

## ORIGINAL ARTICLE

## Randomized controlled trial of daily interruption of sedatives in critically ill children

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### Keywords

children; critical illness; sedatives; interruption; COMFORT score

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### Summary

**Aim:** To study the feasibility of daily interruption of sedatives in critically ill children.

**Methods:** Prospective randomized controlled open-label trial, performed in a pediatric intensive care unit of a tertiary care teaching and referring hospital. 30 children (0–12 years) receiving mechanically ventilation for >24 h were included. In the intervention group, all sedatives were stopped daily and restarted when COMFORT-behavior score  $\geq 17$ . The control group received standard care. Primary end points were amounts of sedatives and number of bolus medications in the first 3 days after enrollment and number of (near) incidents. Secondary end points were duration of mechanical ventilation, length of stay in pediatric intensive care, and changes in COMFORT-behavior score.

**Results:** Midazolam and morphine use were lower in the intervention group compared with the control group ( $P = 0.007$  and  $P = 0.02$ , respectively), whereas the number of bolus medications did not differ between groups. Two complications were recorded: one patient (intervention group) lost his intravenous line, and one patient (control group) had an unplanned extubation. Duration of mechanical ventilation was significantly shorter in the intervention group compared with the control group (median [interquartile range] of 4 [3–8] and 9 [4–10] days, respectively,  $P = 0.03$ ). Length of stay in the PICU in the intervention group was significantly shorter than in the control group (median [interquartile range] of 6 [4–9] and 10 [7–15] days, respectively,  $P = 0.01$ ).

**Conclusions:** Daily interruption of sedatives in critically ill children is feasible, results in decreased use of sedation, earlier extubation, and shorter length of stay.

### Introduction

Critically ill children often need analgo-sedation to relieve them from anxiety and discomfort and to facilitate their intensive care (1). Continuous sedation in children induces tolerance but may also lead to accumulation of sedatives, prolonged coma, prolonged intubation time, and withdrawal syndrome in up to 57% of cases after discontinuation of sedatives (2–4).

In adult intensive care unit (ICU) patients, daily interruption of sedative infusion accelerates recovery and

results in reduction in the duration of mechanical ventilation and ICU length of stay, without an increase in adverse events (5–7).

It is unknown whether adult studies can be extrapolated to critically ill children. The possible risk of complications associated with less sedation, such as accidental self-extubations, is probably higher in children than in adults (8) and the need for intermittent bolus administrations in children treated with intermittent sedation could nullify the reduction in the use of continuous sedatives. On the other hand, interruption of

sedatives could be more beneficial to children because due to a lower renal and hepatic clearance. Young children are prone to accumulation of sedatives, especially if sedatives are given for a longer period of time (9).

Hence, it is unknown if daily interruption of sedatives is feasible in critically ill children. One study on daily interruption in children has been published, showing positive results on clinically relevant parameters such as length of mechanical ventilation, length of stay in the pediatric intensive care unit (PICU) and use of midazolam (10). However, the population, reported mortality, and days on the ventilator described in this study differ from the European and North-American setting, which might preclude extrapolation of these results (11). The aim of the present study was to determine the feasibility of daily interruption of sedatives in critically ill children and its effects on the total amount of sedatives used.

## Methods

The study protocol was approved by the Ethics Committee of the Radboud University Nijmegen Medical Centre and complies with the Declaration of Helsinki including current revisions and the Good Clinical Practice guidelines. Both parents signed written informed consent before participation in the study. Trial registration: Clinicaltrials.gov on NCT00441506.

The study was performed in a medical/surgical subunit of a 13-bed academic PICU. Patients aged 0–12 years that were intubated and received mechanical ventilation were included in the study when ventilated for 24 h and expected to need mechanical ventilation for more than 48 h from the time of inclusion. All patients received midazolam and morphine for sedation and analgesia. The combination of midazolam and morphine will henceforth be referred to as the infusion of sedative drugs.

Exclusion criteria were participation in another trial, inability to evaluate the level of sedation (e.g., because of use of neuromuscular blocking agents, neuromuscular disease, encephalopathy, epilepsy), contra-indications to arousal (e.g., pulmonary hypertension, neurotrauma, raised intracranial pressure) and life expectancy less than a month. Baseline demographic data, commonly used severity of illness scores in pediatric intensive care and the reason for admission to the intensive care unit, were recorded.

