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Nienke J. Vet
Saskia N. de Wildt
Carin W. M. Verlaat
Catherijne A. J. Knibbe
Miriam G. Mooij
Job B. M. van Woensel
Joost van Rosmalen
Dick Tibboel
Matthijs de Hoog

A randomized controlled trial of daily sedation interruption in critically ill children

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Take-home message: Based on this multicenter study, the use of daily sedation interruption in addition to protocolized sedation does not improve clinical outcome and is associated with unexpected mortality in critically ill children.

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The members of SKIC study group are listed in the Acknowledgements section.

N. J. Vet (✉) · S. N. de Wildt · M. G. Mooij · D. Tibboel · M. de Hoog
Intensive Care, Erasmus MC - Sophia Children's Hospital, Dr. Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands
e-mail: n.vet@erasmusmc.nl
Tel.: +31-10-7036922

N. J. Vet · M. de Hoog
Department of Pediatrics, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands

S. N. de Wildt · M. G. Mooij · D. Tibboel
Department of Pediatric Surgery, Erasmus MC - Sophia Children's Hospital, Rotterdam, The Netherlands

C. W. M. Verlaat
Intensive Care, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

C. A. J. Knibbe
Divison of Pharmacology, Leiden Academic Center for Drug Research, Leiden University, Leiden, The Netherlands

C. A. J. Knibbe
Clinical Pharmacy, St Antonius Hospital, Nieuwegein, The Netherlands

J. B. M. van Woensel
Intensive Care, AMC, Emma Children's Hospital, Amsterdam, The Netherlands

J. van Rosmalen
Department of Biostatistics, Erasmus MC, Rotterdam, The Netherlands

Abstract *Purpose:* To compare daily sedation interruption plus protocolized sedation (DSI + PS) to protocolized sedation only (PS) in critically ill children. *Methods:* In this multicenter randomized controlled trial in three pediatric intensive care units in the Netherlands, mechanically ventilated critically ill children with need for sedative drugs were included. They were randomly assigned to either DSI + PS or PS only. Children in both study arms received sedation adjusted on the basis of validated sedation scores. Provided a safety screen was passed, children in the DSI + PS group received daily blinded infusions of saline; children in the PS group received blinded infusions of the previous sedatives/analgesics. If a patient's sedation score indicated distress, the blinded infusions were discontinued, a bolus dose of midazolam was given and the 'open' infusions were resumed: DSI + PS at half of infusion rate, PS at previous infusion rate. The primary endpoint was the number of ventilator-free days at day 28. Data were analyzed by intention to treat. *Results:* From October 2009 to August 2014, 129 children were randomly assigned to DSI + PS ($n = 66$) or PS ($n = 63$). The study was terminated prematurely due to slow recruitment rates. Median number of ventilator-free days did not differ: DSI + PS 24.0 days (IQR 21.6–25.8) versus PS 24.0 days (IQR 20.6–26.0); median difference 0.02 days (95 % CI −0.91 to 1.09), $p = 0.90$. Median ICU and hospital length of stay were similar in both groups: DSI + PS 6.9 days (IQR 5.2–11.0) versus PS 7.4 days (IQR 5.3–12.8), $p = 0.47$, and DSI + PS 13.3 days (IQR 8.6–26.7) versus PS 15.7 days (IQR 9.3–33.2), $p = 0.19$, respectively. Mortality at 30 days was higher in the DSI + PS group than in the PS group (6/66 versus 0/63, $p = 0.03$), though no causal relationship to the intervention could be established. Median cumulative midazolam dose did not differ: DSI + PS 14.1 mg/kg (IQR

7.6–22.6) versus PS 17.0 mg/kg (IQR 8.2–39.8), $p = 0.11$. *Conclusion:* In critically ill children, daily sedation interruption in addition to protocolized sedation did not improve clinical outcome and was associated with increased mortality compared with protocolized sedation only.

Keywords Pediatrics · Critical illness · Sedation · Interruption · Clinical pharmacology

Introduction

Commonly, mechanically ventilated critically ill children are sedated to enhance their comfort and safety. Moreover, a state of sedation facilitates synchronization with mechanical ventilation and enables invasive procedures to be performed.

Although sedation is helpful in the care of critically ill children, it has numerous negative effects. Especially, oversedation should be avoided, as it is associated with longer duration of ventilation, longer hospital stay and adverse patient outcomes, such as withdrawal, delirium and long-term psychological morbidity in adults [1–4]. In recent years, efforts have been made to improve sedation management in children, for example with the use of sedation algorithms and protocols [5–7]. Nonetheless, optimal sedation remains challenging and oversedation is common in pediatric intensive care [8].

In adults, daily sedation interruption (DSI) was found to be an effective method of improving sedation management. Clinical trials have shown that DSI can reduce the duration of mechanical ventilation, hospital stay and amount of sedatives administered, without compromising patient comfort or safety [9]. Several later studies have confirmed this beneficial effect [10], whereas other studies, in different settings, found no benefit [11, 12].

For critically ill children, it is unknown if DSI will improve outcome. Two studies showed that DSI in children is feasible, but these studies were not sufficiently powered to detect differences in clinical outcomes [13, 14]. In a recent study from India comparing DSI with continuous sedation in children, DSI led to improved clinical outcomes, including shorter durations of mechanical ventilation and ICU stay [15]. However, given the differences in patient population and ICU practices between the Indian and the Western setting, these results need further verification [16]. Furthermore, it is unknown if the combined use of DSI and protocolized sedation is beneficial in children, as this appears not to be the case in adults [11]. We hypothesized that mechanically ventilated children managed with DSI combined with protocolized sedation have more ventilator-free days at day 28 than patients managed with protocolized sedation alone.

Methods

Patients

We recruited patients from three tertiary medical-surgical PICUs in The Netherlands: Erasmus MC-Sophia Children's Hospital, Radboud University Nijmegen Medical Center and Academic Medical Center Amsterdam. Approval from each institutional review board and written informed consent from parents or legal representatives was obtained. The trial has been registered in the Dutch Trial Register (http://www.trialregister.nl/trialreg/index.asp), no. NTR2030.

