proportion of time spent at lower SpO_2 levels and a decrease in minimal SpO_2 during sedation with chloral hydrate.

We also observed an increase in the estimated apnea-hypopnea index. Of all the recorded

Table I. Baseline characteristics of participating newborns (n: 42).

Patient Characteristics	Results
Male sex, n (%)	28 (66.7%)
Age at the time of the study, days	16 ± 16
Gestational age, weeks	38 ± 3
Postmenstrual age at the time of the study, weeks	40 ± 2
Birth weight, gr	3,107 ± 803
Weight at the time of the study, gr	3,350 ± 605
Head circumference at birth, cm	34 ± 3
Head circumference at the time of the study, cm	35 ± 1
Apgar score at 5 min,	8 ± 3
Apgar score of > 8 at 5 min, n (%)	22 (52.4%)

Table II. Primary outcome measures.

Variable	Before Sedation ^a	During Sedation ^{a,b}	P ^c	Difference (99.4% CI) ^d
Basal SpO ₂ , %	97.1 ± 1.9	95.1 ± 2.4	<0.001	-2.0 (-2.7 to -1.4)
Basal ETCO ₂ , mmHg	25.6 ± 3.3	29.5 ± 3.9	<0.001	3.9 (2.1 to 5.7)

^aMean ± SD. ^bIn the 4-hour period after administration of chloral hydrate. ^cTwo-tailed Student's t-test for paired data. ^dETCO₂: end-tidal CO₂, SpO₂: arterial oxygen saturation.

Table III. Secondary outcome measures.

Variable	Before Sedation ^a	During Sedation ^{a,b}	P ^c	Difference (99.4% CI) ^d
Time with SpO ₂ <95%, %	11.0 (0.8 to 26.9)	30.1 (12.4 to 55.0)	<0.001	19.1 (11.6 to 26.6)
Time with SpO ₂ <90%, %	0.0 (0.0 to 0.7)	1.9 (0.6 to 7.8)	<0.001	Not applicable
Minimal SpO ₂ , %	90.0 (87.5 to 93.0)	83.0 (81.0 to 85.0)	<0.001	Not applicable
Apnea-hypopnea index, n/h	0.0 (0.0 to 2.1)	3.4 (0.8 to 6.9)	<0.001	3.5 (1.7 to 5.2)
Respiratory rate, min ⁻¹	60.9 ± 14.0	51.3 ± 11.1 ^e	<0.001	-9.6 (-16.7 to -2.5)
Heart rate, min ⁻¹	138.1 ± 17.0	126.8 ± 13.0 ^f	<0.001	-11.3 (-18.0 to -4.6)

^aMedian (IQR) or mean ± SD. ^bIn the 4-hour period after administration of chloral hydrate. ^cTwo-tailed Student's t-test for paired data or two-tailed Wilcoxon signed-rank test. ^dCalculated when data were normally distributed. ^eAt 150 minutes after administration of chloral hydrate, when the mean respiratory rate was the lowest. ^fAt 150 minutes after administration of chloral hydrate, when the mean heart rate was the lowest.
SpO₂: arterial oxygen saturation.

apneas, 89% were central in origin, 3% were obstructive, 1% were mixed and in 7%, the type of apnea could not be reliably determined. Lastly, chloral hydrate sedation affected the respiratory and heart rates (Table III and Figs 1 and 2).

The mean respiratory rate and the mean heart rate gradually decreased during the course of sedation and were at their lowest 150 minutes after the administration of chloral hydrate (Fig. 2). The mean maximum decrease in the respiratory rate was 10±15 breaths per

minute and the mean maximum decrease in the heart rate was 11±14 beats per minute (Table III). A >20% decrease in the respiratory rate was observed in 13 newborns (34%) and a >20% decrease in the heart rate was seen in five newborns (13%). Of these, one newborn (3%) exhibited an abnormally low respiratory rate, while an abnormally low heart rate was measured in three newborns (8%), according to the normative data (lower 10th percentiles for respiratory and heart rates in healthy term newborns).^{21,22}

