Continuous Infusion of Clonidine in Ventilated Newborns and Infants: A Randomized Controlled Trial

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The Clonidine Study Group is listed in **Appendix 1**.

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Objectives: To assess the influence of an infusion of clonidine 1 μg/kg/hr on fentanyl and midazolam requirement in ventilated newborns and infants.

Design: Prospective, double-blind, randomized controlled multicenter trial. Controlled trials.com/ISRCTN77772144.

Setting: Twenty-eight level 3 German PICUs/neonatal ICUs.

Patients: Ventilated newborns and infants: stratum I (1–28 d), stratum II, (29–120 d), and stratum III (121 d to 2 yr).

Interventions: Patients received clonidine 1 μg/kg/hr or placebo on day 4 after intubation. Fentanyl and midazolam were adjusted to achieve a defined level of analgesia and sedation according to Hartwig score.

Measurements and Main Results: Two hundred nineteen infants were randomized; 212 received study medication, 69.7% were ventilated in the postoperative care and 30.3% for other reasons. Primary endpoint: consumption of fentanyl and midazolam in the 72 hours following the onset of study medication (main observation period) in the overall study population. The confirmatory analysis of the overall population showed no difference in the consumption of fentanyl and midazolam. Explorative age-stratified analysis demonstrated that in stratum I ($n = 112$) the clonidine group had a significantly lower consumption of fentanyl (clonidine: 2.1 ± 1.8 μg/kg/hr, placebo: 3.2 ± 3.1 μg/kg/hr; $p = 0.032$) and midazolam (clonidine: 113.0 ± 100.1 μg/kg/hr, placebo: 180.2 ± 204.0 μg/kg/hr; $p = 0.030$). Strata II ($n = 43$)

and III ($n = 46$) showed no statistical difference. Sedation and withdrawal-scores were significantly lower in the clonidine group of stratum I ($p < 0.001$). Frequency of severe adverse events did not differ between groups.

Conclusions: Clonidine 1 μg/kg/hr in ventilated newborns reduced fentanyl and midazolam demand with deeper levels of analgesia and sedation without substantial side effects. This was not demonstrated in older infants, possibly due to lower clonidine serum levels. (*Pediatr Crit Care Med* 2014; XX:00–00)

Key Words: analgesia; clonidine; infant; intravenous infusion; newborn; sedation

Prolonged ventilation of newborns and older infants in the postoperative and conservative treatment is accompanied by the need for analgesic and sedative medication (1), demanding higher dosages with increasing respiratory failure (2). The combination of fentanyl and midazolam is established in pediatric intensive care (3), but long-term use of opioids and benzodiazepines is associated with tolerance and withdrawal (4–6), suppression of respiratory drive with prolonged ventilation, constipation, and delayed enteral feeding (7). Efforts to reduce prolonged opioid and benzodiazepine exposure to prevent the complications of opioid and benzodiazepine therapy are required (1).

By activation of central and peripheral α2 receptors, clonidine leads to reduced norepinephrine release and sympathetic nervous activity with analgesia, sedation combined with arousability, suppression of delirium, and a decrease in blood pressure and heart rate. Clonidine preserves the respiratory drive, renal function, cardiac baroreflex reactivity, and vasomotor baroreflex activity (8). In the animal model, clonidine counteracts the depression of respiratory drive caused by midazolam (9).

Due to these effects, clonidine is now used in pediatric anesthesia and intensive care medicine as a sedative (10, 11), for premedication (12), for the treatment of symptoms of physical abstinence after the use of opioids and other sedatives and narcotics (10), for the treatment of the neonatal abstinence syndrome (13), for caudal or peri- and intradural anesthesia (14, 15), and to reduce the consumption of anesthetics (16, 17) and postoperative analgesics (18).

Up to now, no prospective data are available on potential opioid- and benzodiazepine-sparing effects and the tolerance of a continuous infusion of clonidine in newborns and infants. The IV use of clonidine in pediatric intensive care is a topic of ongoing interest as demonstrated by a recently completed but not yet published trial aimed to compare the sedative effects of clonidine with that of midazolam in the PICU setting (http://www.controlled-trials.com/ISRCTN02639863) (19).

Searches in the PubMed database and the professional network of the German Central Library of Medicine, Cologne, yielded two case series assessing the cardiovascular stability after cardiac surgery (10, 20): one case report (21) and one pharmacokinetic study of a single perioperative dose of clonidine (22) in children.

We conducted this randomized, placebo-controlled multicenter trial to test the hypothesis that clonidine as a comedication with fentanyl-midazolam is superior to fentanyl-midazolam alone in ventilated newborns, and infants up to 2 years of age, as measured by the total dose requirements of fentanyl and midazolam. Additionally, we hypothesized that clonidine would be noninferior to placebo in respect to the need for the rescue thiopentone use.

METHODS

Study Interventions and Cointerventions

Newborn infants with a gestational age from 37.0 weeks on and infants up to the completed second year of life, with a duration of mechanical ventilation of more than 3 days and of expectedly 6 days with the need for continuous analgesia and sedation with fentanyl and midazolam, were eligible for enrollment during the first 96 hours of ventilation. Infants in the postoperative care or with respiratory failure for other reasons were included. Criteria for exclusion were states precluding pain assessment (encephalopathy, encephalitis, severe head injury, cerebral edema, and neuromuscular blockade) and, in newborn infants, maternal drug abuse during pregnancy. The ethic committees of all clinical centers (Appendix 1) had approved the protocol. Written informed consent was obtained from either both parents or the guardians of each study patient.

All participating study centers had agreed on the use of fentanyl, midazolam, and thiopentone as standard analgesia and sedation for all ventilated patients according to the study protocol. Fentanyl and midazolam analgesia and sedation were started with the time of intubation, respectively, with the transfer of the patient from the operation room to the PICU/NICU (**Fig. 1**; fentanyl: starting with 0.5–1.0 μg/kg/hr, increased by 1.0 μg/kg/hr in case of persisting pain up to 10–15 μg/kg/hr, possible bolus dosages of 0.5–5.0 μg/kg; midazolam: starting with 50–100 μg/kg/hr, increased by 50–100 μg/kg/hr in case of persisting agitation up to 300–600 μg/kg/hr, possible bolus dosages of 25–100 μg/kg; thiopentone single dosages titrated to the onset of effect [2–7 mg/kg] to manage acute agitation on the decision of the attending physician). Intraoperative narcotics were not specified. Prescription of nonopioids in case of fever was provided by the study protocol. The administration of analgesics or sedatives not provided by the study protocol was classified as protocol violation.