Eligible patients were children between 0 and 18 years of age, and at least 37 weeks of postconceptual age, requiring mechanical ventilation with an expected duration of at least 48 h and need for sedative drugs. Exclusion criteria were: anticipated death or withdrawal of life support within 48 h; impossibility of assessing level of sedation due to an underlying neurologic condition; neurological, respiratory or cardiac instability that may not tolerate inadequate sedation; therapeutic hypothermia after cardiopulmonary resuscitation; difficult airway; fixed duration of mechanical ventilation (e.g., until planned operation); admission for ECMO; already having been ventilated/sedated for >2 days in a transferring PICU; and no informed consent.

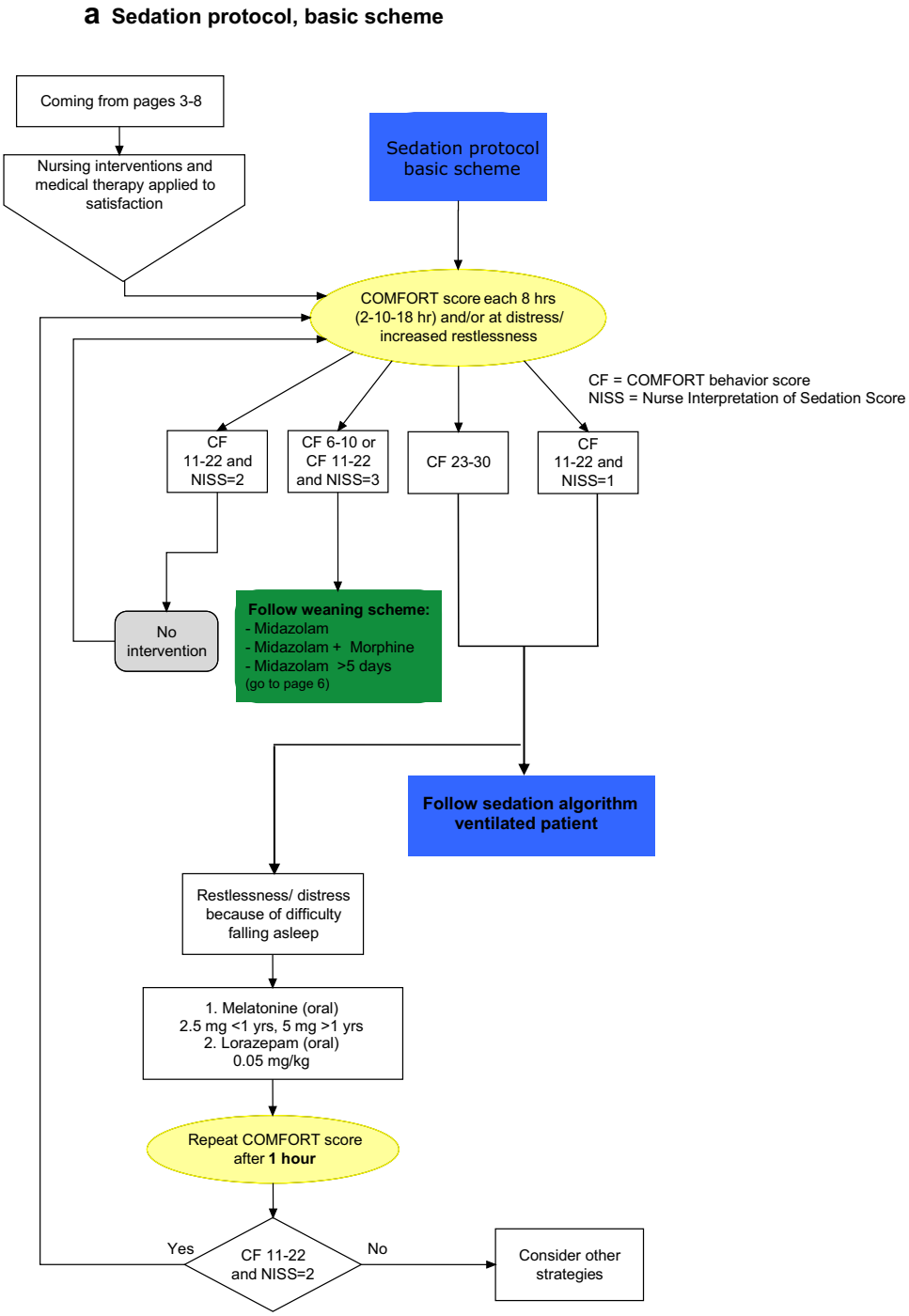
Study design

The study design of this randomized controlled trial has previously been described in detail [17]. In short, within 24 h after intubation, informed consent was obtained and, the morning after enrollment, the patient was assigned to either DSI combined with protocolized sedation (DSI + PS group) or protocolized sedation only (PS group).

Randomization and blinding

Patients were randomly assigned in a 1:1 ratio to either DSI + PS or PS, using blocked randomization with stratification by center and age group (0–30 days, 30 days–2 years, and 2–18 years). An independent

