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Original Article

Continuous sedation *vs.* daily sedation interruption in mechanically-ventilated children

Henri Azis[1], Silvia Triratna[1], Erial Bahar[2]

Abstract

Background A daily sedation interruption (DSI) protocol in ventilated patientsis an effective method of improving sedation management that decreases the duration of mechanical ventilation. In adult patients, it is a safe and effective approach, as well as common practice. For ventilated children,its effectiveness and feasibilityare unknown.

Objective To compare continuous sedation and DSI in mechanically-ventilated children with respect todurationof mechanical ventilation, the time needed for patients to awaken, and the frequency of adverse events.

Method This randomized, controlled, open-label trial, was performed in a pediatric intensive care unit (PICU). Forty children on mechanical ventilation were included. Patients were randomly assigned to receive either continuous sedation or DSI. The duration of mechanical ventilation was the primary outcome, while the time for patients to awaken on sedative infusion and the frequency of adverse events were secondary outcomes.

Results Forty patients were randomized into the continuous sedation protocol (18 subjects) or into the DSI protocol (22 subjects). The median (interquartile range) duration of mechanical ventilation was significantly shorter in the DSI compared to the continuous sedation group [41.50 (30-96) hours *vs.* 61 (30-132) hours, respectively; (P=0.033)]. The time for patients to awaken was also significantly lower in the DSI than in the continuous sedation group [median (interquartile range): 28 (24-78) *vs.* 45.5 (25-12) hours, respectively; (P=0.003)]. The frequencies of adverse events were similar in both groups. The severity of illness contributed to outcome variables.

Conclusion The duration of mechanical ventilation and the time for patients to awaken are significantly reduced in the DSI group compared to the continuous sedation group. **[Paediatr Indones. 2016;56:19-23.]**.

Keywords: *continuous sedation, daily sedation interruption*

Ventilated children are often sedated in order to prevent discomfort or anxiety and to facilitate treatment.[1] Doses are individually titrated, based on sedation assessments, to reach the optimal level of sedation. Both inadequate and excessive sedation may have deleterious effects. Over-sedation delays recovery, promotes tolerance, increases the duration of mechanical ventilation, and leads to distressing symptoms upon withdrawal of the drugs.[2] Under-sedation may result in increased distress and increased adverse events such as unplanned extubation, accidental displacement of catheters, and fighting the ventilator.[3,4] In adults, daily sedation interruption (DSI) protocol is an effective and safe method to decrease the duration of mechanical ventilation.[5] However, the effectiveness and the feasibility of DSI for children has not been well-studied.[6] There have been few randomized controlled trials addressing this issue, and those that are available pertain to adult ICU patients.[2,5,7] Data from adult ICU studies cannot necessarily be extrapolated to children.[7]

From the Department of Child Health[1] and Department of Public Health[2], Sriwijaya University Medical School/Dr. Mohammad Hoesin Hospital, Palembang.

Reprint requests to: dr. Henri Azis, Department of Child Health, Sriwijaya University Medical School/Dr. Mohammad Hoesin Hospital, Jl. Jendral Sudirman KM 3.5, Palembang, Indonesia. Phone. +62-85279000252. Email: dr.ajes@yahoo.co.id.

The DSI improves clinical outcomes and results in a significant decrease in the duration of mechanical ventilation.[5-7] The objective of this study,therefore,was to compare DSI to continuous administration of sedative infusion in mechanically-ventilated children, with respect to the duration of mechanical ventilation, the time for patients to awaken on mechanical ventilation, and the frequency of adverse events.

Methods

The study was a randomized, controlled trial conducted in the PICU of Mohammad Hoesin Hospital between March and May 2015. Children aged 1 month to 18 years, admitted to the PICU,required mechanical ventilation for an expected duration of at least 24 hours, and needed sedative drugs were included. We excluded patients in which we anticipated death to occur within 24 hours or who were scheduled for withdrawal of life support, patients whose level of sedation could not be scored due to underlying neurologic condition, patients who had experienced cardiopulmonary resuscitation, patients who used continuous sedatives for seizure therapy, and patients who were admitted to our PICU after previously having used mechanical ventilation or sedative drugs.