The study was divided into three periods (**Fig. 1**): the preobservation period from intubation to the onset of study medication on day 4 of ventilation, the main observation period (MOP) comprising the first 72 hours of infusion of study medication, and the subsequent postobservation period lasting to discharge.

After random assignment, study participants received a continuous infusion of clonidine (1 μg/kg/hr) or an equivalent volume of normal saline with the same infusion rate started on day 4 of ventilation. Dosages of fentanyl and midazolam infusion had to be adjusted at least 6 hourly according to the

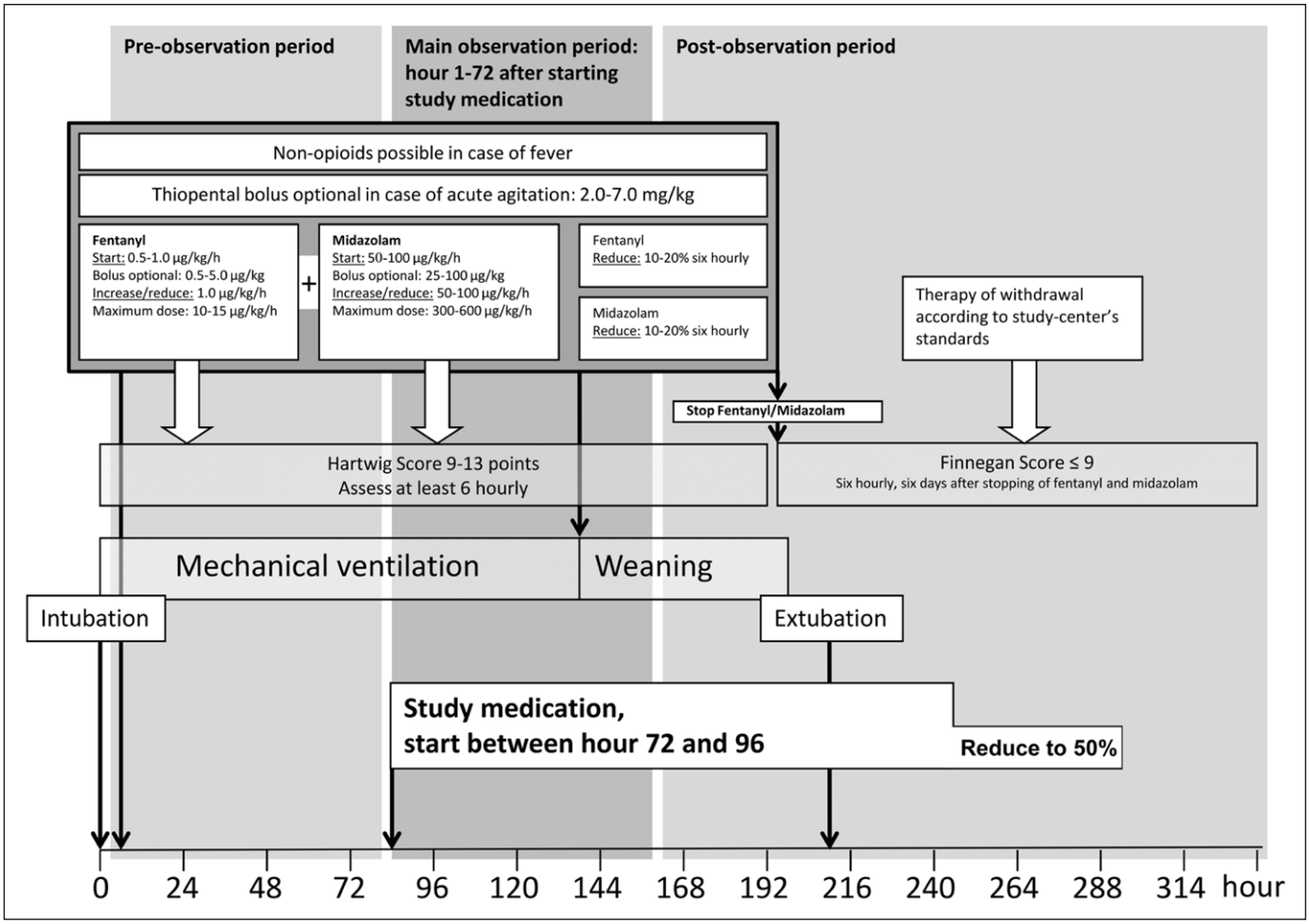

Figure 1. Exemplary study course and standard procedure of analgesia and sedation. Fixed points of time are the start of the study (intubation), start of study medication (variable on day 4 after intubation), start of the main observation period (hour 1–72 after starting of study medication), reduction of study medication (48 hr after discontinuation of fentanyl and midazolam), discontinuation of the study medication (48 hr after reduction), and start of Finnegan score (after discontinuation of fentanyl and midazolam for at least 6 d). Variable and exemplary are duration of mechanical ventilation, start of weaning, extubation, and discontinuation of fentanyl and midazolam. Standard analgesia and sedation was based on fentanyl and midazolam, and thiopental was allowed in case of acute agitation. Assessment of pain and sedation was done by Hartwig score.

study protocol in a predefined dose range accounting for the patients' individual symptoms of pain and agitation and to achieve a Hartwig score of nine to 13 points, reflecting satisfactory analgesia and sedation (23, 24). The Hartwig score was chosen because it was widely used and accepted in German PICUs and NICUs. It is designed to assess pain and sedation in ventilated newborns and infants and comprises the acceptance of mechanical ventilation and the reaction to endotracheal suctioning, grimacing, gross motor movements, and eye-opening with a range of 7–25 points. Comfort score was assessed in parallel but was not accounted for dose adjustment (25). Forty eight hours after termination of the continuous infusion of fentanyl and midazolam, the infusion rate of the study medication (clonidine or placebo) was halved and another 48 hours later stopped (**Fig. 1**). For 6 days following the termination of continuous fentanyl and midazolam infusion, withdrawal symptoms were assessed by the modified Finnegan score (26) and treated if the score repeatedly exceeded 9 points. Pharmacologic treatment of withdrawal was not defined and was according to the study centers' standard.

