Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit (Review)

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[Intervention Review]

Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2010.
Review content assessed as up-to-date: 8 September 2009.

Citation: Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD002052. DOI: 10.1002/14651858.CD002052.

ABSTRACT

Background

Proper sedation for neonates undergoing uncomfortable procedures may reduce stress and avoid complications. Midazolam is a short acting benzodiazepine that is increasingly used in neonatal intensive care units (NICU). However, its effectiveness as a sedative in neonates has not been systematically evaluated.

Objectives

To determine whether intravenous midazolam infusion is an effective sedative, as evaluated by behavioural and/or physiologic measurements, for critically ill neonates undergoing intensive care and to assess clinically significant short and long-term adverse effects associated with its use.

Search strategy

We performed the literature search according to the Cochrane Neonatal Review Group search strategy. Randomized and quasi-randomized controlled trials of intravenous midazolam use in neonates were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2009), MEDLINE (1985 to 2009), EMBASE (1980 to 2009), CINAHL (1981 to 2009), reference lists of published studies, personal files, and abstracts published in Pediatric Research from 1990 to 2009.

Selection criteria

Randomized and quasi-randomized controlled trials of intravenous midazolam infusion in infants less than or equal to 28 days of age for sedation were selected for review.

Data collection and analysis

Data regarding the primary outcome of level of sedation were abstracted. Secondary outcomes such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), death, length of NICU stay, and adverse effects associated with midazolam were assessed. When appropriate, meta-analyses were performed using relative risk (RR), risk difference (RD), along with their 95% confidence intervals (95% CI) for categorical variables and weighted mean difference (WMD) for continuous variables.

Main results

Three trials were included in the review. Using different sedation scales, each study showed a statistically significantly higher sedation level in the midazolam group compared to the placebo group. However, since none of the sedation scales used have been validated in preterm infants, the effectiveness of midazolam in this population could not be ascertained. One study showed a statistically significant higher incidence of adverse neurologic events (death, grade III-IV IVH, PVL), and meta-analysis of data from two studies showed a statistically significant longer duration of NICU stay in the midazolam group compared to the placebo group.

Authors' conclusions

There are insufficient data to promote the use of intravenous midazolam infusion as a sedative for neonates undergoing intensive care. This review raises concerns about the safety of midazolam in neonates. Further research on the effectiveness and safety of midazolam in neonates is needed.

PLAIN LANGUAGE SUMMARY

Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

There is no evidence to show the benefit of midazolam as a sedative for newborn babies in neonatal intensive care. Newborn babies undergoing uncomfortable procedures in intensive care units may need sedation to reduce stress and avoid complications. It is difficult to measure their pain so sedatives or pain killers are sometimes overlooked for newborn babies. Midazolam is a short acting sedative increasingly used in neonatal intensive care. The review of trials found no evidence to support the use of midazolam as a sedative for neonates undergoing intensive care. Babies receiving midazolam stayed in hospital longer and had more adverse effects. More research is needed to address the safety and effect of midazolam.

BACKGROUND

Description of the condition

Term and preterm infants are capable of perceiving pain and stress (Anand 1987). In the neonatal intensive care unit (NICU), supportive and investigative management of sick infants frequently requires painful and/or uncomfortable procedures. However, since pain and stress are subjective phenomena and are difficult to evaluate in pre-verbal infants, the use of appropriate analgesia and of sedatives is often overlooked by care providers. It has been suggested that responses to pain may compromise clinical conditions (Anand 1992), and that adequate sedation during mechanical ventilation may decrease stress (Quinn 1993) and facilitate effective ventilation so that complications such as pneumothoraces and intraventricular hemorrhages may be prevented (Greenough 1983; Perlman 1985).

Description of the intervention

Benzodiazepines, administered as intravenous infusions or as intravenous boluses, are used to provide sedation, but not analgesia, in many clinical settings. Midazolam is a short acting benzodiazepine that has increasingly been used in the NICU.

How the intervention might work

The Benzodiazepines are a class of sedatives that acts on specific receptors in the central nervous system. These receptors, which are present in the fetus from seven weeks gestation (Hebebrand 1988), potentiate the neuronal inhibitory pathways mediated by gamma-aminobutyric acid (GABA) (Jacqz-Aigrain 1996). The pharmacokinetics of midazolam in neonates have been studied. It is preferred over other benzodiazepines because of its water solubility and rapid clearance (Jacqz-Aigrain 1992). Although its elimination half-life is significantly shorter than that of other benzodiazepines such as diazepam, its elimination is delayed in preterm neonates

compared with older infants and children (Lee 1999). Functional immaturity of the hepatic and renal systems in preterm neonates probably accounts for the slower elimination of midazolam.