Patients were randomly assigned into one of two groups after 24 hours of intubation. Group A was the continuous sedative protocol (control) group and group B was the DSI protocol (intervention) group. Intravenous midazolam was first given as a 0.2-0.3 mg/kg bolus over 2-3 minutes, followed by infusion at 0.1 mg/kg/hour, and increased to 0.3 mg/kg/hour titration to achieve a COMFORT pain scale score of 11-22.[8] Group A continued to receive the above protocol until interruption was done at 4-6 hours before the planned weaning from mechanical ventilation. For group B patients, after the first 24 hours of mechanical ventilation, the sedative infusion was discontinued. During the interruption, some patients woke up, and were therefore, monitored frequently. Patient comfort was routinely assessed every 2 hours using the COMFORT score and at any time patients appeared distressed. The COMFORT score was also used to assess the level of sedation/wakefulness. The sedative infusion was started again if the patient became uncomfortable or agitated, according to the COMFORT score. After a loading dose of midazolam (0.1 mg/kg, intravenously), the sedative infusion was restarted at half the previous dose, then titrated according to the sedation protocol to achieve adequate sedation.

The primary outcome of this study was to measure total duration of mechanical ventilation, while secondary outcomes were the time for patients to awaken on mechanical ventilation and the frequency of adverse events. Assuming a failure rate of 20% in both groups, with an α error of 5% and power of 80%, we calculated that a minimum of 32 subjects were required in each group. We used interim data analysis in which analysis of data was conducted before data collection had been completed. This design feature reduced study participants' exposure to inferior treatment and saved time and resources. The interim analysis was conducted every end of the month, after data was collected.

This study was approved by the Committee of Medical Research Ethics at the Sriwijaya University Medical School. Subjects' parents provided informed consent. Demographic and clinical characteristics were described using standard statistical analysis methods. Descriptive data were presented as percentages, mean (SD) for normally distributed variables, and median (interquartile range) for non-normally distributed variables. The two study groups (continuous sedative *vs.* DSI) were compared using independent T-test or Mann Whitney U test. All tests were two-tailed and P values < 0.05 wereconsidered to be statistically significant.

Results

Forty patients were randomized into two groups, 18 children in the continuous sedation group (group A) and 22 in the DSI group (group B). Both the groups were matched with respect to age, sex, primary diagnosis, severity of illness (PELOD scores), and initial ventilation variables (**Table 1**).

The duration of mechanical ventilation and the time for patients to awakening the continuous group were significantly longer compared to the DSI group. The number of patients who developed adverse events were similar in both groups. Three patients developed

hypotension, one in Group A and two in group B. A total of four episodes of spontaneous extubation were recorded, two in each group. Two episodes of accidental removal of medical equipment were noted, one in each group (**Table 2**). Linear regression analysis revealed that the severity of the disease (PELOD score) contributed to the duration of mechanical ventilation and the time for patients to awaken.

in concordance with a previous study which showed that DSI improved outcomes in pediatric patients. The length of mechanical ventilation was significantly reduced in the interrupted sedation group compared to the continuous sedation group (10.3 *vs.* 7.1 days, respectively; P=0.021).[9] Other studies in adult patients also showed significant reductions in the lengths of ventilation and ICU stay. Kress *et al.* demonstrated a