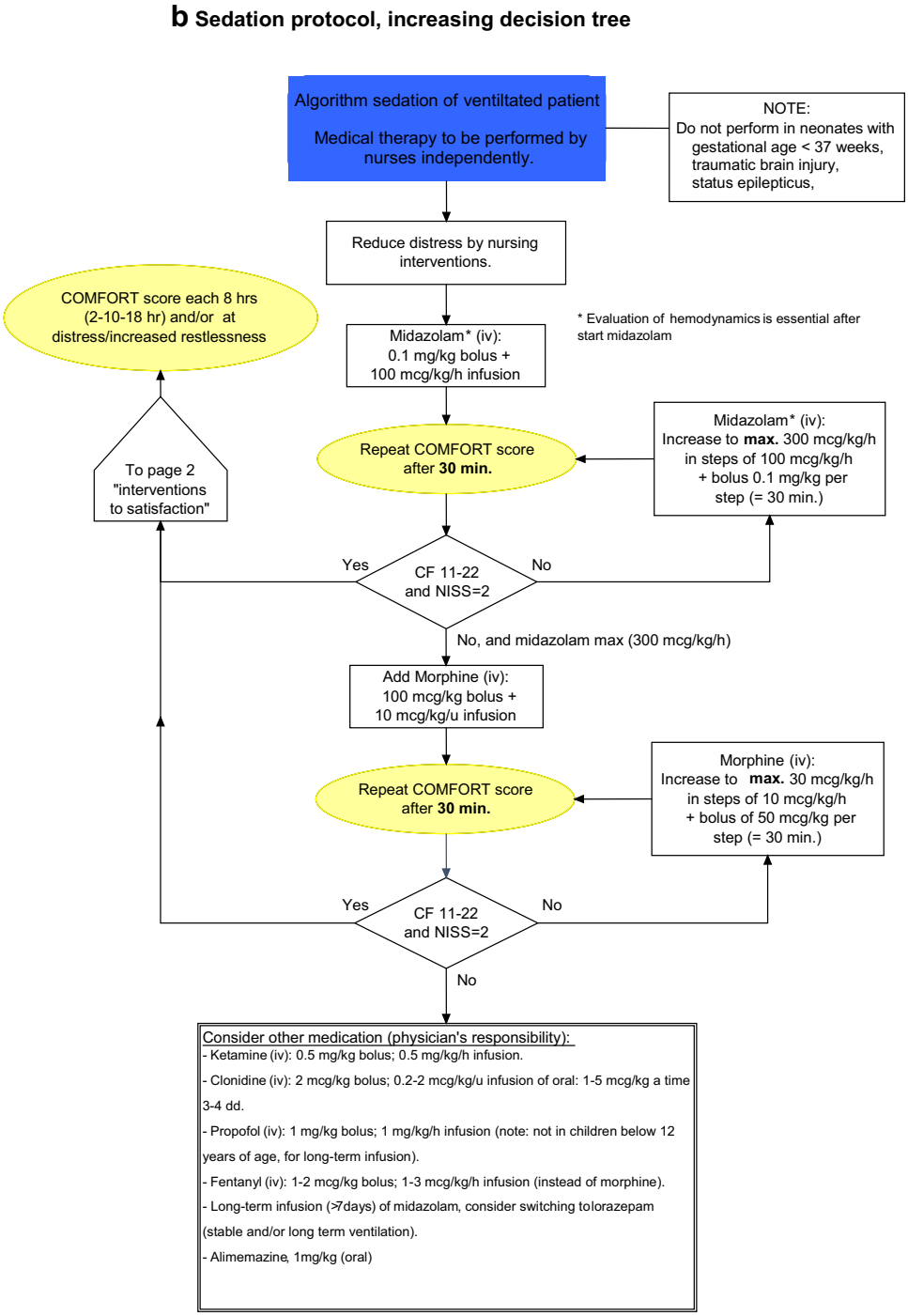
Fig. 1 Sedation protocol



biostatistician carried out computer randomization in advance.

In both groups, the syringes containing sedatives/ analgesics were replaced each morning with blinded syringes, provided a safety screen was passed. The pharmacist had access to group allocation to be able to prepare blinded infusions. In the DSI + PS group, the infusions were replaced with saline infusions, in the PS group, the infusions were replaced with blinded infusions containing the same sedative and analgesic drug concentrations. In this way, the caregiving nurse was blinded for group allocation, so as to minimize bias in assessing the sedation level. If a patient's sedation score indicated distress, the blinded infusions were discontinued, a bolus dose midazolam was given and the original 'open' infusions were restarted at 50 % of the rate for the DSI + PS

Fig. 1 continued



group and at the original rate for the PS group. This infusion rate was visible for the caregiving medical team. For restart of the 'open' infusions, the bedside nurse opened an envelope placed in the study binder at the patient's bedside to identify group allocation. The envelope was then closed again and returned to the study binder. This procedure was repeated on every study day. Effectively, only the first start of the blinded infusions resulted in a complete blinding of treatment for the medical team. After the first restart, they could be aware of the patient's allocation, if they deduced that the full or 50 % resumption of the infusion rate the day before indicated group assignment. For safety reasons, complete blinding was deemed not to be feasible.