Why it is important to do this review

The effectiveness of intravenous midazolam as a sedative in neonates has not been systematically reviewed. Moreover, its safety at the currently recommended dosage in critically ill neonates is not well established.

OBJECTIVES

The primary objective of this review was to assess the effectiveness of intravenous midazolam infusion for sedation, as evaluated by behavioural and/or physiologic measurements of sedation levels, in critically ill neonates in the NICU.

Secondary objectives included:

1. Incidence of intraventricular hemorrhage/periventricular leukomalacia

2. Mortality

3. Occurrence of adverse effects associated with the use of midazolam (hypotension, neurologic abnormalities)

4. Days of ventilation

5. Days of supplemental oxygen use

6. Incidence of pneumothorax

7. Length of NICU stay

8. Long-term neurodevelopmental outcome

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials or quasi-randomized trials in which the use of intravenous midazolam infusion was compared to placebo or other sedatives in neonates undergoing intensive care.

Types of participants

Infants less than or equal to 28 days of age admitted to the NICU and who required sedation for medical interventions.

Types of interventions

Continuous intravenous infusion of midazolam in the dose range of 20 to 60 mcg/kg/hr administered for at least 24 hours for sedation during mechanical ventilation and radiologic investigative procedures.
Studies using a combination of midazolam and an analgesic for neonates undergoing painful procedures were excluded. Studies that investigated the use of intravenous bolus doses of midazolam were excluded, unless the bolus was followed by an infusion. Studies on the use of midazolam as an anesthetic induction agent or as an anticonvulsant were also excluded.

Types of outcome measures

Primary outcomes

Primary outcome was level of sedation, evaluated by:
Behavioural measures: facial actions, excitability, muscle tone, physical movements and respiratory behaviour which may be evaluated by age-appropriate scoring systems; and
Physiologic parameters: changes in heart rate, respiratory rate, blood pressure, oxygen saturation, and plasma cortisol or catecholamine levels, measured at baseline and at regular intervals during midazolam administration.

Secondary outcomes

1. Intraventricular hemorrhage [defined by classification of Papile et al (Papile 1978)]
2. Periventricular leukomalacia (defined as periventricular cysts on brain imaging, but excluding subependymal or choroid plexus cysts)
3. Mortality (death within 28 days of life)
4. Adverse effects associated with use of midazolam: hypotension (significant drop from baseline compared with controls), neurologic abnormalities (epileptiform activities, movement disorders, myoclonus, hypertonia, hypotonia)
5. Days of mechanical ventilation
6. Days of supplemental oxygen use
7. Pneumothorax
8. Days of NICU stay
9. Neurodevelopmental outcome, as evaluated by a validated developmental assessment tool

Search methods for identification of studies

See: Collaborative Review Group Search Strategy.

Electronic searches

Randomized and quasi-randomized controlled trials of intravenous midazolam in infants were identified from the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2009), MEDLINE (from 1985 to September 2009), EMBASE (1980 to 2009) and CINAHL (1980 to 2009) using the MeSH headings: midazolam; infant, newborn. Language restrictions were not imposed. Attempts were made to contact investigators of studies meeting the inclusion criteria to gather additional data for analysis. No attempt was made to identify unpublished studies.

Searching other resources

In addition, bibliographies of articles, personal files, and abstracts published in Pediatric Research from 1990 to 2009 were manually searched. Language restrictions were not imposed. Attempts were made to contact investigators of studies meeting the inclusion criteria to gather additional data for analysis. No attempt was made to identify unpublished studies. Studies involving neonates and older infants and children were excluded if data for neonates could not be extracted.

Clinical trials registries were also searched for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp)

Data collection and analysis

Standard methodology for performing systematic reviews according to the Cochrane Neonatal Review Group was used.

Selection of studies

Studies included in the review were randomized or quasi-randomized controlled trials involving neonates less than or equal to 28 days of age) with a treatment group and a placebo group. Studies reporting outcome measures including physiological, behavioural, and hormonal changes, as well as adverse neurological outcomes were accepted for review

Studies involving neonates and older infants and children were excluded if data for neonates could not be extracted.