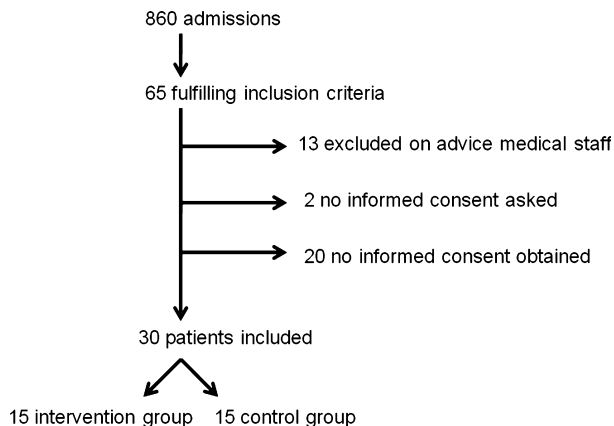
After enrollment in the study, patients were randomly assigned by blinded envelopes to the intervention group or the control group. In the intervention group, all sedatives were stopped daily at 1 : 00 PM, because this is a relatively quiet part of the day usually without interventions such as physical examinations, clinical rounds. In the control group, patients received standard of care. At

the time of the study, no institutional protocol for sedation in children was used. Standard sedation consisted of midazolam and morphine. The amounts were prescribed on clinical judgment of the doctors. Maximum dose of midazolam was  $0.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ; maximum dose of morphine was  $30 \text{ mcg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ . Additional sedatives were given when patients were uncomfortable despite maximum dose of midazolam and morphine. Patient consciousness was monitored using the COMFORT-B score, a modification of the original COMFORT score, varying between 6 and 30 (12–15). COMFORT-B scoring was frequently performed (especially shortly after interruption of sedatives in the intervention group) to avoid potential complications related to a decrease in sedation. In the intervention group, the COMFORT-B score was assessed every 30 min from 1 PM until 4 PM, every hour from 4 PM until 6 PM, and every 2 h from 6 PM until 1 PM the next day. If the COMFORT-B score was  $\geq 17$ , sedatives were restarted at the infusion rate used before. In the control group, the COMFORT-B score was assessed 5 times per day. If signs of agitation were observed, bolus amounts of sedatives were administered and sedatives were restarted (intervention group) or increased (control group). These bolus amounts were included in the analysis of the total amounts of sedatives used (Supporting information: Data S1. DOC Cop Report, part 1).

The study period was ended upon planned or unplanned extubation, withdrawal of informed consent from the parents, or administration of a paralytic agent.

The primary endpoints were total amounts of administered sedatives for each medication in  $\text{mg}\cdot\text{kg}^{-1}$  in the first 3 days after inclusion, the number of intermittent bolus administrations during the first 3 days, and (near) incidents (e.g., accidental extubations, removal of intravenous lines) during the entire study period. Based on the median length of mechanical ventilation in our unit, the period during which the amount of sedatives was measured was restricted to the first 3 days of the study to limit the possible imbalance of patients with an ICU length of stay of  $>3$  days between the groups. Because the study groups were relatively small and baseline-differences in use of sedatives could influence outcome, the % change in sedative use was compared with the time of inclusion. Secondary endpoints were duration of mechanical ventilation, length of stay in the intensive care unit and changes in COMFORT-B score. In the intervention group, time-interval between interruption of sedatives and arousal of patients was measured ( $=\text{COMFORT-B score} \geq 17$ ).

Average midazolam use was  $0.2 \pm 0.05 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  in our unit. We considered a reduction of 25% clinically relevant. With an alpha of 0.05 and a power of 75–80%,



**Figure 1** Flowchart of patients.

15 subjects per group would be needed. Data were analyzed on an intention-to-treat basis. All patients were followed until discharge from the PICU. With regard to the small sample size, normality was not assumed; therefore, data are expressed as median (interquartile range) unless specified otherwise. Continuous data were analyzed with Mann–Whitney U-tests. Categorical data were analyzed by Fisher's exact test. Kaplan–Meier survival analysis was used to assess the effects of daily interruption of sedation on length of mechanical ventilation and length of stay in the PICU. *P*-values in Kaplan–Meier analyses were calculated by Log-Rank test. A two-sided *P*-value of  $< 0.05$  was considered statistically significant. Analyses were performed using GRAPHPAD PRISM 5.0 (Graphpad Software, San Diego, CA, USA).