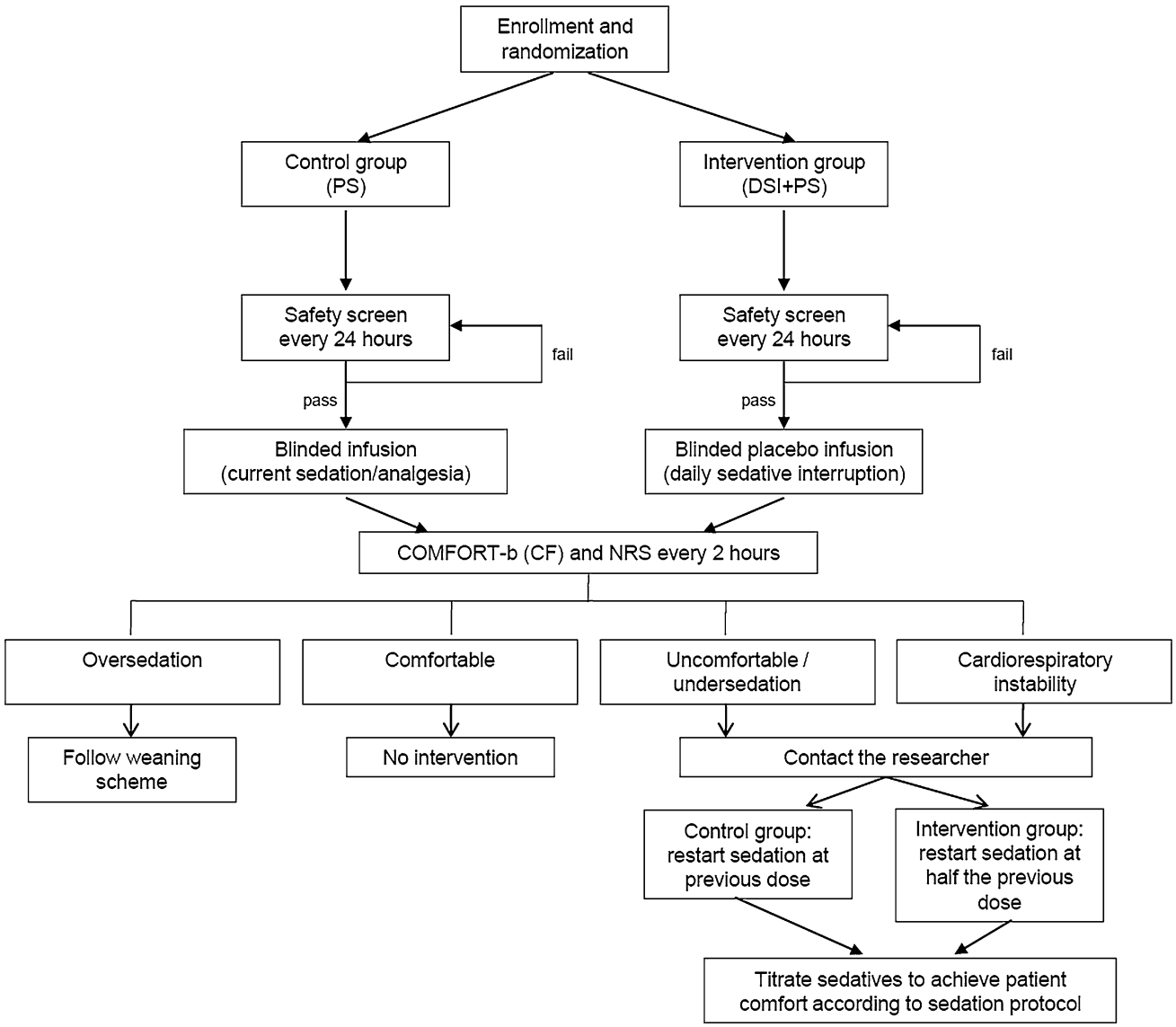


Fig. 2 Flowchart of study design

Protocolized sedation

All study centers used a standardized sedation protocol for adjustment of sedatives and analgesics, based on scores on validated instruments for this population [COMFORT behavior scale (COMFORT-B), nurse interpretation of sedation score (NISS), numeric rating scale (NRS)] [18, 19]. All nurses had been trained to use these instruments. Inter-observer variability was satisfactory, with $\kappa > 0.65$ for all nurses. Adequate sedation was defined as a COMFORT-B score ≥ 11 and ≤ 22. A COMFORT-B score of <11 implied oversedation, a score >22 implied undersedation. Upon a patient's admission to the PICU, the need of sedation was assessed. If sedation was needed, midazolam was initiated and titrated up to a maximum of 300 μg/kg/h. When sedation was still considered insufficient, morphine (up to 30 μg/kg/h) was added to the midazolam treatment. If a patient remained distressed and sedation still seemed inadequate, other sedative drugs were added according to local standard practice (see Fig. 1a, b).

Intervention group (DSI + PS)

After having been on mechanical ventilation for 24 h, a patient was assessed for a safety screen daily at 1000 h, after routine care. A patient passed the screen unless he/