Table 1. Baseline characteristics of study subjects

Characteristics	Group A (n = 18)	Group B (n = 22)
Median age, months(interquartile range)	54.5 (2-184)	12 (1-168)
Gender, n		
Male	13	16
Female	5	6
Nutritional status, n		
Good nutrition	9	13
Malnourished	9	9
Severity of illness		
Median PELOD(interquartile range)	11(2-31)	11(2-31)
Underlying disease, n		
Neurology	10	11
Respiratory	2	6
Non neurology-respiratory	6	5
Ventilator parameters		
Pressure control mode		
Median PEEP (range), mmHg	5 (5-6)	5 (5-6)
Median PIP (range), mmHg	16 (15-20)	16 (15-21)
Median FiO_2 (range),%	60 (50-85)	60 (50-90)
Volume control mode		
Median PEEP (range), mmHg	5 (5-60)	5 (5-6)
Median tidal volume (range), mL	112 (72-350)	150 (72-300)
Median FiO_2 (range), %	60 (50-85)	60 (55-85)

PEEP=positive end-expiratory pressure, PIP=peak inspiratory pressure , FiO2=fraction of inspired oxygen

Table 2. Continuous *vs.* DSI protocol: primary and secondary outcomes

Variables	Continuous (n=18)	DSI (n=22)	P value
Median length of mechanical ventilation, hours (interquartile range)	61 (30-132)	41.50 (30-96)	0.033
Median time for patients to awaken, hours (interquartile range)	45.5 (25-121)	28 (24-78)	0.003
Adverse events, n			
Spontaneous extubation	2	2	
Hypotension	1	2	0.973
Accidental removal of medical equipment	1	1	

Discussion

We found that the duration of mechanical ventilation was significantly reduced in the DSI protocol compared to the continuous sedation protocol. Our findings were

decrease in the median ICU length of stay to 3.5 days in the interrupted sedation group, while Brook *et al.* found that protocol-based sedation was better as it showed a reduction in the length of ICU stay from 19.9 (SD 24.2) to 14.0 (SD 17.3) days (P=0.01).[10,11] In patients who

underwent coronary artery bypass grafting, Another study demonstrated a reduced ICU stay in patients with the modified sedation protocol, compared to the conventional sedation protocol.[12] However, it should be noted that most of these studies were in adults.

In our study, the time for patients to awaken was significantly longer in the continuous group compared to the DSI group. Gupta *et al*. reported that the percentage of days a patient was awake in the continuous group was significantly lower compared to that in the interrupted sedation group [61%; 95%CI 50.8 to 71.32% *vs.* 78.8%; 95%CI 73.0 to 84.5%, respectively; (P=0.005)].[9] Kress *et al*. also showed that the percentage of days during which the patients were awake while receiving a sedative infusion was greater in the interrupted sedation group than in the continuous sedation group [85.5% *vs.* 9.0%, respectively; (P<0.001)].[10] They also found that stopping the sedative infusion for a stipulated time during the day in the interrupted sedation protocol helped the clinician to neurologically assess patients.

The frequencies of adverse events were similar in both groups. The overall frequency for accidental extubation was 10%, similar to a previous study thatreported an accidental extubation rate of 3-13% for both neonates and children.[13] Another study also reported spontaneous extubations in three (4%) and four (7%) of the adult patients with interrupted and continuous sedation, respectively (P=0.88).[10]

Sedation is an integral part of intensive care, especially in children receiving mechanical ventilation.[13] Sedatives reduce the stress response, act as anxiolytics, improve tolerance to ventilator support, and facilitate nursing care.[14-16] Unfortunately, sedation has the potential to prolong mechanical ventilation. Hence, protocols aimed at minimizing the complications of cumulative sedation have been developed.[15,16] In this regard, daily interruption of sedative infusions was found to be a better option, as it reduced the duration of mechanical ventilation.[17-19] The length of mechanical ventilation is an important determinant of outcomes in ventilated patients.[2,9,17]

In conclusion, the duration of mechanical ventilation and time for patients to awaken are significantly reduced in the DSI group compared to the continuous sedation group. The frequencies of adverse events are similar in both groups. The DSI protocol minimizes the complications from cumulative sedation, without an increase in adverse events or other complications.

Conflict of interest

None declared.

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