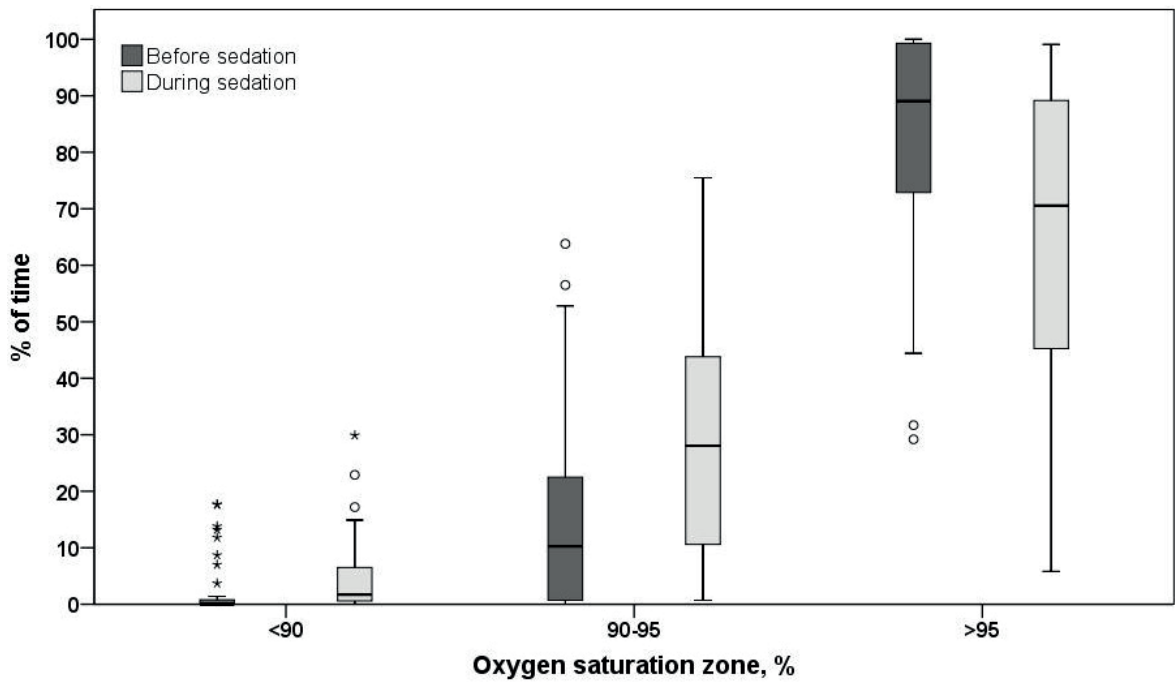


Fig. 1. Box plot of time spent with SpO₂ within certain zones before sedation with chloral hydrate (dark gray) and during sedation with chloral hydrate (light gray) at a dose of 40 mg/kg. The line across each box represents the median value. The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile. The lower and upper bars that extend from each box (whiskers) extend to 1.5 times the height of the box or to the minimum or maximum value. The closed circles indicate outliers and the asterisks are extreme outliers (values more than three times the height of the boxes).

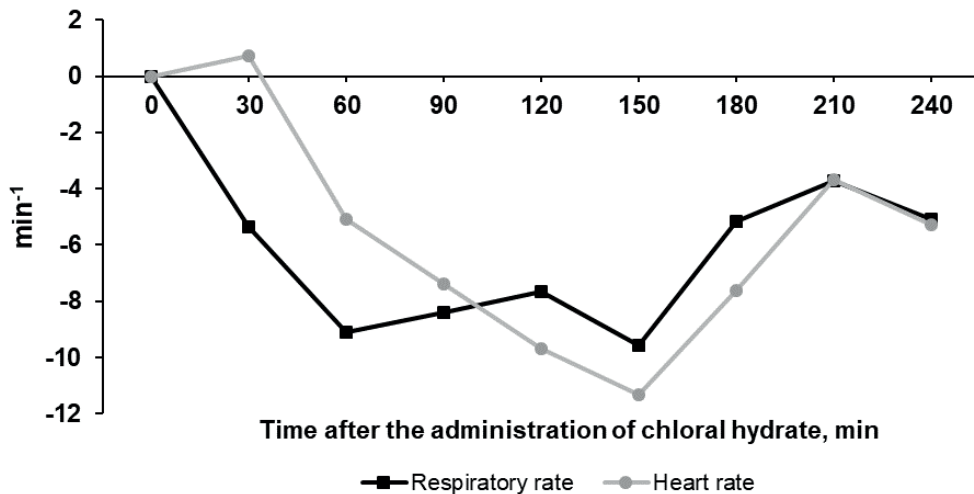


Fig. 2. Time course of the mean changes in the respiratory rate (black line) and heart rate (gray line) during sedation with chloral hydrate at a dose of 40 mg/kg relative to the mean baseline values before sedation (starting point is marked as a zero value).