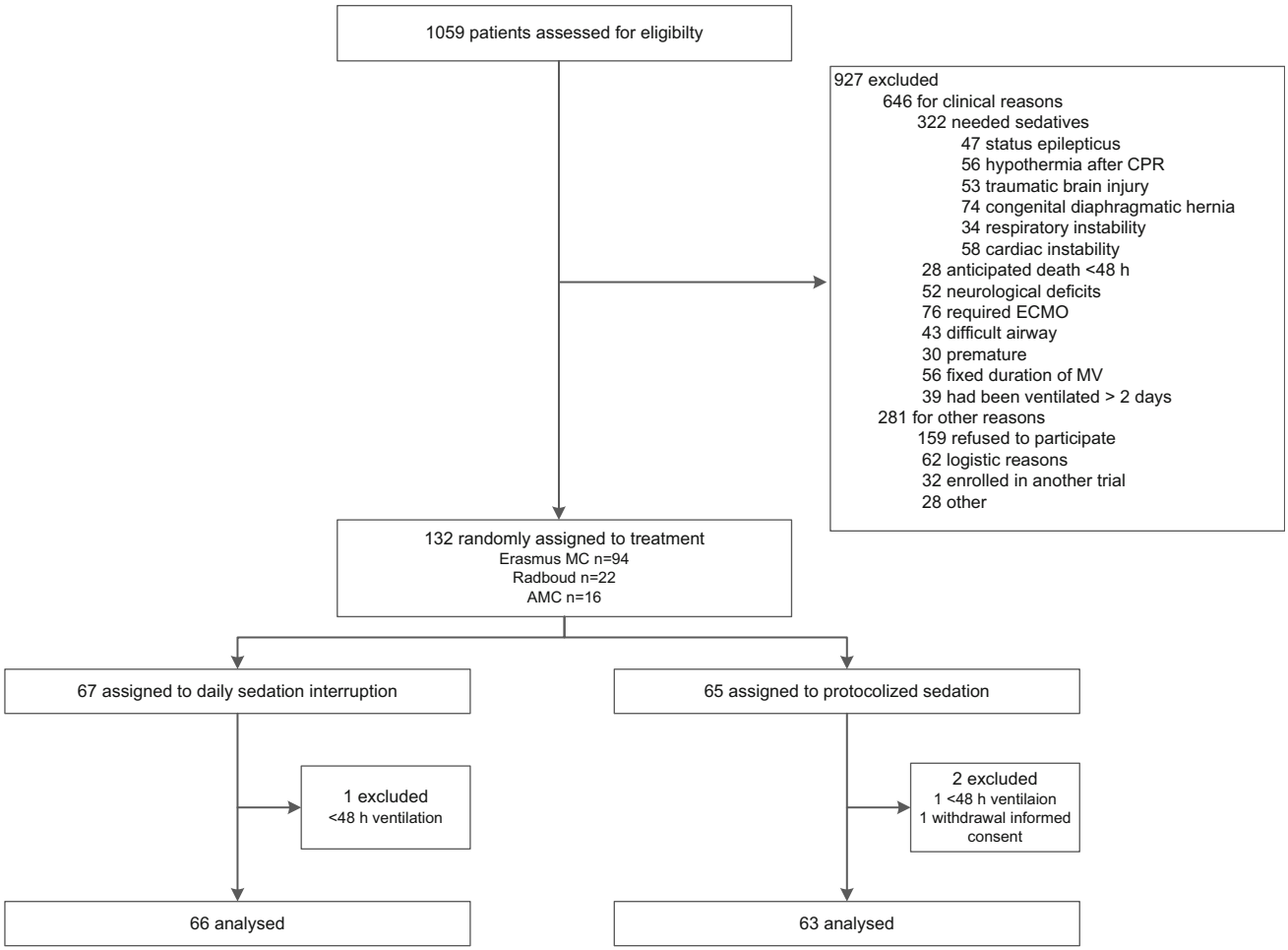


Fig. 3 Flowchart of recruited patients

she received a sedative infusion for active seizures, escalating sedative doses due to ongoing agitation, neuromuscular blockers, had evidence of increased intracranial pressure or in cases of cardiorespiratory instability as judged by the bedside clinician. Patients who did not pass the screen were reassessed after 24 h. If the patient passed the screen, all sedative and opioid infusions were replaced with blinded infusions containing saline. Analgesics needed for active pain were continued (e.g., pleural drain, <24 h after surgery). During blinded infusions, the patient was strictly monitored and comfort was assessed at least every 2 h using the COMFORT-B and NRS scores or earlier if distress was apparent. The sedative and opioid infusions were restarted if the patient appeared uncomfortable or if this was deemed necessary in view of cardiorespiratory instability. After a loading dose of midazolam (0.1 mg/kg, intravenously), sedative infusions were restarted at half the previous dose and then titrated according to the sedation protocol to achieve adequate sedation (Fig. 2).

Control group (PS)

In the control patients, following the safety screen, blinded infusions were started at the same infusion rate as the patient was receiving, containing the same medication, effectively continuing the sedation. Level of sedation was assessed in the same way as in the DSI + PS group. When assessments indicated distress, a loading dose of midazolam was given, and the blinded infusions were replaced with the sedative infusions at a similar rate as before the start of blinded infusions and subsequently titrated according to the sedation protocol to achieve adequate sedation.

Endpoints

The primary endpoint was the number of ventilator-free days at day 28, defined as the number of days a patient had breathed without mechanical ventilation for at least

Table 1 Baseline characteristics

	DSI + PS ($n = 66$)	PS ($n = 63$)
Age (months)	2.8 (1.1–17.1)	2.7 (1.3–14.0)
0–30 days (group A)	12 (18.2 %)	11 (17.5 %)
30 days–2 years (group B)	40 (60.6 %)	38 (60.3 %)
2–18 years (group C)	14 (21.2 %)	14 (22.2 %)
Gender (male/female)	38/28 (57.6/42.4 %)	41/22 (65.1/34.9 %)
Weight (kg)	5.0 (3.7–10.0)	4.6 (3.7–11.0)
PRISM II	16.5 (13–24)	16 (11–21)
Predicted mortality PIM 2 (%)	4.3 (1.6–10.0)	3.2 (1.5–7.6)
PELOD	11 (8–20)	11 (11–20)
Diagnosis on admission		
Respiratory disorder[a]	47 (71.2 %)	40 (63.5 %)
Cardiac disorder[b]	3 (4.5 %)	4 (6.3 %)
Sepsis	7 (10.6 %)	6 (9.5 %)
Surgery		
Cardiac	7 (10.6 %)	7 (11.1 %)
Non-cardiac	1 (1.5 %)	2 (3.2 %)
Other	1 (1.5 %)	4 (6.3 %)
Sedation before randomization (mg/kg)[c]		
Midazolam	3.6 (2.4–5.7)	3.1 (2.4–5.2)
Morphine	0.25 (0.12–0.43)	0.35 (0.14–0.46)

Data are in median (IQR) or *n* (%)

PRISM II pediatric risk of mortality, *PIM 2* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction

[a] Viral/bacterial pneumonia, ARDS and asthma

[b] Congenital heart disease and cardiomyopathy

[c] Cumulative dose (infusion and bolus) in the first 24 h after intubation

Table 2 Main study outcomes

	DSI + PS ($n = 66$)	PS ($n = 63$)	p value
Ventilator free days at 28 days (days)	24.0 (21.6–25.8)	24.0 (20.6–26.0)	0.90
Duration of mechanical ventilation (days)	5.1 (3.7–7.3)	5.2 (3.6–9.0)	0.71
Reintubation <24 h	2 (3.0 %)	9 (14.3 %)	0.03
Tracheostomy	1 (1.5 %)	1 (1.6 %)	1.00
Length of stay ICU (days)	6.9 (5.2–11.0)	7.4 (5.3–12.8)	0.47
Length of stay hospital (days)	13.3 (8.6–26.7)	15.7 (9.3–33.2)	0.19
30-day mortality	6 (9.1 %)	0 (0 %)	0.03
Adverse events			
Self-extubations	1	4	0.20
Of which requiring reintubation	0	2	0.24
Oversedation–flumazenil	0	1	0.49
Fixation (need for soft wrist restrainers)	1	0	1.00

Data are in median (IQR) or *n* (%)

48 h continuously during a 28-day period after randomization. Patients who died during this 28-day period were assigned zero ventilator-free days.

Secondary outcomes included: length of stay in the ICU and hospital (days); 30-day mortality; total and median dose of midazolam and morphine (mg/kg); number of COMFORT-B scores <11 and >22; use of additional sedative drugs during ventilation; incidence of withdrawal symptoms [Sophia Observation withdrawal Symptoms (SOS) scale [20]]; adverse events; total number of safety screen assessments; and number and reason for failure to pass.