## Results

Between November 2004 and October 2006, 65 patients of 860 admitted to the PICU fulfilled inclusion criteria. A total of 35 patients were excluded, of which 13 by the medical staff for other reasons than exclusion criteria (Figure 1). Reasons for exclusion were mainly based on safety (eight patients with a difficult upper airway with fear of loss of endotracheal tube and one patient with circulatory instability). In three patients, informed consent was not asked because it was presumed that this would be too demanding for the parents, and in one patient informed consent was not asked because of a semi-emergent surgical procedure.

A total of 30 patients were enrolled in the study. 15 Patients were randomly assigned to the intervention group and 15 to the control group. The demographic characteristics, PIM and PRISM scores were similar in both groups (Table 1). Diagnoses on admission are shown in Table 1.

**Table 1** Baseline characteristics

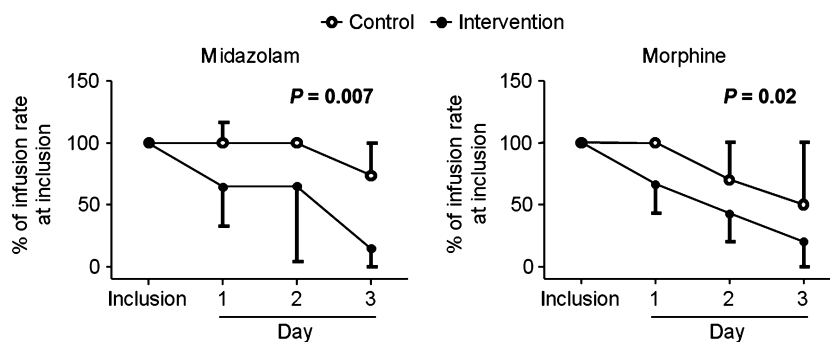
	Control ( <i>n</i> = 15)	Intervention ( <i>n</i> = 15)	<i>P</i> -value
Sex (% male)	40	73	0.14
Age (months)	2 (0–35)	1 (0–14)	0.67
Weight (kg)	6 (5–16)	5 (3–7)	0.15
PRISM	13 (10–18)	16 (9–23)	0.39
Predicted mortality PRISM (in %)	11 (6–26)	19 (5–44)	0.30
PIM	−2.6 (−3.4 to −1.4)	−2.5 (−3.0 to −1.7)	0.80
Predicted mortality PIM (in %)	7 (3–19)	7 (5–16)	0.80
Diagnosis on admission (no)			
Bronchiolitis	7	9	
Pneumonia	2	2	
Status asthmaticus	0	1	
Septic shock	2	0	
Meningitis	0	1	
Cancer	2	0	
Cardiomyopathy	1	0	
Postoperative	1	2	

Data represented as median (interquartile range). *P*-values calculated by Fisher exact (sex) and Mann–Whitney *U*-tests.

Baseline use of midazolam and morphine was not significantly different between groups (midazolam: control group 0.20 [0.10–0.28] mg·kg<sup>−1</sup>·h<sup>−1</sup>, intervention group 0.12 [0.10–0.20] mg·kg<sup>−1</sup>·h<sup>−1</sup>, *P* = 0.15; morphine: control group 0.010 [0.008–0.020] mg·kg<sup>−1</sup>·h<sup>−1</sup>, intervention group 0.009 [0.007–0.011] mg·kg<sup>−1</sup>·h<sup>−1</sup>, *P* = 0.13). The use of both sedatives decreased in the first 3 days after enrollment in the study in both groups, most likely due to improvement in the majority of the patients. However, the decrease in the intervention group was significantly more pronounced (midazolam *P* = 0.007 and morphine, *P* = 0.002, Figure 2).

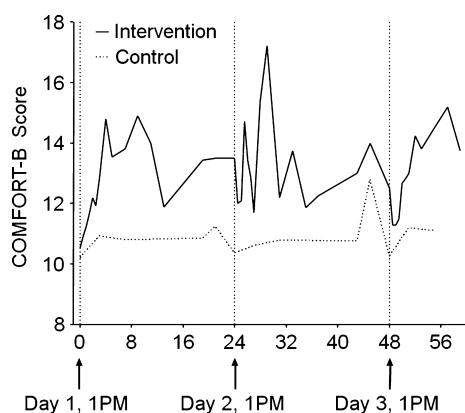
The total number of intermittent boluses of sedation administered to all patients in the first 3 days after enrollment was 35 in the control group and 29 in the intervention group. The number of bolus administrations per patient did not differ between the two groups (control group 1 [0–4], intervention group 1 [0–3], *P* = 0.98). No differences in incidents were found between the groups. One patient in the intervention group removed a peripheral intravenous infusion line, and one patient in the control group had an accidental extubation.

