

# Prospective multicentre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children: the SLEEPS (Safety profile, Efficacy and Equivalence in Paediatric intensive care Sedation) study

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**Declared competing interests of authors:** none

Published December 2014

DOI: 10.3310/hta18710

## Scientific summary

### The SLEEPS study

Health Technology Assessment 2014; Vol. 18: No. 71

DOI: 10.3310/hta18710

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# Scientific summary

## Background

Seriously ill children admitted to paediatric intensive care for treatment and supportive therapy require both analgesia and sedation as part of their management to maintain comfort and provide pain relief that is associated with invasive procedures, mechanical ventilation and the need to lie relatively still. Sedation is also needed to prevent distress from the presence of unfamiliar personnel and from the high level of background noise, which can disturb sleeping patterns. Undersedation and oversedation are both harmful. Inadequate sedation is unacceptable in a vulnerable child: the child may 'fight' the ventilator leading to ineffective gas exchange, adverse haemodynamic/stress responses, accidental extubation or the loss of invasive access or monitors. In intensive care, agitation and inadequate sedation have been correlated with adverse short- and longer-term outcomes. In contrast, oversedation delays recovery, promotes tolerance to the drugs and leads to distressing symptoms on withdrawal of the drugs: agitation, seizures, hallucinations, psychosis, fever and tachycardia.

## Objectives

To determine whether or not:

- intravenous (i.v.) clonidine can provide equivalent control of sedation in the critically ill child when compared with i.v. midazolam
- clonidine reduces side effects that are associated with sedation practice in intensive care compared with midazolam at clinically appropriate dosing regimens
- there are any benefits on clinical outcomes using clonidine compared with midazolam.

## Methods

**Population:** Children admitted to paediatric intensive care units (PICUs), who are likely to require intubation and ventilation.

**Setting:** Ten PICUs across the UK.

### Inclusion criteria:

- (a) children aged 30 days to 15 years, inclusive
- (b) admitted to PICU, ventilated and likely to require ventilation for > 12 hours
- (c) recruitment within 120 hours of arrival in the PICU/intensive care unit
- (d) child is  $\leq 50$  kg in weight
- (e) able to perform a COMFORT score on the child
- (f) adequately sedated: COMFORT score within the range of  $\geq 17$  and  $\leq 26$
- (g) fully informed written proxy consent.

**Exclusion criteria:**

- (a) those patients with open chests following cardiac surgery
- (b) those patients chronically treated for raised blood pressure (BP)
- (c) current treatment with beta-blockers (if patients have not received beta-blockers for 24 hours prior to entry into the trial then they are eligible to participate)
- (d) acute traumatic brain injury
- (e) status epilepticus or active fitting (two or more seizures regularly on a daily basis)
- (f) those patients requiring haemodialysis or haemofiltration
- (g) those patients requiring extracorporeal membrane oxygenation treatment
- (h) those patients with severe neuromuscular problems/impairment on whom you cannot perform a COMFORT score
- (i) known allergy to either of the trial medications (clonidine, midazolam or morphine)
- (j) current treatment with continuous or intermittent muscle relaxants
- (k) those patients known to be pregnant
- (l) currently participating in a conflicting clinical study or participation in a clinical study involving a medicinal product in the last month
- (m) previously participated in Safety profile, Efficacy and Equivalence in Paediatric intensive care Sedation (SLEEPS) trial.

**Interventions**

A loading dose of clonidine 3 µg/kg or midazolam 200 µg/kg was given over the first hour of treatment. Both treatment groups also received morphine 100 µg/kg over 15 minutes at the outset of the study, followed by an infusion with morphine, commencing at 20 µg/kg/hour. After the 1-hour loading period, the clonidine and midazolam infusions were continued at maintenance doses (1.5 µg/kg/hour clonidine or 100 µg/kg/hour midazolam). Subsequent delivery of clonidine or midazolam were adjusted according to behavioural assessment (COMFORT score). Morphine dose could be increased to a maximum of 60 µg/kg/hour if necessary.

**Outcomes****Primary outcome**

Adequate sedation defined as at least 80% of total evaluated time spent sedated within a COMFORT score in the range of 17–26.

**Secondary outcomes****During study treatment phase**

1. Percentage of time spent adequately sedated.
2. Time to reach the maximum permitted dose of sedation.
3. Time to reach the maximum permitted dose of morphine.
4. Profile in rise of daily cumulative sedative infusion.
5. Profile in rise of daily cumulative morphine infusion.
6. Maximum permitted dose of sedative reached.
7. Maximum permitted dose of morphine reached.
8. Fall in BP judged by clinician to require intervention.
9. Increased inotropic support required in first 12 hours after randomisation.
10. Supplementary analgesia required during sedation.
11. Daily urine output.

12. Treatment failure defined as inadequate sedation after 1 hour of maximum doses of sedative and morphine infusions (determined by a COMFORT score of > 26) or treatment failure defined as three 'events'\* for which rescue medications are needed to re-establish sedation or pain control occurring within any one 12-hour period during trial treatment.
13. Blood biochemistry and urinalysis.
14. Urinary concentration of gamma-glutamyl transpeptidase (Bristol only).\*\*
15. Urinary concentration of alkaline phosphatase (Bristol only).\*\*

\*An 'event' is described as a point when control of sedation is deemed to be acutely lost requiring immediate intervention. The intervention can involve more than one drug given over a short period of time to establish rapid control (within approximately a 30-minute window to allow safe titration if necessary).

\*\*The pharmacokinetic/pharmacodynamic substudy at the Bristol site did not go ahead as planned so these data were not collected.