Statistical analysis

The Erasmus MC institutional admission data for the year 2008 showed that 168 children were mechanically ventilated for at least 48 h in our PICU with a mean number of 16.5 (SD 9.9) ventilator-free days. On this basis, including 100 patients per group would be sufficient to detect a clinically significant difference of 25 % in ventilator-free days (i.e. mean 20.6 days in the DSI + PS group vs. 16.5 days in the PS group), with a power of 80 %, based on a Mann–Whitney test with a significance level of 5 %.

Table 3 Sedation profiles

	DSI + PS ($n = 66$)	PS ($n = 63$)	p value
Midazolam	$n = 66$	$n = 63$	
Cumulative dose infusion (mg/kg)	13.0 (6.9–22.3)	17.0 (8.1–39.8)	0.08
Mean infusion rate (μg/kg/h)	126 (59–185)	134 (90–221)	0.02
Cumulative dose bolus (mg/kg)	0.74 (0.24–1.21)	0.52 (0.20–1.19)	0.21
Total cumulative dose (mg/kg)	14.1 (7.6–22.6)	17.0 (8.2–39.8)	0.11
Number of exposure days	4.5 (3.4–6.7)	4.9 (2.8–8.7)	0.79
Morphine	$n = 54$	$n = 52$	
Cumulative dose infusion (mg/kg)	0.89 (0.5–1.4)	1.15 (0.6–2.8)	0.12
Mean infusion rate (μg/kg/h)	9.7 (6.3–13.0)	11.9 (10.0–16.4)	0.004
Cumulative dose bolus (mg/kg)	0.15 (0.06–0.36)	0.10 (0.02–0.14)	0.03
Total cumulative dose (mg/kg)	0.92 (0.60–1.56)	1.16 (0.65–2.86)	0.17
Clonidine	$n = 13$	$n = 11$	
Cumulative dose infusion (μg/kg)	55.2 (15.8–95.1)	92.6 (43.2–208.3)	0.04
Mean infusion rate (μg/kg/h)	0.56 (0.42–0.92)	0.98 (0.66–1.52)	0.01
Cumulative dose bolus (μg/kg)	4.08 (2.24–4.73)	6.43 (3.04–10.50)	0.15
Total cumulative dose (μg/kg)	47.4 (8.0–86.7)	75.7 (41.2–204.8)	0.10
Ketamine	$n = 9$	$n = 17$	
Cumulative dose infusion (mg/kg)	15.3 (6.8–108.0)	35.8 (6.4–94.9)	0.85
Mean infusion rate (mg/kg/h)	0.54 (0.27–1.14)	0.74 (0.30–0.97)	0.83
Cumulative dose bolus (mg/kg)	0.92 (0.50–1.89)	1.09 (0.50–3.48)	0.72
Total cumulative dose (mg/kg)	4.51 (0.52–26.20)	35.63 (3.11–56.17)	0.11
Fentanyl	$n = 34$	$n = 28$	
Cumulative dose (μg/kg)	4.1 (2.1–12.3)	2.3 (1.2–7.9)	0.15
Propofol	$n = 24$	$n = 29$	
Cumulative dose (mg/kg)	6.5 (2.8–26.2)	10.8 (2.6–40.7)	0.57
Number of different sedatives received	2 (2–3)	2 (2–4)	0.31
Number of patients with >2 sedatives	24 (36.4 %)	26 (41.3 %)	0.57
COMFORT-B scale			
Total number of assessments	3389	3924	
Median number of assessments per patient	41 (28–59)	47 (26–76)	0.45
Median COMFORT-B score	12 (11–15)	12 (10–14)	0.048
Oversedation (COMFORT-B <11), *n* (%)	824 (24.3 %)	998 (25.4 %)	0.27
Undersedation (COMFORT-B >22), *n* (%)	107 (3.2 %)	93 (2.4 %)	0.04
SOS score			
Number of patients	19	20	
Total number of assessments	317	540	
Median number of assessments per patient	9 (3–21)	16.5 (9–39)	0.07
Median SOS	1.0 (0.5–2.0)	1.0 (1.0–2.8)	0.23
SOS ≥4, *n* (%)	32 (10.1 %)	66 (12.2 %)	0.35

Data are in median (IQR) or *n* (%)
n the number of patients receiving the drug

Data were analyzed blinded, with an intention-to-treat approach. Descriptive data are presented as percentage, mean ± SD for normally distributed variables, and median ± IQR for non-normally distributed variables. Distribution of categorical variables between groups was compared with Fisher's exact tests; continuous variables with Mann–Whitney tests. The primary outcome was also compared between groups with correction for baseline variables [age, sex, pediatric logistic organ dysfunction (PELOD) score and type of disease], using robust multiple linear regression analysis to account for the non-normal distribution of the model residuals. Effects of treatment on length of stay in the ICU and hospital were assessed with time-to-event analysis, i.e. Kaplan–Meier analysis and log-rank test. These tests also served to assess the effect on 30-day mortality. Penalized Cox analysis was used to assess differences between the groups after adjustment for the baseline variables mentioned above. All statistical tests were two-tailed and the significance level was set at 0.05. Statistical analyses were performed using SPSS (v.21) and R (v.3.1.2) for robust regression analysis.

An interim analysis was not scheduled, but an independent data and safety monitoring board (DSMB) continuously evaluated possible adverse events.

Results

Participants

Of 1059 eligible patients, 132 patients were included in the study between October 2009 and August 2014.