The decision to include or exclude a specific study was made independently by two review authors (EN, AT). In case of discrepancies a decision was made by consensus of the three authors (EN, AT, AO).

Data extraction and management

A data collection form was created and the following data were abstracted from the included studies: demographics of the participants, age at enrollment into study, inclusion and exclusion criteria, sample size, treatment and control groups regimens, and outcomes. Data were abstracted by two review authors independently (EN, AT) and differences resolved by consensus.

Assessment of risk of bias in included studies

Quality of the trials included was evaluated using the following criteria: 1) Blinding of randomization; 2) Blinding of intervention 3) Complete follow-up; 4) Blinding of outcome measurement. This information was added to the table 'Characteristics of Included Studies'.

In addition, the following issues were evaluated and entered into the Risk of Bias Table:

1. Sequence generation: Was the allocation sequence adequately generated?
2. Allocation concealment: Was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?
4. Incomplete outcome data: Were incomplete outcome data adequately addressed?
5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?
6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

Measures of treatment effect

Statistical analyses were performed using Review Manager software. Categorical data were analyzed using relative risk (RR), risk difference (RD) and the number needed to treat (NNT). Continuous data were analyzed using weighted mean difference (WMD). The 95% Confidence interval (CI) was reported on all estimates.

Assessment of heterogeneity

We examined heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If we detected statistical heterogeneity, we planned to explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using *post hoc* sub group analyses.

Data synthesis

When there were at least two randomized controlled trials that evaluated the effectiveness of intravenous midazolam infusions using the same outcome measures, the results were pooled to obtain an overall estimate of effect size using Revman 5 (Cochrane Collaboration). For estimates of typical relative risk and risk difference, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. All meta-analyses were done using the fixed effect model.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were prospectively planned.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

For details see: Tables 'Characteristics of Included Studies', and 'Characteristics of Excluded Studies'.

Six randomized, controlled trials on the use of intravenous midazolam in infants were identified. One trial using a single bolus dose of intravenous midazolam was excluded (McCarver-May 1996). Another trial using intravenous midazolam for anesthetic induction was excluded (Kawakami 1998). In the third excluded trial (Parkinson 1997), midazolam was used for sedation in patients from one day to 15 years of age, and data for the neonates could not be extracted. The three trials included in this review (Jacqz-Aigrain 1994; Anand 1999; Arya 2001) reported on the effectiveness of midazolam infusion and included a total of 146 infants.

The literature search conducted in September 2009, did not identify any additional trials.

In the study by Jacqz-Aigrain et al (Jacqz-Aigrain 1994), 46 preterm infants (25 were < 33 weeks, and 21 were ≥ 33 weeks gestation) ≤ 48 hours of age were randomly assigned to receive midazolam infusion or manufactured placebo for five days while mechanically ventilated for respiratory distress syndrome. Twenty-four infants received midazolam and 22 received placebo infusions. One infant in the midazolam group was withdrawn because of major neurologic abnormality at 24 hours of age. Two infants from the midazolam group and two from the placebo group were withdrawn from the study within 72 hours due to rapid clinical improvement. Contamination was noted in one infant in the placebo group (midazolam was detectable in the serum at 24 hours). Baseline characteristics did not differ between groups. Severity of illness, as measured by the mean airway pressure (MAP) while ventilated and the fraction of inspired oxygen (FiO2) from the time of enrollment to the end of the study, were not significantly different between groups. Midazolam was administered as an infusion at 60 mcg/kg/hr for up to five days in infants > 33 weeks gestation, and at 60 mcg/kg/hr for one day followed by 30 mcg/kg/hr for up to a total of five days in infants ≤ 33 weeks gestation. Duration of the infusion was not reported. Weaning of sedatives was allowed after at least 48 hours of administration; a weaning protocol, however, was not specified. The primary outcome was adequacy of sedation as measured by a behavioral score adapted from the clinical neurologic and behavioral scoring system by Barrier (Barrier 1989), and changes in physiologic variables (heart rate and blood pressure). The sedation score consists of five items, assessing facial expression, sucking, spontaneous motor activity, excitability / responsiveness to stimulation, and excessive flexion, with score ranging from 0 (sedated) to 5 (inadequate sedation). The sedation score was performed four times per day during treatment, twice by nurses and twice by physicians. Secondary outcomes included days of ventilation support, days of supplemental oxygen use, surfactant use, duration of NICU stay, and common complications of preterm birth (pneumothorax, pulmonary interstitial emphysema, hypotension, chronic lung disease, necrotizing enterocolitis, intracranial hemorrhage, persistent pulmonary hypertension of the newborn, death). Outcomes were reported on all 46 infants.