Serum samples were taken on the third day of infusion of study medication for analysis of clonidine concentration (27).

Randomization and Masking

A randomization scheme was computed by the Institute for Medical Statistics, Informatics and Epidemiology of the University of Cologne (IMSIE) with SAS. Randomization was done in blocks, stratified according to study center and age (stratum I: 1–28 d; stratum II: 29–120 d; stratum III: 121 d to 2 yr). A designated pharmacist at each study center received the lists of treatment group assignments. Upon inclusion, the study patient was assigned to the appropriate age stratum and treatment arm and study medication in neutral, blinded ampoules was forwarded to the local investigator by the local pharmacy. Clonidine (Paracefan) was supplied by Boehringer Ingelheim, Germany.

Outcomes

The primary outcome measures of this trial were the consumption of fentanyl (µg/kg/hr) and midazolam (µg/kg/hr)

and the use of thiopentone during the MOP. Secondary outcome measures were number of protocol violations (administration of analgesics or sedatives not provided by study protocol), blood pressure, heart rate, catecholamines and volume replacement, diuresis, Therapeutic Intervention Scoring System (TISS 28) (28), Hartwig and Comfort scores during the MOP, withdrawal symptoms (Finnegan score), therapy for withdrawal symptoms, length of ICU stay, mortality, and serum concentration of clonidine in steady state.

Data Acquisition

During the preobservation period and MOP, Hartwig and Comfort scores; heart rate; systolic, mean, and diastolic blood pressures; F_{IO_2}; and mean airway pressure had to be documented 6 hourly. Diuresis, crystalline and colloidal volume replacement, catecholamine consumptions, and TISS 28 had to be documented daily. Dosages of fentanyl, midazolam, and thiopentone had to be documented hourly, of other analgesics or sedatives daily. Finnegan score was documented 6 hourly for 6 days after terminating continuous analgesia and sedation. Patients were followed up until death or hospital discharge. Data acquisition and assurance of quality of study conduct in the centers were done by regular study monitor visits, and ambiguous entries were clarified by written queries. All data were double fed into a Good Clinical Practice-compliant database located at the Center of Clinical Studies Cologne.

Statistical Analysis

The analysis of this trial tested the superiority of the clonidine group in terms of the reduction of fentanyl and midazolam consumption during the MOP. Additionally, noninferiority of the clonidine arm regarding the use of thiopentone had to be shown. From published data (11, 16–18), we assumed a reduction in consumption of analgesics and sedatives induced by clonidine infusion by 30%. Using the inverse normal method (29), a group sequential design with two interim analyses and monotonously declining critical limits (one-sided p values of $p \leq 0.0003$, $p \leq 0.0071$, and $p \leq 0.0225$) (30) resulted in an estimated sample size of 105 patients in each group and 210 patients overall (one-sided type I error = 2.5 %, power = 80%). The noninferiority margin of thiopentone use was set to 20%. Two interim analyses were performed after 70 patients each.

Results of fentanyl, midazolam, and thiopentone were analyzed according to closed testing procedures (31). Within the stages, the results of the endpoints were combined using the ordinary least squares test (32), and the results of the three stages were combined using the inverse normal method. In addition, an explorative analysis of primary and secondary outcome measures was done in the three age strata (stratum I: 1–28 d; stratum II: 29–120 d; stratum III: 121 d to 2 yr) without accounting for the interim analyses. In case of extubation during the MOP, the dosages of fentanyl and midazolam 12 hours before extubation were carried forward for the rest of the MOP (last observation carried forward). All randomized patients receiving study medication and fentanyl and midazolam for at least 12 hours during the MOP were analyzed (modified intention-to-treat [ITT] population). In the confirmatory analysis, outcome measures of fentanyl and midazolam were compared between study groups by analysis of variance techniques accounting for variance heteroscedasticity and age strata as cofactors. Thiopentone use was analyzed using the test of Farrington and Manning (33). Additionally, an explorative analysis of primary and secondary outcome measures was done for the three age strata without accounting for the interim analyses. For continuous variables, mean and SD or median and quartiles are given, for categorical variables, proportions are calculated. Raw values before and during MOP and change in periods were compared between the two groups. Differences in the study groups were tested using Student t test, Wilcoxon rank sum test, and Fisher exact test. Confidence limits for the differences between the study groups are given. Pearson Correlation was obtained to demonstrate the dependence between Hartwig and Comfort scores. Two-sided p values are given if not stated otherwise. Statistical analysis was done by the IMSIE with the SAS 9.2 software (Statistical Analysis Software, SAS Institute Inc., Cary, NC).

RESULTS

Study Population

Of the 630 patients screened, a total of 219 patients were enrolled between September 12, 2003, and November 27, 2008, in 21 university and teaching tertiary neonatal ICUs and PICUs throughout Germany (Appendix 1; **Fig. 2**).

Of the randomized patients, 212 received study medication and 201 met the criteria of the ITT population. The majority of the patients of the ITT population were in the neonatal age (112), 43 were 29 to 120 days old, and 46 were 121 days to 2 years old; 69.7% were ventilated in the postoperative care and 30.3% for other reasons (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A99). The mean age of the ITT population was 86 ± 146 days, 121 patients (60%) were male, mean body weight was 4.65 ± 2.50 kg, and mean Pediatric Risk of Mortality (PRISM) III score was 13.3 ± 6.7 points.

There was no statistical difference in the baseline demographic characteristics of the two groups at randomization neither in the overall population nor in the single age strata with exception for gender in age stratum III where male gender was predominant (**Table 1**).

Study Interventions and Cointerventions

Median duration of infusion of study medication was 167.8 hours (Q1–Q3: 127–240 hr) for all patients without difference between both study groups ($p = 0.964$). The number of protocol violations during the MOP did not differ between group C (clonidine) and group P (placebo). In group C 24.2% and in group P 18.9% of the patients received analgesics or sedatives to provide analgesia and sedation in the context of painful or stressful procedures that were not provided by the study protocol ($p = 0.393$).