Table 4 Safety screen

	DSI + PS ($n = 66$)	PS ($n = 63$)
Median number of assessments per patient	4 (3–5)	4 (3–6)
Total number of assessments	302	354
Pass	198 (65.6 %)	261 (73.7 %)
Fail	69 (22.8 %)	76 (21.5 %)
No sedation	35 (11.6 %)	17 (4.8 %)
Reason for failure		
Active seizures	0 (0 %)	3 (3.9 %)
Ongoing agitation	24 (34.8 %)	33 (43.4 %)
Neuromuscular blockade	7 (10.1 %)	24 (31.6 %)
Increased ICP	0 (0 %)	0 (0 %)
Cardiorespiratory instability	38 (55.1 %)	16 (21.1 %)
No. of patients with		
0 fail	40 (60.6 %)	40 (63.5 %)
1 fail	10 (15.2 %)	8 (12.7 %)
2 fail	6 (9.1 %)	8 (12.7 %)
3 fail	3 (4.5 %)	1 (1.6 %)
4 fail	3 (4.5 %)	2 (3.2 %)
5 fail	3 (4.5 %)	2 (3.2 %)
>5 fail	1 (1.5 %)	2 (3.2 %)

Data are in median (IQR) or *n* (%)

Recruitment rates were lower than foreseen, and the study was terminated prematurely, before the recruitment of 200 patients. Three patients were excluded from the analysis because they were on mechanical ventilation for <48 h or informed consent was withdrawn before the start of the study (Fig. 3). Consequently, 129 children were analyzed, 66 in the DSI + PS group and 63 in the PS group.

Eight patients (12 %) in the DSI + PS group discontinued the protocol. Three of those were placed on ECMO, two were withdrawn by the medical team (one because of clinical instability and one because deeper sedation was thought necessary), two patients were withdrawn by parents (concerned that their child was insufficiently sedated), and one patient was transferred to the neonatology ward. In the PS group, four patients (6 %) discontinued the protocol. Two of those were placed on ECMO, one was withdrawn by the medical team (because of clinical instability), and one was withdrawn by the parents. Baseline characteristics of the two groups were similar (Table 1). Most patients (67 %) were admitted for a non-surgical condition such as respiratory disorders.

Main outcomes

Table 2 shows that the median number of ventilator-free days was 24.0 days in both groups [median difference 0.02 (95 % CI −0.91 to 1.09), $p = 0.90$]. Adjustment for baseline variables gave similar results [mean difference 0.04 (95 % CI −1.04 to 1.11), $p = 0.95$]. In the PS group, more re-intubations were needed (9 vs. 2, $p = 0.03$). The number of accidental extubations was not different between groups (DSI + PS group $n = 1/66$, PS group $n = 4/63$, $p = 0.20$). ICU and hospital length of stay did not differ significantly between the groups (Table 2).

Mortality at 30 days was significantly higher in the DSI + PS group [6 (9.1 %) vs. 0 (0 %), $p = 0.02$ using log-rank test], also after adjustment for baseline variables. The DSMB reviewed the causes of mortality and could not determine a causal relation between intervention and outcome for these six deaths in the DSI + PS group. The intervals between last blinded infusion and death were 1, 7, 20, 23 and 27 days, while one patient did not receive blinded infusion at all. Three of these six patients were withdrawn prematurely from the study because of the start of ECMO. Two others died from ongoing sepsis with progressive deterioration and multiple organ failure, and one patient suffered from a pneumonia in aplasia with critical illness neuropathy.

Sedative medication

Sedation profiles are presented in Table 3. As a reflection of the protocol, mean infusion rates were lower in patients treated with DSI + PS. However, cumulative dose was not different between the groups, as patients treated with DSI + PS received more boluses of midazolam [median cumulative midazolam dose (infusion + boluses) 14.1 mg/kg (IQR 7.6–22.6) vs. 17.0 mg/kg (IQR 8.2–39.8), $p = 0.11$]. Also, for the other sedative drugs, no significant difference was found in cumulative dose. Median number of days of exposure to midazolam and number of agents received were not different. The median duration of blinded infusions was 25.9 h (IQR 10.1–48.8 h) in the DSI + PS group versus 41.4 h (IQR

23.8–75.7 h) in the PS group, $p = 0.003$. In nine patients in the DSI + PS group, there was no need to restart sedation after the first interruption. These patients were comfortable without sedation for a median of 48.5 h (range 23.5–74.5 h) until extubation.

Distress assessments

Median COMFORT-B scores were slightly lower in the PS group than the PS + DSI group, indicating that they were more deeply sedated [12 (IQR 10–14) vs. 12 (IQR 11–15), $p = 0.048$] (Table 3). The median (IQR) number of assessments per subject was not different between groups. Univariate analysis revealed that 824 (24.3 %) of the scores in the DSI + PS group indicated oversedation (COMFORT-B <11), versus 998 (25.4 %) of the scores in the PS group ($p = 0.27$). Undersedation (COMFORT-B >22) was more frequent in the DSI + PS group [3.2 % ($n = 107$) vs. 2.4 % ($n = 93$), $p = 0.04$].

All patients were oversedated at some point during the study period, whereas 62 of 129 patients ($n = 34$ patients in the DSI + PS group and 28 in the PS group) were undersedated at some point.

Median SOS scores were comparable between groups (Table 3). Total number of SOS assessments was significantly higher in the PS group (540 vs. 317 scores, $p = 0.001$). In total, 25 patients had a SOS score of ≥4 during the study period ($n = 10$ in the DSI + PS group, $n = 15$ in the PS group, not significant), indicating withdrawal symptoms.

Safety screen

Two-thirds of all safety screens were passed, 198 (65.6 %) of 302 in the DSI + PS group and 261 (73.7 %) of 354 in the PS group. Agitation and cardiorespiratory instability were the main reasons for failing the safety screen (Table 4). Approximately 60 % of the patients passed all safety screens performed (60.6 % in the DSI + PS group and 63.5 % in the PS group).

Discussion

This multicenter randomized controlled trial showed no difference in ventilator-free days and ICU or hospital length of stay for children treated with daily interruption of sedation combined with protocolized sedation compared with children receiving protocolized sedation alone. Additionally, DSI + PS was not associated with the administration of less sedative drugs compared with the use of PS.

These findings contradict those of two earlier studies on DSI in children, in both of which DSI was associated with shorter durations of mechanical ventilation, shorter ICU stays and less use of sedatives [13, 15].

This discrepancy can perhaps be explained as follows. First, we compared DSI in the setting of a protocolized sedation strategy for all patients, the latter being standard of care in the participating PICUs. A nurse-driven sedation protocol is assumed to be beneficial to minimize sedation, although this was recently questioned in a study in critically ill children [6, 21]. The effect of protocolized sedation itself on the clinical endpoints might have outweighed the effect of DSI. This is in line with an adult study in which DSI offered no benefit over a nurse-driven protocol already targeting light sedation [11]. Also, the previous pediatric pilot study used no sedation protocol and patients in the control group were deeply sedated [13], which could explain the beneficial effect of DSI.