In the multicenter pilot study by Anand et al (Anand 1999), 67 preterm infants of 24 to 32 weeks gestation who were ≤ 72 hours of age and who were ventilated for < 8 hours were randomly assigned to receive midazolam infusion, morphine infusion, or dextrose placebo infusion for as long as sedation was considered necessary up to a maximum of 14 days. Twenty-two infants received midazolam infusion, 24 received morphine infusion, and 21 received dextrose placebo. The three groups did not differ significantly in baseline characteristics. Severity of illness at birth, assessed by the clinical risk index for babies (CRIB) score (Cockburn 1993), did not show any significant difference among groups at birth (p = 0.24). However, severity of illness measured by the neonatal medical index (NMI) score (Korner 1993) using response variables during the hospital stay, showed significant differences in the distribution of risk categories among the three groups at discharge (p = 0.01). Midazolam was administered at 200 mcg/kg loading dose followed by an infusion of 20, 40, or 60 mcg/kg/hr for infants of gestational ages 24 to 26, 27 to 20, or 30 to 33 weeks, respectively. Morphine was administered at 100 mcg/kg loading dose followed by an infusion of 10, 20 or 30 mcg/kg/hr for infants of gestational ages 24 to 26, 27 to 29, or 30 to 33 weeks, respectively. Duration of the infusion was not different among groups (5.1 vs. 3.4 vs. 5.0 days in the midazolam, morphine and placebo groups, respectively, p = 0.37). Additional sedation, if necessary, was provided by boluses of morphine, and the frequency and amount given were documented as a measure of inadequate sedation. Weaning of sedatives was done according to a standardized protocol. Primary outcome was the incidence of adverse neurologic events (defined as neonatal death, grade III or IV intraventricular hemorrhage, or periventricular leukomalacia). Adequacy of sedation was measured by the COMFORT score, an 8-item behavioural and physiologic measurement of distress in the pediatric intensive care unit (Ambuel 1992). The score includes assessment of: Alertness, calmness/agitation, respiratory response, physical movement, mean arterial blood pressure, heart rate, muscle tone, and facial tension, with score ranging from 8 (sedated) to 40 (not adequately sedated). Adequacy of analgesia was measured by the Premature Infant Pain Profile (PIPP) (Stevens 1996) in response to tracheal suctioning. The PIPP score includes assessment of: Gestational age, behavioural state, heart rate, oxygen satura-

tion, brow bulge, eye squeeze, and nasolabial furrow, with score ranging from 0 (adequate analgesia) to 21 (inadequate analgesia). The two scores were performed on all infants at baseline, after 24 hours of infusion, and 10 to 12 hours after discontinuation of the infusion. Other secondary outcomes included days of mechanical ventilation, continuous positive airway pressure, supplemental oxygen use, incidence of pneumothorax, duration of NICU and hospital stay, days to full enteral (full strength, full gavage, full oral) feeds, daily weight gain, and neurodevelopmental outcome at 36 weeks corrected age using the Neurobehavioral Assessment of the Premature Infant examination cluster scores (NAPI) (Korner 1991). Outcomes were reported on all 67 infants.