Primary Outcome

Confirmatory Results. The final confirmatory analysis of the overall patients of all strata showed a significant reduction

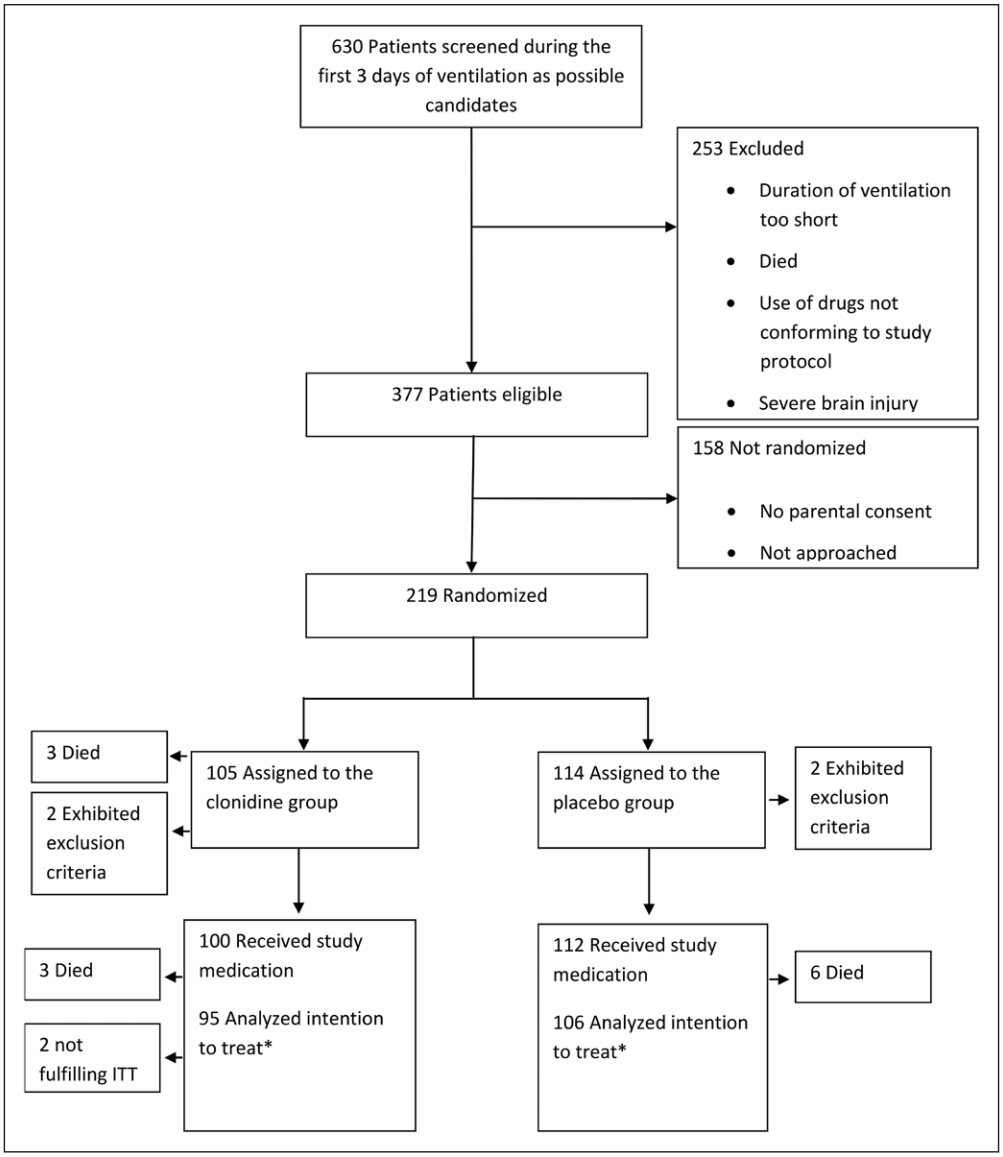

Figure 2. Screening and randomization and death. *Intention to treat (ITT): received fentanyl and midazolam during main observation period for at least 12 hr.

of fentanyl consumption ($p = 0.011$ [one-sided]) and a nonsignificant reduction of midazolam consumption ($p = 0.117$ [one-sided]) during MOP with clonidine 1 μg/kg/hr compared with placebo. Mean reduction for fentanyl was 0.86 μg/kg/hr (95% CI, 0.14–1.57 μg/kg/hr) and 25.71 μg/kg/hr (95% CI, 16.74–68.15 μg/kg/hr) for midazolam. Overall 24.9% of patients received thiopentone (mean single dose: 4.7 ± 3.8 mg/kg [C] vs 5.7 ± 8.8 mg/kg [P]). Patients with at least one thiopentone administration were 7.75% ($p < 0.001$) less in group C. Using the closed testing procedure, only noninferiority of clonidine versus placebo regarding thiopentone use could be confirmed.

An analysis of the results adjusted for the values of the preobservation period showed a reduction of fentanyl of 0.26 μg/kg/hr (95% CI, –0.43 to 0.95 μg/kg/hr; p [one-sided] = 0.223) and of midazolam of 32.33 μg/kg/hr (95% CI, –12.86 to 77.51 μg/kg/hr; p [one-sided] = 0.076) in favor of group C. Values for Hartwig scores were equal in the preobservation period ($p = 0.323$) but differed between the treatment groups during MOP, showing significantly lower values for group C ($p = 0.002$).

Explorative Results. Explorative results of the different age strata are given in **Table 2**.

Age Stratum I. Mean fentanyl and midazolam consumption during the preobservation period was not statistically different between groups (fentanyl: $p = 0.295$; midazolam: $p = 0.481$). During the MOP, mean fentanyl consumption (2.1 ± 1.8 μg/kg/hr [C] vs 3.2 ± 3.1 μg/kg/hr [P]; $p = 0.032$) as well as mean midazolam consumption (113.0 ± 100.1 μg/kg/hr [C] vs 180.2 ± 204.0 μg/kg/hr [P]; $p = 0.030$) were significantly lower in group C than in group P (**Fig. 3**). Compared with the consumption during the preobservation period, the mean consumption of fentanyl decreased by about 42% (C) and 20% (P) and the mean consumption of midazolam decreased by about 39% (C) and 12% (P) in MOP. Adjusting for the consumption during the preobservation period, the mean reduction of fentanyl was 0.7 μg/kg/hr (95% CI, –0.02 to 1.4 μg/kg/hr; $p = 0.056$) and the mean reduction of midazolam was 51.3 μg/kg/hr (95% CI, 10.2–92.3 μg/kg/hr; $p = 0.015$) in favor of clonidine.