Discussion

Our study confirmed the impact of chloral hydrate at a dose of 40 mg/kg on cardiorespiratory parameters in newborns. All primary and secondary outcomes changed significantly after the administration of chloral hydrate. Nevertheless, the cardiorespiratory parameters remained within the normal ranges in the majority of newborns. For instance, one of our primary outcomes – mean basal SpO₂ – decreased by 2%, but the mean value after the administration of chloral hydrate remained above 95%. At the same time, there was a small but important number of patients in whom we measured changes in cardiorespiratory parameters that differed considerably from the accepted normal ranges.

We also investigated the impact of chloral hydrate on the noninvasively measured ETCO₂, which has been shown to be an accurate measure of ventilation in nonintubated newborns with normal respiratory function.¹⁸⁻²⁰ Changes of ETCO₂ during sedation with chloral hydrate have previously only been investigated in two retrospective studies, both of which included older children.^{3,10} The increase in ETCO₂ to an average of 30 mmHg and to a maximum of 38 mmHg with a decrease of respiratory rate from 61 to 51 breaths per minute in our study may indicate bradypneic hypoventilation.^{18,19,26} However, it is important to note that we measured only basal ETCO₂ and that our results do not provide information on the percentages of time during which ETCO₂ was above the expected levels. The equipment we used also does not allow quantitative measurement of tidal volumes. We therefore cannot conclude whether our patients had hypopneic hypoventilation or not.^{26,27} A >20% increase in basal ETCO₂ was found in 9 of 27 of our studied newborns (33%). In contrast, in their retrospective study, Heistein et al.³ reported a >20% increase from the baseline ETCO₂ measurement after the administration of chloral hydrate in only 40 of 603 patients (6.6%). This discrepancy could be attributed to the differences in age – the age of the patients in the study by Heistein et al.³ was between 1 month

and 3 years, whereas our study included only newborns.

We also observed significantly higher percentages of time when SpO₂ was <95% after the administration of chloral hydrate in comparison with pre-sedation values. At the same time, the percentages of time when SpO₂ was <90% remained very low in most newborns both before and during sedation with chloral hydrate. There are currently no reference data on the normal percentages of time spent in each saturation zone for healthy full-term infants.²³ The cut-off level of 95% was chosen because this was reported as the 5th percentile of basal SpO₂ for healthy term newborns.²⁴

Our study also showed a significant increase in the estimated apnea-hypopnea index during sedation with chloral hydrate. The mean apnea-hypopnea index in the period after the administration of chloral hydrate was 3.4 events per hour. However, apneas of short duration are common in healthy term newborns, and are mostly central.^{23,28} The median central apnea index for 1-month-old newborns was reported to be 5-10 events per hour and the 95th percentile was 45.²³ Thus, given the fact that most of the recorded apneas were central in origin, the apnea-hypopnea index remained within normal limits even during sedation with chloral hydrate. It should be emphasized, however, that we used a nasal thermistor instead of a nasal pressure transducer to detect hypopneas, hence it is possible that we underestimated the number of hypopneas.²⁹ Furthermore, since we did not objectively determine the total sleep time by analyzing neurophysiological variables, our calculation of the apnea-hypopnea index was only an approximation based on the number of apneas and hypopneas per hour of estimated sleep time.

During the course of sedation, the respiratory and heart rates decreased in most patients. The mean maximum decrease in the respiratory rate from 61 to 51 breaths per minute and the mean decrease in the heart rate from 138 to 127 beats per minute do not represent a deviation from the

reported normal ranges.^{21,22} It is less plausible that the decrease in respiratory and heart rates was secondary to hypoxia or hypercapnia since both changes were clinically non-significant and because the mean SpO₂ and ETCO₂ remained within normal limits. However, the effects of chloral hydrate varied considerably among the newborns. While the respiratory and heart rates actually increased in some of the studied newborns, one newborn experienced a clinically important decrease in the respiratory rate and three participants experienced a clinically important decrease in heart rate. These findings are consistent with the report by Treluyer et al.⁸, who observed a decrease in the respiratory rate outside the normal limits for age in three of 19 children aged 2.13±1.43 years. Our results are also compatible with the study by Heistein et al.³, where alterations in heart rate beyond the published normal ranges occurred in a minority (1.4%) of the children between one month and three years of age, sedated with chloral hydrate.