In the study by Arya et al (Arya 2001), 33 infants with birth weight < 2000 grams and requiring mechanical ventilation during the first week of life were randomized to receive midazolam or placebo infusion for sedation. Seventeen infants received midazolam and 16 received placebo. The two groups were similar in baseline characteristics. Severity of respiratory illness, as measured by peak inspiratory pressure (PIP), mean airway pressure (MAP), oxygenation index (OI), and the alveolar-arterial oxygen gradient (AaDO2), were similar between the two groups at the time of enrolment. Midazolam was administered intravenously at 200 mcg/kg loading dose followed by an infusion of 60 mcg/kg/hr. Infants in both groups also received morphine infusion at 10 mcg/kg/hr during the study period. The study concentrated on the first 48 hours of midazolam infusion and did not report on duration of benzodiazepine use and on the method of weaning. Three infants in each group did not complete the first 24 hours of the study, and four in each group did not complete the 48 hours of the study. Reasons for withdrawal were death (13 infants) and extubation (one infant). They were included in the analyses on an intention-to-treat basis. The primary outcome was adequacy of sedation as measured by a behavioural score adapted from the clinical neurologic and behavioural scoring system by Barrier (Barrier 1989). This is the same scoring system used in the study by Jacqz-Aigrain et al (Jacqz-Aigrain 1994). The study infants were assessed for adequacy of sedation prior to midazolam administration and then every six hours over the 48-hour study period. Other outcomes measured include changes in physiologic variables (heart rate and blood pressure), changes in oxygen requirement (FiO2), ventilation requirement (PIP, PEEP, ventilator rate) and arterial blood gas as measured by mean daily values. Complications related to mechanical ventilation (air leak, intraventricular hemorrhage), potential adverse effect of midazolam (epileptiform movements, hypotension, tachycardia, and oliguria) were also documented. The duration of ventilation was reported. No long-term outcome was reported. Outcomes were reported on all 33 infants in the study.

Risk of bias in included studies

For details see: table of included studies

Jacqz-Aigrain et al (Jacqz-Aigrain 1994)

Infants were randomized using sealed envelopes in a box; however, adequacy of allocation concealment was unclear from the description of the study methodology. Blinding of intervention and outcome measures was ensured. Outcomes were reported on all infants who received the study drug.

Anand et al (Anand 1999)

Balanced randomization in blocks, stratified by each participating center of the NOPAIN trial, was performed via a 24 hour automated telephone response system. Blinding of randomization was ensured. The identity of the study drug was concealed, and blinding of both the intervention and the outcome measures was achieved. Outcomes were reported on all infants enrolled in the study.

Arya et al (Arya 2001)

Randomization was performed using opaque envelopes containing computer-generated random numbers. Blinding of intervention was ensured by providing placebo with colour and vial volume similar to midazolam. Blinding of outcome measures was achieved. Outcomes were reported on all infants enrolled in the study.

Sample size calculation was performed only in the study by Arya et al (Arya 2001), although the study by Anand et al (Anand 1999) was stated as a pilot trial. Statistical analyses were performed using an intention-to-treat approach in all three studies.

Effects of interventions

MIDAZOLAM INFUSION VS. PLACEBO (COMPARISON 01)

In the study by Anand et al (Anand 1999), outcomes were evaluated by analysis of variance to detect statistically significant differences among the midazolam, morphine, and placebo groups. For this review we have performed comparisons between the midazolam group and the placebo group on relevant continuous outcome variables using the information available from the publication (sample size, mean, standard deviation, standard error of the mean).

Level of sedation

Jacqz-Aigrain et al (Jacqz-Aigrain 1994)

Sedation scores were not different between groups at baseline. The midazolam group had consistently lower scores (more sedated) than the placebo group on all days as assessed by both nurses and physicians ($p < 0.05$). Significant decreases in sedation scores from baseline [mean (SD) score 1.9 (0.4)] to day one [score 1.1 (0.3), $p < 0.01$] , day two [score 0.8 (0.2), $p < 0.01$] and day three [score 1.1 (0.3), $p < 0.05$] were observed in the midazolam group (per nurses' score), while significant increases were observed in the placebo group from baseline [mean (SD) score 1.7 (0.3)] to day one [score 2.6 (0.3), $p < 0.01$] (per physicians' score). Heart rates and blood pressures did not differ between groups at baseline, but were significantly lower in the midazolam group than in the placebo group on days one and two. These trends continued through to day five, although they were not statistically significant. One infant

in the midazolam group and seven in the placebo group ($p < 0.05$) were inadequately sedated and required fentanyl and muscle relaxants within 72 hours. Two infants in the midazolam group received fentanyl within 72 hours.

Anand et al (Anand 1999)

Compared to the placebo group, statistically significantly lower COMFORT score (more sedated) was noted in the midazolam group during the infusion [mean (SD) score 14.9 (4.6) vs. 17.5 (4.2), $p = 0.04$], although there was no statistically significant difference in scores between these two groups before the infusion and 12 hours after stopping the infusion [mean (SD) score 15.9 (3.8) vs. 15.6 (3.2), $p = 0.8$, before the infusion and 15.8 (4.7) vs. 16.2 (4.1), $p = 0.76$, after the infusion]. In response to tracheal suctioning, the midazolam group had significantly lower PIPP scores (more sedated) during the infusion compared with the placebo group [mean (SD) score 8.9 (3.3) vs. 12.7 (3.8), $p < 0.001$]. The requirement for additional morphine was not statistically different between the midazolam and the placebo groups, but there was a trend of the midazolam group to require fewer additional morphine doses than the placebo group.