COMFORT-B scores during the first 3 days after enrollment are shown in Figure 3. Baseline COMFORT-B scores did not differ between the two study-groups. Scores in the control group were relatively stable, whereas those in the intervention group showed more variation and remained above those of the control group throughout the first 3 days after enrollment. Time



**Figure 2** Use of midazolam and morphine first 3 days after inclusion. Data are represented as median % increase/decrease compared to the

infusion rate at day of inclusion. *P*-values indicate comparison between area under the curve of both groups (Mann-Whitney *U* tests).



**Figure 3** COMFORT scores during first 3 days after inclusion. Data are represented as medians. X-axis indicates hours after first interruption of sedatives in intervention group.

interval between interruption of the sedatives and arousal (COMFORT-B score >17) in the intervention group showed considerable variation (day 1: 8 [4–12] h; day 2: 5 [1–8] h; day 3: 6 [2–12] h).

After randomization, participation was stopped in two patients in the intervention group because of persistent agitation (on days 3 and 6, respectively). In the control group, the study was stopped in one patient on day 2 because of the administration of neuromuscular blockers.

In the intervention group, both days on ventilator and time until discharge from the PICU were significantly shorter compared with the control group (Table 2, Figure 4).

All patients survived until PICU discharge. After 1 year of follow-up, two patients had died, one from the intervention group and one from the control group. Both patients suffered of a lethal disorder.

**Discussion**

In the present study, we demonstrate that daily interruption of sedation in children is feasible, results in decreased

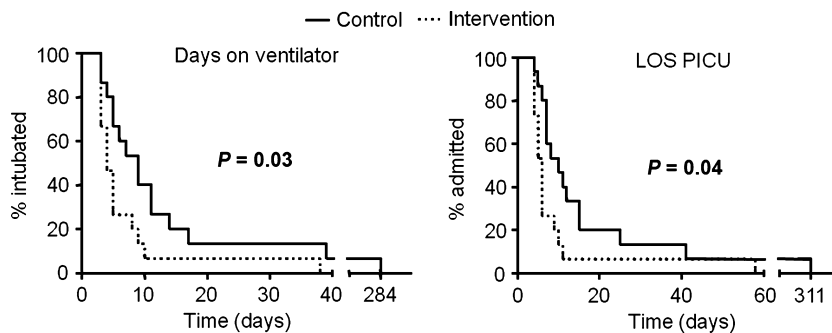
**Table 2** Ventilator days, length of stay

	Control ( <i>n</i> = 15)	Intervention ( <i>n</i> = 15)	<i>P</i> -value
Ventilator days	9 (5–14)	4 (3–8)	0.03
Length of stay	10 (7–15)	6 (4–9)	0.02

Ventilator days and length of stay in days from day of inclusion. Data represented as median (interquartile range). *P*-values calculated by Mann-Whitney *U*-tests.

use of sedatives, shorter length of mechanical ventilation, and shorter length of stay in the PICU. These beneficial effects were not associated with an increase in (near) incidents or complications in our group of patients. Time interval between interruption of the sedatives and arousal varies considerably, illustrating the need for intense monitoring of the level of sedation (Supporting information: Data S2. DOC Cop report, part 2).

There are only a few studies evaluating the effects of daily interruption of sedatives in children. In adults, however, it was shown to have beneficial effects (5–7). In the study of Kress *et al.*, 128 adult patients were randomly assigned to daily interruption or continuous sedation, and comparable beneficial effects were found compared with the present study. Similar to our study, dosage of sedatives in the continuous sedation (control) group was left to the discretion of the ICU team. A nurse-driven sedation protocol might prevent oversedation and have positive effects on length of mechanical ventilation. Presently, we have a nurse-driven sedation protocol in our institution, in which sedation is decreased when COMFORT-B scores decreases below 11. In a recent multicenter study of Mehta, daily sedation interruption combined with protocolized sedation was combined with protocolized sedation alone (16). In this adult study, no beneficial effect was seen of daily interruption. However, daily interruption was associated with higher doses of sedatives and higher nurse workload. This suggests that, in adults, daily interruption and protocol-based decreasing of sedatives have similar effects on clinical endpoints.



