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Does daily interruption of sedation do better than continuous sedation in ventilated children with respect to lengths of mechanical ventilation and intensive care unit stay? Critical appraisal as per the CONSORT 2010 checklist of information of an article Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. Gupta K, Gupta VK, Jayashree M, Singhi S. *Pediatr Crit Care Med*. 2012;13:131–5

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ABSTRACT

Question: To compare daily interrupted vs. continuous administration of sedative infusions in mechanically ventilated children with respect to the lengths of mechanical ventilation (MV) and intensive care unit (ICU) stay, number and percentages of day awake on MV, frequency of adverse events and dose and cost of midazolam required.

Methods: This was a prospective randomized controlled trial (RCT), conducted in the pediatric intensive care unit (PICU) of a referral and teaching hospital in North India. Included in the study were 102 patients, mechanically ventilated for >48 h from Jan, 2007 to December, 2007, including 32 patients from a pilot study, in the same unit with exactly the same methodology from June, 2004 to July, 2005. Patients who required peak inspiratory pressure (PIP) >28 mm Hg, were excluded from the study. The Institute's Ethics Committee approval and informed written consent from the parents were obtained. The patients were randomized into two groups, Group I: Continuous infusion of sedative protocol; Continued to same protocol with interruption as per the advice of the treating team. Group II: Daily interruption of sedative infusion protocol at 8.00 AM. Intravenous midazolam was given as 0.1–0.3 mg/kg bolus followed by infusion of 0.1–0.3 mg/kg/h, titrated to achieve Ramsay score of 3–4; in combination with morphine infusion by 0.01–0.03 mg/kg/h. Interruption was continued until the patient become fully awake or become agitated or uncomfortable to restart infusion again. Wakefulness was assessed as respond to verbal commands. A percentage of days out of total no of days on sedative infusion, on which the patient was awake, were recorded. Randomization by stratification was done at 48 h of ventilation, by faculty member not directly involved in the

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study, using computer generated numbers, to distribute patients with neuromuscular illness into both groups evenly. Participants and those administering the interventions were not blinded. Sample size was calculated assuming a failure rate of 30% in Group I; Failure rate of 10% in Group II; α error of 5%; power of 80%; 47 subjects were recruited in each group.

Main results: Of the 102 patients included in the study, 56 were randomized into the Group I and 46 into the Group II. Both the groups were similar except that the Group II had lower PIP and positive end expiratory pressure (PEEP) requirement at the start of ventilation. The mean length of MV between the Group I and II was 10.3 ± 8.4 vs. 7.0 ± 4.8 days ($p = 0.021$). The median length of PICU stay between the Group I and II was 14 vs. 10.7 days ($p = 0.048$). The mean total dose and total calculated cost of midazolam were significantly lesser in Group II compared to Group I ($p = 0.002$ & 0.020 respectively) (Table 1).

Conclusion: The length of MV, ICU stay, total dose and cost of midazolam were significantly lesser in interrupted as compared to continuous group of sedation. This article was critically appraised as per the CONSORT 2010 checklist of information.

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1. Commentary

This is probably the first study conducted in children in the Northern India concluding the efficacy of intermittent sedation in developing country setup, thus improving the ICU outcome with reduced financial constraints to the family. However there were few limitations of the study which should be considered while planning for further study. Therefore the article was critically appraised as per the CONSORT 2010 checklist of information.¹ Present article is identified as a randomized trial in the title. Scientific background and explanation of rationale were appropriate. Objectives were specific. However there was no description of trial design including allocation ratio. Whether any changes in method were done after trial commencement has not been mentioned. Eligibility criteria for participants were defined, but there was no description of PICU unit and formal protocol to be followed in the PICU. The interventions for each group with sufficient details to allow replication were explained but the number of patients who required interruption of sedation in Group I was not mentioned. These patients were further continued in Group I or they were excluded from Group I is not clear. Probably the word

limit had restricted the authors to explain the all these details. Primary and secondary outcomes were completely defined. Definition of term “Failure rate” for sample size calculation was not explained. Calculated sample size of 47, mentioned in the article is for one tailed test of significance, while considering two tailed test of significance sample size would be 62 in each group. There was no explanation of any interim analyses and stopping guidelines. Randomization and sequence generation were explained properly. Both the participants and those administering the interventions were not blinded, however allocation was kept in the sealed numbered envelope to conceal the sequence. Statistical methods were defined adequately, but the criteria for confounders including the coding not defined for regression analysis. There seems to be overlapping between the confounders (general vs. specific organ illness, respiratory vs. non-respiratory illness and neurological vs. non-neurological illness). The article had no participant flow diagram which is strongly recommended for a RCT article. Moreover registration number including name of trial registry and assess to full trial protocol had not been mentioned. Trial limitations were not addressed in the present article. There are a number of other studies related to this article which should be addressed^{2–5} for further studies. Thus it is concluded that this study provides a platform for further studies which can be conducted as double-blind parallel RCT examining the impact of a routine, daily interruption in sedation vs. standard care or the impact of protocol based sedation in comparison to non-protocol based sedation.

Table 1 – Continuous vs. intermittent sedation – primary and secondary outcomes.

Variables	Group I	Group II	p-Value
Length of MV (mean $\pm$ SD)	10.3 ± 8.4	7.1 ± 4.8	0.021
No of days awake (mean $\pm$ SD)	2.3 ± 4.7	3.3 ± 3.9	0.103
Percentages of days awake (mean $\pm$ SD)	61.1 ± 38	78.8 ± 19.3	0.005
Duration of PICU stay (mean $\pm$ SD)	14.1 ± 9.8	10.7 ± 6.1	0.048
Total dose of midazolam (mean $\pm$ SD)	11.0 ± 6.9	7.1 ± 4.7	0.002
Total cost of midazolam (mean $\pm$ SD)	$13,865 \pm 25,338$	4827 ± 5445	0.020
Adverse events (n, %)	8 (14.3)	6 (13.0)	0.86
Pneumothorax	7 (12.5)	5 (10.9)	0.79
Spontaneous extubation	1 (1.8)	1 (2.2)	0.88

Conflicts of interest

The author has none to declare.

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