The frequencies of administration of at least one thiopentone dose were similar between the treatment groups ($p = 0.839$). Noninferiority can be confirmed (p [one-sided] = 0.001). Mean dose of thiopentone per administration was insignificantly lower in group C (3.5 ± 1.4 mg/kg [C] vs 4.8 ± 2.2 mg/kg [P]; $p = 0.266$). Hartwig score values did not differ between groups during the preobservation period ($p = 0.75$) but were significantly lower in group C during MOP (11.1 ± 2.0 [C] vs 12.5 ± 2.4 [P]; $p < 0.001$) (**Fig. 3**).

Age Strata II and III. The consumption of fentanyl and midazolam was not significantly different between the treatment groups in age strata II and III (**Table 2**). The frequencies of administration of at least one thiopentone dose in stratum II were comparable ($p = 0.801$) and higher for placebo in stratum III ($p = 0.021$). The mean dose of thiopentone per

TABLE 1. Patients' Baseline Characteristics at Randomization

	Stratum I (0–28 d)			Stratum II (29–120 d)			Stratum III (121 d to 2 yr)		
Parameter	Clonidine (55)	Placebo (57)	*p*	Clonidine (20)	Placebo (23)	*p*	Clonidine (20)	Placebo (26)	*p*
Age at ICU admission (d)	3.0 (0.0–8.0)	2.0 (0.0–8.0)	0.432	57.0 (43.0–79.5)	36.0 (8.0–52.0)	0.499	237.0 (186.0–341.5)	315.5 (180.0–424.0)	0.692
Male sex, *n* (%)	32 (58.2)	38 (66.7)	0.436	11 (55.0)	11 (47.8)	0.763	9 (45.0)	20 (76.9)	0.035
Weight (g)	3,316 ± 488	3,419 ± 515	0.290	4,417 ± 930	3,827 ± 1,039	0.057	7,940 ± 2,974	8,497 ± 3,033	0.558
Pediatric Risk of Mortality III	12.0 (9.0–15.0)	12.0 (9.0–17.0)	0.614	14.5 (9.0–18.5)	14.0 (8.0–17.0)	0.529	11.5 (7.0–17.5)	14.0 (8.0–20.0)	0.268
Mean airway pressure[a] (cm H2O)	9.1 ± 3.4	9.2 ± 2.0	0.920	10.6 ± 4.2	11.2 ± 3.8	0.641	11.1 ± 3.5	11.1 ± 3.3	0.990
F_{IO_2}[a]	0.48 (0.31–0.65)	0.46 (0.35–0.55)	0.467	0.45 (0.30–0.72)	0.46 (0.35–0.68)	0.578	0.42 (0.31–0.59)	0.38 (0.27–0.61)	0.524
Cardiac surgery, *n* (%)	40 (72.7)	37 (64.9)		12 (60.0)	14 (60.9)		5 (25.0)	11 (42.3)	
Surgery other than cardiac, *n* (%)	6 (10.9)	4 (7.0)	0.290	1 (5.0)	3 (13.0)	0.60	4 (20.0)	3 (11.5)	0.43
No surgery, *n* (%)	9 (16.4)	16 (28.1)		7 (35.0)	6 (26.1)		11 (55.0)	12 (46.2)	

[a]On day before start of study medication.
Values are given as means ± SD or median and interquartile range.

administration was not significantly different in stratum II ($p = 0.482$) or stratum III ($p = 0.811$).

Hartwig score values of age strata II and III did not differ significantly between treatment groups neither in the preobservation period (stratum II: $p = 0.97$; stratum III: $p = 0.09$) nor during MOP (stratum II: $p = 0.75$; stratum III: $p = 0.31$).

Cardiac Surgery

Concerning the patients with cardiac surgery of all three strata ($n = 119$, group C = 57, group P = 62), consumptions of fentanyl and midazolam during MOP statistically did not differ (fentanyl: 2.9 ± 2.8 μg/kg/hr [C] vs 3.7 ± 3.5 μg/kg/hr [P]; $p = 0.18$; midazolam: 155.9 ± 123.3 μg/kg/hr [C] vs 177.1 ± 153.5 μg/kg/hr [P]; $p = 0.41$).

For age, the patients of stratum I with cardiac surgery in the explorative analysis did not show a significant difference in fentanyl and midazolam consumption in the preobservation period (fentanyl $p = 0.736$; midazolam $p = 0.903$), but fentanyl and midazolam requirements during MOP considering the consumptions in the preobservation period were lower in group C than in group P (fentanyl: 0.68 μg/kg/hr in favor of C [$p = 0.070$]; midazolam: 47.0 μg/kg/hr in favor of C [$p = 0.022$]).

In strata II and III, the results for patients with cardiac surgery demonstrated no difference in the consumptions of fentanyl and midazolam between the groups neither during the preobservation period nor during MOP (stratum II: fentanyl $p = 0.631$, midazolam $p = 0.784$; stratum III: fentanyl $p = 0.263$, midazolam $p = 0.759$).

Secondary Outcome Variables

Total Study Population. During the MOP, systolic and mean arterial blood pressures were significantly lower in group C compared with group P (systolic: 76.9 ± 15.1 mm Hg [C] vs 79.6 ± 13.6 mm Hg [P], $p = 0.047$; mean: 54.3 ± 8.5 mm Hg [C] vs 57.2 ± 8.3 mm Hg [P], $p = 0.020$). Comfort scores in the MOP and Finnegan scores after discontinuation of fentanyl and midazolam were significantly lower in group C (Comfort: 14.6 ± 3.0 [C] vs 15.8 ± 3.2 [P], $p = 0.006$; Finnegan: 6.5 ± 2.7 [C] vs 7.4 ± 2.6 [P], $p = 0.020$). These results for the total study population are biased by the large number of patients in age stratum I. There was no difference between group C and group P concerning all other secondary outcome variables.

Age Strata I, II, and III. Secondary outcome variables for age strata I–III are presented in **Supplemental Table 2** (Supplemental Digital Content 2, http://links.lww.com/PCC/A100).