Arya et al (Arya 2001)

Sedation scores were not significantly different between the two groups at baseline. The midazolam group had statistically significantly lower sedation scores (more sedated) than the placebo group from 18 hours after starting infusion [median (range) score 0 (0 to 3) vs. 1 (0 to 4), $p < 0.05$]. This trend continued for the study duration (up to 48 hours), with statistical significant difference noted at 36, 42, and 48 hours of the study drug infusion. Mean daily heart rates and blood pressures were not significantly different between the two groups throughout the study (data not reported).

Even though Jacqz-Aigrain et al (Jacqz-Aigrain 1994) and Arya et al (Arya 2001) both used the same sedation score, results on adequacy of sedation could not be combined by meta-analysis, as Arya et al (Arya 2001) presented the sedation scores as median and range.

Intraventricular hemorrhage (Outcome 01.1):

Neither Jacqz-Agrain et al (Jacqz-Aigrain 1994) nor Anand et al (Anand 1999) found a statistically significant difference between the midazolam and placebo groups in the incidence of intraventricular hemorrhage (IVH). In the study by Arya et al (Arya 2001), no intracranial hemorrhage was observed during the 48-hour study period in all of the enrolled neonates. Meta-analysis of the results of the three studies showed no statistically significant difference in the incidence of IVH of any grade [relative risk (RR) 1.68, 95% CI 0.87, 3.24; risk difference (RD) 0.12, 95% CI -0.02, 0.26].

Mortality (Outcome 01.2):

Neither Jacqz-Aigrain et al (Jacqz-Aigrain 1994) nor Anand et al (Anand 1999) found a statistically significant difference between the midazolam and placebo groups in mortality. Arya et al (Arya 2001) did not report mortality as an outcome measure. However, six infants in the midazolam group and seven in the placebo group died before completing the 48-hour study period. Meta-analysis of the results of the three studies shows no evidence of effect (RR 0.79, 95% CI 0.40, 1.56; RD -0.05, 95% CI -0.18, 0.09).

Occurrence of adverse effects associated with midazolam administration:

Jacqz-Aigrain et al (Jacqz-Aigrain 1994)

No adverse neurologic effect was reported. However, one infant in the midazolam group was excluded from the study within 24 hours due to major neurological abnormalities. Details around the case were not described. There was no statistically significant difference in the incidence of hypotension requiring albumin or vasoactive drugs between groups (8/24 vs. 6/22).

Anand et al (Anand 1999)

No adverse neurologic effect associated with midazolam administration was noted. The incidence of hypotension was not reported.

Arya et al (Arya 2001)

No adverse neurologic effect associated with midazolam administration was noted. Epileptiform movements of unknown cause were noted in two infants in the placebo group. Significant hypotension was not noted in any infant during the study period.

Pulmonary outcomes (Outcomes 01.3 - 01.5):

Jacqz-Aigrain et al (Jacqz-Aigrain 1994)

No statistically significant difference was noted between groups in days of ventilation, days of supplemental oxygen use, incidence of pneumothorax, and incidence of pulmonary interstitial emphysema.

Anand et al (Anand 1999)

No statistically significant difference was noted between the midazolam group and the placebo group in days of ventilatory support, days of supplemental oxygen use, and incidence of pneumothorax.

Arya et al (Arya 2001)

Oxygenation status, ventilation parameters, and blood gas measurements were not significantly different between the two groups. Days of ventilation were similar between the two groups. Days of oxygen use were not reported. Pneumothorax was not observed in any infant during the study period.

Data on days of ventilation in the study by Arya et al (Arya 2001) were presented as median and range and therefore cannot be combined with data from the other two studies. Meta-analyses of the results of the studies by Jacqz-Aigrain et al (Jacqz-Aigrain 1994) and Anand et al (Anand 1999) showed no statistically significant difference in days of ventilation [weighted mean difference (WMD) 3.6 days, 95% CI -0.2, 7.4], and days of supplemental oxygen use (WMD 0.6 days, 95% CI -5.3, 6.6).