### Following study treatment phase

1. Time from stopping all sedation to being fully awake (determined by a sustained\* score of 4 on the alertness category of the COMFORT score).
2. Rebound hypertension.
3. Signs of withdrawal measured using an 11-point assessment for abnormal behaviour (to be recorded until 5 days after treatment cessation or until discharge, whichever is soonest).
4. Withdrawal symptoms requiring clinical intervention (to be recorded until 5 days after treatment cessation or until discharge, whichever is soonest).

\*Sustained for 2 hours or more.

### Throughout the duration of study

1. Adverse reactions and serious adverse events (to be recorded until 14 days post-trial treatment cessation).

### Health economics

1. Cost per additional case of adequate sedation (see also separate Statistical Analysis Plan in *Appendix 4* for health economics).

## Results

The study planned to recruit 1000 children. The first patient was randomised on 18 November 2009, and the last patient on 19 May 2012. A total of 10,023 children were screened to enter the trial. Overall, 129 participants were randomised, with 61 of 65 (93.8%) and 59 of 64 (92.2%) contributing data for the primary outcome analysis for clonidine and midazolam, respectively. Therefore, the trial is underpowered due to the substantially smaller sample size.

The Independent Data and Safety Monitoring Committee met in person or by telephone or e-mail on four occasions: initially to agree the Charter and other relevant documentation, and on three subsequent occasions to consider interim data. They saw no reason to recommend early stopping or amendment of the protocol.

The proportion of children who were adequately sedated for  $\geq 80\%$  of the time were 21 of 61 (34.4%) on clonidine, and 18 of 59 (30.5%) on midazolam. The difference in proportions for clonidine–midazolam was 0.04 [95% confidence interval (CI)  $-0.13$  to  $0.21$ ], and with the 95% CI including values outside the range of equivalence ( $-0.15$  to  $0.15$ ), equivalence was not demonstrated. Non-inferiority of clonidine to midazolam was established with the only values outside the equivalence range favouring clonidine. Participants in the midazolam group were sedated for longer than those receiving clonidine (38.25 hours vs. 22.83 hours) and took less time to become fully awake once sedation was stopped (medians 6.22 hours vs. 11.17 hours; hazard ratio 0.64, 95% CI 0.38 to 1.08).

Fewer treatment failures were observed with midazolam: 12/64 (18.8%) on clonidine; 7/61 (11.5%) on midazolam; risk ratio (RR) 1.63, 95% CI (0.69 to 3.88). One child developed significant bradycardia without hypotension 2.58 hours after commencing clonidine. Treatment was stopped and recovery was spontaneous without intervention. Post treatment, only one case of rebound hypertension was observed (clonidine group). There were no discernible differences in the urine analysis or blood biochemistry results, and no differences in the proportions of participants experiencing withdrawal symptoms; however, a higher proportion of participants who were allocated to midazolam required clinical intervention for those symptoms [11/60 (18.3%) clonidine; 16/58 (27.6%) midazolam; RR 0.66, 95% CI 0.34 to 1.31].

The cost-effectiveness analysis suggests that clonidine may be cheaper and more effective than midazolam, although the differences in mean costs and benefits were not statistically significant.

## Conclusions

The SLEEPS study demonstrates that clonidine is a viable alternative to midazolam, without substantial safety issues. Although both drugs can produce withdrawal effects, patients who have been sedated with midazolam may require additional treatment for withdrawal phenomena afterwards. Our trial-based economic evaluation suggests that clonidine is likely to be a cost-effective sedative agent in the PICU in comparison with midazolam (probability of cost-effectiveness exceeds 50%).

Neither drug in combination with morphine at conventional doses can provide ideal sedation. Additional sedation either with more of the same drug or with another agent is needed to maintain patients reliably within the targeted sedation level. The ability to maintain individuals in the tight confines of ideal sedation require both very regular assessment and the ability to provide rescue sedation very rapidly.

### Implications for health care

Clonidine and midazolam have different pharmacological characteristics, requiring the clinician to select them on individual needs and pathologies of the child. Specific attention needs to be taken during the loading and early infusion phase (first 12 hours after onset) when clonidine is used because of its potential to reduce heart rate and BP. Once the drug has been established the drug does not appear to be associated with major cardiovascular side effects. Selection criteria for midazolam and clonidine will be different, based on the individual needs, pathologies of the child in intensive care and expected duration of stay.

### Implications for future research

- The disappointing recruitment rates reflect a reluctance of parents to provide consent when established on a sedation regimen and the reluctance of clinicians to allow sedation to be studied in unstable critically ill children.
- Future studies will require less-exacting protocols, allowing increased patient numbers to provide enhanced recruitment.
- Future study needs to focus on improving clinical effectiveness without introducing further side effects either during or after sedation.

- Research directions should include investigation on routine use of a third agent as a 'sparing drug' to reduce side effects (as has been implemented in the current CloSed Consortium study).
- Efforts to replace morphine with a higher-efficacy opioid, such as fentanyl or alfentanil, may be valuable, combined with encouraging development of a novel high-efficacy sedative agent to replace midazolam.
- Development of techniques that allow earlier extubation and reduce both duration and quantity of sedation such as non-invasive ventilation and fast-track surgery will hasten recovery and discharge from PICU with profound effects of reducing UK NHS costs for PICU stays and increasing PICU bed availability.
- Use of external pilots in two to three centres prior to upscaling to several centres for the main trial may guard against the need for more research and maximise the value of return for research investment.

## Trial registration

This trial is registered as ISRCTN02639863.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 05/515/01. The contractual start date was in May 2009. The draft report began editorial review in August 2013 and was accepted for publication in April 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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