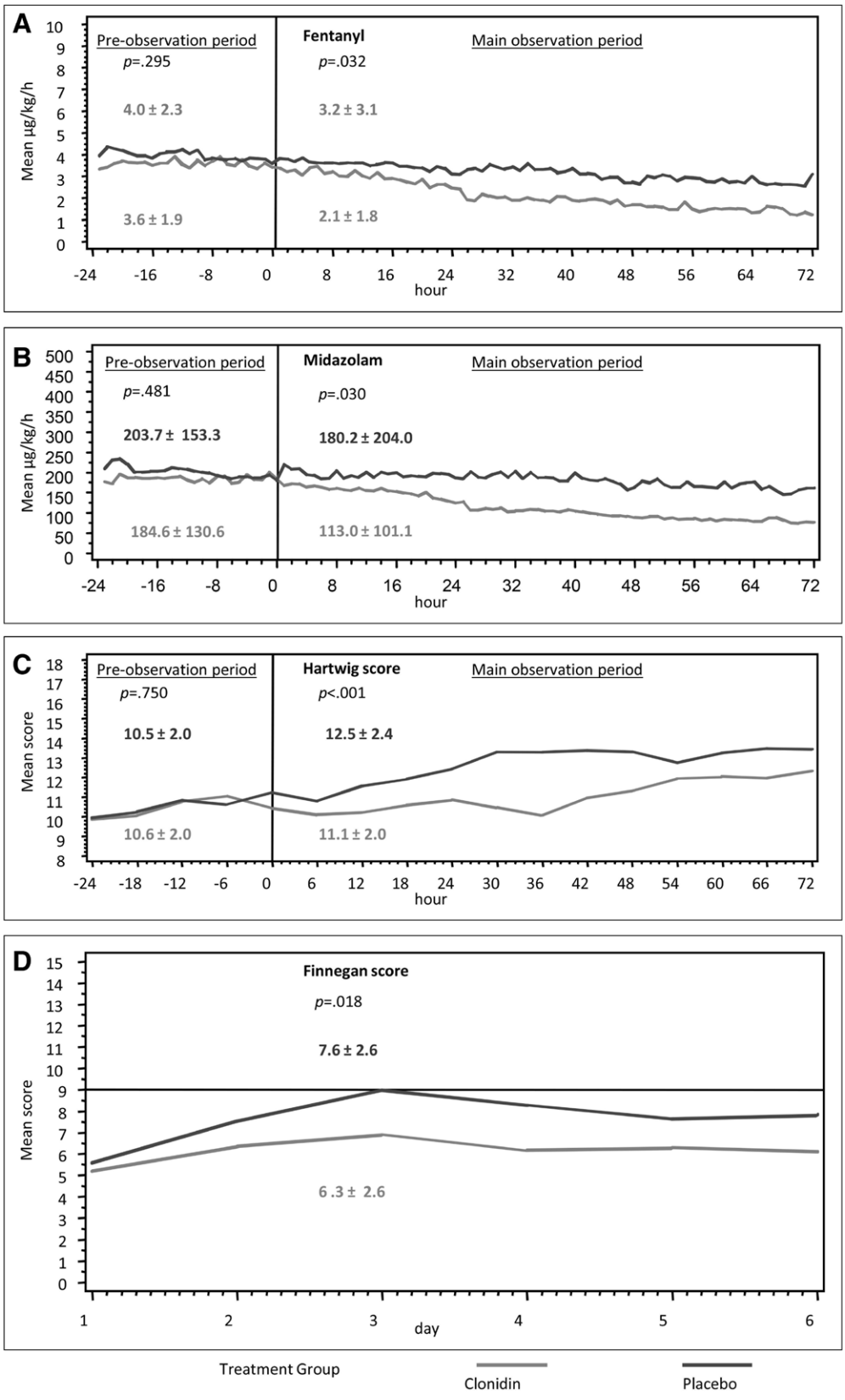

Figure 3. Stratum I, results of the explorative analysis: course of fentanyl (**A**), midazolam (**B**), Hartwig score (**C**) during the 24 hr preceding the start of study medication (*vertical line* indicates start of study medication) and during main observation period. Course of Finnegan score (**D**) during the first 6 d after discontinuation of fentanyl and midazolam. Values are given as means ± SD and *p* values calculated using *t* tests.

During the MOP, systolic and mean blood pressures were significantly lower in the patients of group C compared with group P of age stratum I ($p = 0.029$ and $p = 0.011$, respectively) but not in strata II and III. Heart rate levels did not differ between groups in all strata. There was no difference in frequency of use and dosage of catecholamines, in the amounts of colloidal and crystalline volume replacements, and diuresis between groups in all age strata.

Comfort score values paralleled Hartwig score values: in age stratum I, mean Comfort score values were significantly lower in group C ($p = 0.004$). In strata II and III, no significant differences were observed. Pearson correlation coefficient between Hartwig and Comfort score was 0.77 ($p < 0.001$), the target range of nine to 13 points of the Hartwig score corresponded to a median Comfort score of 14.0 (interquartile range [IQR], 12.0–14.0) (Hartwig score 7–8 points = median Comfort score of 10.0 [IQR, 10.0–12.0]; Hartwig score of 14–25 points = median Comfort score of 18.0 [16.0–21.0]) (**Fig. 4**).

Finnegan scores after discontinuation of fentanyl and midazolam infusions were significantly lower in group C of age stratum I ($p = 0.018$) (**Fig. 3**), with comparable pharmacological treatment. Finnegan scores did not differ significantly between groups in strata II and III. Length of ICU stay, duration of ventilation, TISS 28, severe adverse events, and mortality did not differ between groups; six patients of each treatment arm died during the study period.

Clonidine serum concentrations determined in 79 patients

TABLE 2. Explorative Results of the Main Outcome Measures of Fentanyl and Midazolam for Age Strata I–III