In our study, the impact of chloral hydrate on the respiratory and heart rates was greatest 150 minutes after administration of chloral hydrate. Our results are not in agreement with the previously reported time-course of chloral hydrate sedation in patients aged between six months and six years, where the maximum clinical sedative effect was observed after 30 minutes, following which it gradually decreased.⁸ In another study in patients aged between three months and twelve years, the effects of sedation completely disappeared within the span of about 60 minutes.⁵ This disagreement could be attributed to the prolonged terminal serum elimination half-life of chloral hydrate and its active metabolite in newborns, compared to the older population.^{6,15} Our findings imply that newborns should be monitored for at least three hours after sedation with chloral hydrate. Further studies should explore the temporal association between the clinically apparent effects of sedation and the measured effects of chloral hydrate on cardiorespiratory parameters.

It should also be emphasized that there was high inter-individual variability in our study, as evident from the large statistical dispersion of the measured variables. Furthermore, the variability of some of the cardiorespiratory parameters (e.g. time with SpO₂ <95%, time with SpO₂ <90% and the apnea-hypopnea index) was markedly greater after the administration of chloral hydrate than before sedation. This clearly shows that chloral hydrate does not have the same effects on all newborns. As a consequence, we recorded values outside the normal limits only in individual newborns, while the average values remained within the normal range.

This is one of the few existing studies focusing on the effects of chloral hydrate sedation in the most vulnerable pediatric age group. We did not rely solely on monitoring the clinically discernible adverse events of sedation. Instead, we measured the impact of chloral hydrate on cardiorespiratory parameters in a prospective manner, which is a significant advantage of our study. To our knowledge, this is the first study that investigated the effects of chloral hydrate using polygraphy. In previous studies, vital signs were recorded at fixed intervals (every 5 minutes^{3,4} or every 15-30 minutes^{8,9}), whereas in our case, we used computer processing to analyze continuously measured parameters. Consequently, our findings do not support the results of a prior observational study by Treluyer et al.⁸ in 20 children aged 2.13±1.43 years, in whom no statistically significant change in the vital functions was found after rectal administration of 75 mg/kg of chloral hydrate. Similar results were found in the study by Coskun et al.³⁰ in 360 patients aged 19 ± 4.5 months.

The major limitation of the present study is the difference in the duration of polygraphic recordings before and after the administration of chloral hydrate. For a more accurate comparison of these two periods, the recording time should be the same length for both parts of the study. Furthermore, the two parts of the study are not

entirely comparable due to the unequal external conditions during the recording and thus possible confounding factors. Future studies are therefore needed, together with a superior study protocol involving cardiorespiratory recording on two separate, consecutive days, of the same duration and at the same time of the day in each case, on the first day without sedation and on the second day after the administration of chloral hydrate. To directly distinguish between the effects of chloral hydrate and the influences caused by varying sleep stages, a full-channel polysomnography, rather than polygraphy, would be the more appropriate investigation method.

The small sample size is another limitation of our research, especially for the subgroup in which we measured ETCO_2 . In addition, our study population was not homogeneous. Participating newborns differed in gestational age, antenatal history, Apgar score and clinical diagnoses. At the same time, great inter-individual variability could very well be the advantage of our research, since this sample is representative – it reflects the actual population in which we use chloral hydrate sedation in clinical practice.

To conclude, in a group of term newborns with normal cardiovascular and respiratory physiology, sedation with oral chloral hydrate at a dose of 40 mg/kg caused mild changes in cardiorespiratory parameters. Oxygenation and ventilation remained adequate in most cases, but the cardiorespiratory effects of chloral hydrate varied considerably among newborns. Our results could serve as a pilot for a larger study to determine the safety of chloral hydrate sedation in newborns.

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