**Figure 4** Kaplan Meijer curves of days on ventilator and length of stay (LOS) in PICU. *P*-values calculated using log rank tests.

Recently, Gupta *et al.* showed that in a pediatric group, interruption of sedation leads to shorter duration of mechanical ventilation, shorter length of stay in PICU, and reduction in dose of midazolam (10). However, important differences between this and our study related to the studied population and clinical practice appear to be present (11). First, mortality was 26.5% compared with no PICU mortality in our study. Second, the case mix of the study was different to that of the present study; around 70% of the patients had neurological problems, while in our study, we only included one patient with a neurological problem. Third, although patients with high inspiratory peak pressures were excluded from the study, the rate of complications such as pneumothorax was relatively high (12%). Fourth, the dose of midazolam used was very high, roughly equalling 2–4 times the midazolam dose used in the present study. With regard to these differences, we and others believe that the data obtained in this previous study, although promising, cannot be readily extrapolated to the European/North-American setting. Nevertheless, our results confirm the results obtained in this study with regard to several endpoints, such as use of midazolam, length of mechanical ventilation and length of stay in the PICU, thereby affirming the beneficial effects of daily interruption of sedation in critically ill children in our setting.

In our study, 13 patients were excluded by the medical staff for reasons not mentioned in the exclusion criteria. Although upper respiratory problems were not part of the exclusion criteria, in practice the medical staff decided to exclude some patients with a difficult airway because of fear of accidental extubation. Because these patients were excluded before randomization, it did not influence our results. As in the Gupta study, daily interruption of sedation did not result in an increase in incidents in our study. One other study, in which sedation was discontinued in 20 neonates on ECMO, showed no accidental extubations, decannulations or bleeding

complications, corroborating results from our study (17). Nevertheless, we emphasize that complications with a low incidence might be missed in our relatively small study. Furthermore, we would like to stress the importance of frequent monitoring of the level of sedation. In some patients, a sudden rise in COMFORT-B score occurred. Those patients might be at risk of complications, such as accidental extubations or unwanted removal of lines. Frequent monitoring is warranted to prevent such incidents.

We found considerable interindividual differences between the patients in the ability to tolerate interruption of sedatives. Many factors can influence the need of sedatives in children, such as age, changes in volume of distribution, hepatic and renal function, inflammation, and concomitant administration of CYP3A inhibitors, suggesting that there may be no straightforward relation between concentrations of midazolam and its sedative effects (9,18,19).

An important limitation of this study is its small group size. Therefore, interindividual differences in patient characteristics could have a relatively large impact on the results. Nevertheless, patients were randomized, and more complex patients were found in both groups. The small group size also precludes proper assessment of the safety of daily interruption of sedation in critically ill children. Both groups consisted of relatively young children, and results from this study might not be extrapolatable to older children. Another limitation of this study is its open label design. Furthermore, a relatively deep sedation of the control group in our study (median COMFORT-B scores between 10 and 11) could have biased our results. Finally, no pharmacokinetic analyses were performed to combine these data with clinical outcomes. Currently, a larger multicentre trial of daily interruption combined with protocolized sedation vs protocolized sedation is being undertaken in the Netherlands, in which both clinical and pharmacoki-



netic data will be investigated, including safety aspects (Supporting information: Data S3. DOC Cop Report, part 3).

## Conclusion

Daily interruption of sedatives in critically ill children is feasible, appears to be safe, leads to a reduction in the use of sedatives, higher level of consciousness, shorter duration of mechanical ventilation, and shorter length of stay in the PICU.

## Disclosure/Acknowledgments

We are indebted to the parents of the children and to the nurses and doctors in the pediatric intensive care

unit at the Radboud University Nijmegen Medical Centre for making this study possible. This research was carried out without funding.

## Conflict of interest

No conflicts of interest declared.

## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Data S1.** DOC Cop Report (part 1).

**Data S2.** DOC Cop Report (part 2).

**Data S3.** DOC Cop Report (part 3).

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