			Preobservation Period	
Stratum	**Treatment Arm**		**Clonidine**	**Placebo**
Stratum I (≤ 28 d)	Fentanyl (μg/kg/hr)	Mean ± SD	3.6 ± 1.9	4.0 ± 2.3
		Median (Q1–Q3)	3.8 (2.1–4.5)	3.5 (2.3–4.4)
Clonidine *n* = 55		Difference (95% CI)	−0.4 (−1.2; 0.4)	
Placebo *n* = 57		*p* (two-sided)	0.295	
	Midazolam (μg/kg/hr)	Mean ± SD	184.6 ± 130.6	203.7 ± 153.3
		Median (Q1–Q3)	153.9 (104.2–216.7)	158.3 (104.2–250.0)
		Difference (95% CI)	−19.1 (−72.5; 34.4)	
		p (two-sided)	0.481	
Stratum II (29–120 d)	Fentanyl (μg/kg/hr)	Mean ± SD	5.0 ± 3.2	6.1 ± 3.6
		Median (Q1–Q3)	4.9 (3.3–5.9)	5.0 (3.3–7.1)
Clonidine *n* = 20		Difference (95% CI)	−1.0 (−3.2; 1.1)	
Placebo *n* = 23		*p* (two-sided)	0.331	
	Midazolam (μg/kg/hr)	Mean ± SD	266.7 ± 122.9	338.3 ± 254.6
		Median (Q1–Q3)	250.0 (200.0–336.3)	313.2 (198.3–368.4)
		Difference (95% CI)	−71.6 (−198.4; 55.1)	
		p (two-sided)	0.260	
Stratum III (121 d to 2 yr)	Fentanyl (μg/kg/hr)	Mean ± SD	6.1 ± 3.1	8.1 ± 5.3
		Median (Q1–Q3)	6.4 (4.0–8.3)	6.1 (4.4–12.5)
Clonidine *n* = 20		Difference (95% CI)	−2.1 (−4.8; 0.6)	
Placebo *n* = 26		*p* (two-sided)	0.125	
	Midazolam (μg/kg/hr)	Mean ± SD	411.9 ± 300.4	385.9 ± 256.1
		Median (Q1–Q3)	388.3 (215.0–501.2)	383.2 (178.2–512.5)
		Difference (95% CI)	26.0 (−139.5; 191.5)	
		p (two-sided)	0.753	

MOP = main observation period.

[a]Adjusted for value before main observation.

p values were computed using *t* tests. Means, medians, and differences refer to the 72 hr of the MOP (hours 1–72 of infusion of the study medication) and to the 24 hr of the preobservation period immediately preceding the MOP.

(83.2%) in steady state on the third day of infusion of clonidine were highest in age stratum I ($n = 44$) with a median value of 4.92 μg/L (IQR, 3.36–5.62); in stratum II ($n = 16$) the median concentration was 2.81 μg/L (IQR, 2.06–3.51); and in stratum III ($n = 19$) it was 3.21 μg/L (IQR, 2.15–4.59).

DISCUSSION

To our best knowledge, this is the first prospective multicenter, randomized, placebo-controlled trial of IV clonidine in ventilated newborns and infants. The study population comprised newborn infants and infants up to 2 years ventilated for more than 3 days, irrespectively of the underlying indication for mechanical ventilation and thereby representing an average patient population of the NICU/PICU. Although according to the confirmatory analysis there was no homogeneous statistical effect of clonidine on fentanyl, midazolam, and thiopental consumption in the total study population, we found that clonidine infusion in term newborn infants of stratum I started on day 4 of ventilation resulted in a significantly lower consumption of fentanyl and midazolam during the first 72 hours of infusion (MOP) with a comparable use of thiopentone as rescue sedative in both groups. The observed reduction of mean fentanyl and midazolam consumption in age stratum I (42% and 39%, respectively) approximated the range of about 30% we had expected from published data (11, 16–18).

Simultaneously, the newborn infants of group C had a deeper degree of sedation and better analgesia even though the observed difference in Hartwig score may clinically not be

MOP		Change (Preobservation – MOP)	
Clonidine	Placebo	Clonidine	Placebo
2.1 ± 1.8	3.2 ± 3.1	1.5 ± 1.7	0.9 ± 2.3
1.6 (1.1–2.4)	1.9 (1.0–4.1)	1.4 (0.4–2.4)	1.0 (–0.1 to 2.1)
–1.0 (–2.0; –0.1)		0.7 (–0.02; 1.4)[a]	
0.032		0.056[a]	
113.0 ± 100.1	180.2 ± 204.0	71.7 ± 98.6	23.5 ± 122.4
87.8 (50.3–175.6)	102.8 (57.6–233.3)	50.5 (9.2–106.9)	32.4 (–21.4 to 77.8)
–67.2 (–127.7; –6.7)		51.3 (10.2; 92.3)[a]	
0.030		0.015[a]	
4.3 ± 3.9	4.7 ± 4.4	0.7 ± 2.7	1.4 ± 3.6
3.6 (0.9–6.3)	3.0 (2.1–5.1)	1.0 (0.1–1.8)	0.7 (0.1–3.3)
–0.3 (–2.9; 2.3)		–0.5 (–2.5; 1.5)[a]	
0.807		0.606[a]	
208.7 ± 100.6	270.5 ± 310.1	58.0 ± 93.8	64.6 ± 236.1
213.5 (149.3–251.5)	200.0 (109.7–318.1)	52.7 (0.0–121.0)	43.5 (–7.7 to 150.0)
–61.9 (–208.4; 84.6)		8.3 (–106.2; 122.8)[a]	
0.399		0.884[a]	
6.6 ± 4.1	7.6 ± 4.9	–0.6 ± 1.8	0.6 ± 3.5
7.2 (3.3–10.1)	6.0 (4.4–10.6)	0.0 (–1.8 to 0.6)	0.4 (–1.7 to 1.2)
–1.0 (–3.7; 1.8)		–0.7 (–2.4; 1.0)[a]	
0.4734		0.418[a]	
402.8 ± 357.1	387.9 ± 347.6	9.1 ± 218.2	–2.0 ± 196.2
334.3 (175.4–461.4)	320.9 (162.7–494.8)	4.7 (–49.1 to 87.8)	0.1 (–83.3 to 71.0)
14.9 (–195.9; 225.8)		12.0 (–113.0; 137.0)[a]	
0.887		0.848[a]	

relevant. Additionally, newborn infants of group C displayed significantly weaker physical withdrawal symptoms after discontinuation of fentanyl and midazolam infusion—as measured by lower Finnegan scores—an effect known from the therapy of neonatal abstinence syndrome (13). Meanwhile, more appropriate tools to monitor withdrawal and delirium in pediatric intensive care patients as the Withdrawal Assessment Tool-1 (34) or Sophia Observation withdrawal Symptoms scale (35) are recommended.

The significantly lower systolic and mean arterial blood pressures of the newborn infants of group C are attributed to the central α2-receptor agonism of clonidine. The measured serum concentrations of clonidine in the subjects of stratum I were higher as required to achieve a hypotensive effect in adults (36, 37). Nevertheless, the mean statistical difference in blood pressure of 2.8 mm Hg between groups was of no clinical relevance and did not result in an increased demand for IV fluid or catecholamines in group C. In the age strata II and III, all these effects could not be observed; there was a trend toward a reduction in fentanyl and midazolam consumption, but this reduction was of no statistical significance in the staged analysis. This age-related difference in response to the infusion of clonidine 1 μg/kg/hr is most probably due to age-specific pharmacokinetic characteristics with lower clonidine serum concentrations in the older children. Potts et al (38) and Xie et al (39) demonstrated a reduced clearance in the immediate neonatal period which is in line with our data for age stratum I (mean age, 7.9 ± 6.5 d).