Second, there are important differences between the present study and that of Gupta and colleagues which could explain the different study outcomes [15]. In the latter, around 70 % of the patients had neurological illnesses, while we did not include patients with neurological problems. Moreover, mean duration of mechanical ventilation was 10.3 days in the continuous group, versus 5.2 days in our population. Lastly, the daily dose of midazolam was almost twice that in the present study (mean 11.0 vs. 6.1 mg/kg/day in the control groups and mean 7.1 vs. 4.4 mg/kg/day in the DSI groups).

In the present study, cumulative drug doses did not significantly differ between the two groups. The need for intermittent bolus administration in the DSI + PS group counterbalanced the reduction in continuous sedation. However, in nine patients in the DSI + PS group, there was no need to restart sedation. It seems that there are two groups of patients: (1) patients who may not need sedation at all and (2) patients who become agitated after sedation interruption and even need more (bolus) medication to become comfortable again. Therefore, a continuous critical appraisal of the need to continue sedation is warranted. Active tapering of sedation is still needed as this may improve outcome, in particular in the first group.

More reintubations were needed in the PS group. Patients in the DSI + PS group were possibly more alert and therefore extubation may have been more successful, as also demonstrated in adult DSI studies [10]. Overall, around a quarter of the distress assessments indicated oversedation. This is somewhat lower than described in the literature [8], possibly due to the use of a sedation protocol. Judging from the higher number of SOS assessments in the PS group, these patients showed more clinical withdrawal symptoms, although no statistically significant difference was found in the number of scores ≥4, sedative drug doses, and length of exposure to midazolam between the two groups.

This study shows that DSI in children is feasible. Around 60 % of patients passed all safety screens, and DSI was not related to more adverse events, in line with

earlier studies. However, the higher mortality in the first 30 days in the DSI + PS group (9.1 %) compared to the control group was totally unexpected, as also was the absence of mortality in the control group (0 %). Reassuringly, overall 30-day mortality in our total patient cohort (6/129; 4.6 %) was not higher than the reported ICU mortality in the Netherlands [22]. Moreover, an independent DSMB could not identify a causal relationship between the study intervention and cause of death for individual patients. All six patients were seriously ill, with a high mortality risk in advance. Furthermore, the timeframe between active participation in the study and death makes a causal relationship unlikely.

In previously published DSI studies, mortality was never increased. In adult studies, reported ICU mortality was 29.8 % in the DSI group and 31 % in the usual care group (RR 0.96, 0.77–1.21) [23]. Pooled adult data also demonstrated no difference in overall mortality (RR 0.88, 0.75–1.05) and 28-day mortality (RR 0.82, 0.5–1.12) between DSI and control groups [23]. In children, Gupta reported a mortality of 26.1 % in the DSI group and 26.8 % in the control group [15]. Both percentages are higher than our reported mortality due to a different ICU setting and different population, but mortality was not increased in DSI patients. In the pediatric pilot study, all patients survived until PICU discharge [13]. We could not establish a theoretical framework explaining the increased mortality found in our study. Considering all this, and given that meta-analyses of trials had not previously identified an adverse mortality risk with DSI, it is highly unlikely that there is a relationship with DSI. Nevertheless, while our finding may be due to a type I error, we cannot exclude that the increased mortality in our study is due to an unexpected impact of the study protocol.

A limitation of our study is the smaller-than-planned sample size. The planned inclusion of 200 patients was not reached due to slow recruitment rates. The number of eligible patients was lower than expected and around 50 % of parents declined to provide consent [24]. The reasons for these refusals were not recorded, but it is not unreasonable to assume that these parents found the concept of discontinuing drugs given to promote comfort not acceptable, as also suggested in an adult DSI trial with the same consent rate [25]. It would probably take another 2.5 years to finish recruitment of all planned 200 patients. This timeframe was deemed not feasible by the study group, and at this point it was decided to stop the study. The decision was not influenced by interim results as data were still blinded at the time of the decision. Still, we believe our results are valuable. A post hoc power analysis resulted in a power of 62 % with 129 patients, although the expected mean number of ventilator-free days in the sample size calculation was lower than observed in the study, likely due to the selection of relatively more stable patients. Since we did not even find a trend in the number of ventilator-free days or the length of stay between both groups, it is unlikely that we would find a clinically meaningful difference with 200 patients. Furthermore, this study can provide useful data to assist others who might be planning a trial or performing a meta-analysis. Another consideration of the study is that, in the DSI + PS group, 22.8 % of the safety screens were not passed, and for that day sedation was not interrupted. This could have diminished the differences between the two groups. However, this reflects clinical practice and is comparable with adult DSI studies [11]. Furthermore, there may be a Hawthorne effect in the control group [26], as sedation practice was closely monitored in both groups possibly leading to a better adherence to the sedation protocol. A strength of this study is the multicenter design. This reflects actual practice in different PICUs and enhances the generalizability of these findings.

Conclusions

Based on this multicenter study, there is no beneficial effect of daily sedation interruption in addition to protocolized sedation for critically ill children. Daily sedation interruption did not reduce the duration of mechanical ventilation, the length of stay, or the amounts of sedative drugs administered, but was associated with a higher 30-day mortality. Therefore, daily sedation interruption is not the sedation strategy of choice in critically ill children provided protocolized sedation is implemented in the pediatric intensive care.

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On behalf of SKIC study group: Joris Lemson, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; PP Roeleveld, Leiden University Medical Center, Leiden, The Netherlands; Nicolaas JG Jansen, University Medical Center Utrecht, Utrecht, The Netherlands; Martin C Kneyber, University Medical Center Groningen, Groningen, The Netherlands; Dick A van Waardenburg, Maastricht University Medical Center, The Netherlands; Marc van Heerde, VU Medical Center Amsterdam, The Netherlands.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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