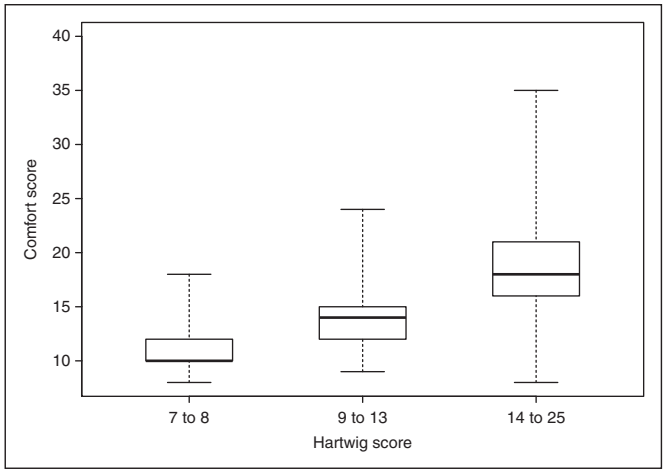

Figure 4. Box plot of Hartwig score ranges (9–13 points = target range) and the corresponding Comfort score (median, interquartile range). All assessments acquired in the preobservation and main observation period are analyzed.

Published data exist with higher dosages (maximum 3.6 μg/kg/hr) that were well tolerated (10), indicating that in older children higher dosages may be necessary to achieve a comparable effect.

In all age strata, there was no difference between treatment groups with regard to serious adverse events possibly related to clonidine. Clonidine 1 μg/kg/hr in our study population was well tolerated regardless of age or diagnosis. This includes the large group of patients with cardiac surgery, a fact described by other authors (10, 20). Death occurred in 12 (5.5%) of the patients enrolled. Three patients died before receiving study medication. Nine of the patients had severe congenital heart disease and three patients died of multiple organ failure and had underlying systemic diseases with septicemia (severe combined immunodeficiency, congenital renal insufficiency, and unknown syndrome). A mean PRISM III score of 13.3 ± 6.7 points predicts a mortality rate of 7–8%. Regarding the severity of disease and complexity of the infants after cardiac surgery, the observed mortality rate of 5.5% is comparable to published data (40–42). In the light of the positive opioid- and benzodiazepine-sparing effect of clonidine with better sedation and analgesia and decreased signs of physical withdrawal in stratum I, an additional trial with a higher initial clonidine dosage and the possibility for titration in older age strata is desirable.

This trial has limitations. The number of patients in age strata II and III is too low to show discrete differences. Different dose regimens of the study drug for the different age strata were not provided for reasons of safety because of deficient knowledge about IV clonidine in this population at the time the study was planned. The study population was inhomogeneous, including postoperative patients and patients ventilated for respiratory failure. We intended to test our hypothesis in all ventilated patients with the need for fentanyl/midazolam analgesia and sedation, irrespectively of the underlying medical condition, assuming that the effect of clonidine on opioid and benzodiazepine consumption was not limited to specific indications for its use. Interestingly, nonsurgical patients by trend had higher requirements of fentanyl and midazolam, possibly due to severe respiratory distress. The results for the patients with cardiac surgery were comparable to the results for the total population of the single age strata, equally demonstrating the positive effect of clonidine in stratum I.

CONCLUSIONS

In ventilated newborn infants, but not in older infants, a continuous infusion of clonidine 1 μg/kg/hr reduced the consumption of fentanyl and midazolam, provided better analgesia and sedation, and reduced physical withdrawal symptoms. Continuous infusion of clonidine had no apparent short-term risks. Hence, a comedication with clonidine might be beneficial to reduce the negative consequences associated with prolonged use of opioids and benzodiazepines in this setting.

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APPENDIX 1: Members of the Clonidine Study Group

The following investigators and hospitals participated in the Clonidine Study (Study sites are ordered according to the number of patients they enrolled): Klinik für Kinderkardiologie und angeborene Herzfehler, Deutsches Herzzentrum München des Freistaates Bayern, Klinik an der TUM—G. Balling and C. Röhlig; Universitätsklinikum Köln, Klinik und Poliklinik für Kinderheilkunde, Neonatologie und pädiatrische Intensivmedizin—C. Hünseler and B. Roth; Universitätsklinikum Köln, Klinik für Anästhesiologie und operative Intensivmedizin—U. Trieschmann; DRK-Kinderklinik Siegen, Anästhesie-/Intensiv-Abteilung—R. Blickheuser; Klinikum d. Medizinischen Fakultät d. Martin-Luther-Universität Halle-Wittenberg, Kinder-und Jugendmedizin—U. Lieser; Universitätsklinikum Essen, Zentrum für Kinderheilkunde—C. Dohna-Schwake; Klinik und Poliklinik für Kinder und Jugendliche des Universiätsklinikums Leipzig—M. Knüpfer and C. Gebauer; Georg-August-Universität Göttingen, Zentrum Kinderheilkunde; Pädiatrische Kardiologie und Intensivmedizin—O. Möller; Kliniken der Stadt Köln, Kinderkrankenhaus, Intensivmedizin—F. Hering and T. Pabst; Heinrich-Heine-Universität Düsseldorf, Klinik für Allgemeine Pädiatrie, Neonatologie und Pädiatrische Intensivmedizin—T. Höhn; Deutsches Herzzentrum Berlin, Klinik für angeborene Herzfehler/Kinderkardiologie—S. Schubert; Universitätsklinikum Bonn, Zentrum f. Kinderheilkunde der Universität Bonn, Neonatologie—A. Müller; Universitätsklinikum Freiburg, Zentrum f. Kinderheilkunde und Jugendmedizin—R. Hentschel; Klinikum der Joh. Gutenberg-Universität Mainz, Kinderklinik—H. G. Huth; Klinikum Saarbrücken GmbH, Kinder- und Jugendmedizin—J. Möller; Uniklinikum Heidelberg, Zentrum f. Kinder- und

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