From the three studies, meta-analysis of the results on incidence of pneumothorax between the midazolam and placebo groups showed no evidence of effect (RR 1.08; 95% CI 0.41, 2.84; RD 0.01; 95% CI -0.10, 0.12).

Length of NICU stay (Outcome 01.6):

In the study by Jacqz-Aigrain et al (Jacqz-Aigrain 1994) and Anand et al (Anand 1999), the length of NICU stay was not statistically significantly different between the midazolam group and the

placebo group. Arya et al (Arya 2001) did not report on the length of NICU stay.

Meta-analysis of the data by Jacqz-Aigrain et al (Jacqz-Aigrain 1994) and Anand et al (Anand 1999) showed that the midazolam group had a statistically significantly longer length of stay in the NICU than the placebo group (WMD 5.4 days, 95% CI 0.4, 10.5).

Neurodevelopmental outcome:

Jacqz-Aigrain (Jacqz-Aigrain 1994)

Long-term neurodevelopmental outcome was not reported.

Anand et al (Anand 1999)

No statistically significant difference in NAPI score at 36 weeks corrected gestational age was noted between the midazolam group and the placebo group.

Arya et al (Arya 2001)

Long-term neurodevelopmental outcome was not reported.

DISCUSSION

Since the introduction of midazolam into the NICU in the 1980's, little information has been published on its effectiveness and safety when administered to critically ill neonates. The majority of reports to date are case series and case reports of midazolam use in patients of diverse age groups (from three days to 18 years of age), in variable doses (from 0.025 to 0.3 mg/kg administered as a bolus, to 24 to 400 mcg/kg/hr administered as an infusion) (Hartwig 1991, Pellier 1999, Rosen 1991, Stenhammar 1994). The three studies included in this review (Jacqz-Aigrain 1994, Anand 1999, Arya 2001) are the only randomized, controlled trials on the use of midazolam infusion for sedation in infants to date. The repeat literature search in September 2009 did not identify any additional trials.

There is a paucity of tools to measure level of sedation in preterm infants (AAP/CPS 2000). Sedation level in such infants is currently measured by scales previously validated in older infants and children. Whether these scales are appropriate in preterm infants are unknown. Therefore, in the three randomized, controlled trials included in this review (Jacqz-Aigrain 1994; Anand 1999; Arya 2001), although intravenous infusion of midazolam appeared to be an effective sedative compared to placebo, a definite conclusion on the its effectiveness as a sedative in preterm infants could not be drawn. Anand et al (Anand 1999) assessed level of sedation by the COMFORT score, a composite scale using eight behavioral and physiologic items to assess distress (Ambuel 1992). Although the items are applicable to preterm infants, the score has only been validated in older infants and children (mean age of 37.1 months). Jacqz-Aigrain et al (Jacqz-Aigrain 1994) and Arya et al (Arya 2001) both used a sedation scale adapted from the scoring system by Barrier (Barrier 1989), which was not validated in preterm infants, by choosing five of the 10 items from the scoring system. The validity of such adapted score in assessing sedation level in neonates is unknown.

The study by Jacqz-Aigrain et al (Jacqz-Aigrain 1994) showed similar incidence of intracranial hemorrhage between the midazolam and control groups. However, the midazolam-treated infant who was excluded within 24 hours for major neurologic abnormalities raises concern about the safety of midazolam. In the study by Anand et al (Anand 1999), the incidence of poor neurological outcome (death, severe intraventricular hemorrhage, periventricular leukomalacia) was higher in the midazolam group compared to the placebo group and the morphine group (32% vs. 24% vs. 4%, respectively, p = 0.03). It should be noted, however, that the morphine group included a higher percentage of female infants with slightly higher birth weight and more mature gestational age. These baseline characteristics may have contributed to the difference in neurologic outcomes in the groups.

Adverse neurologic effects associated with midazolam in term and preterm neonates have been reported in the literature (Bergman 1991; Collins 1991, van den Anker 1992; Magny 1994; Adams 1997; Ng 2002). A variety of transient neurologic effects have been reported after boluses and/or infusions of midazolam, including impaired level of consciousness, lack of visual following, hypertonia, hypotonia, choreic movements, dyskinetic movements, myoclonus, and epileptiform activity. Abnormalities in electroencephalograms were also noted in some cases. In all of these cases, the effects were transient, although long term neurodevelopmental outcomes were not reported. Two studies (van Straaten 1992; Harte 1997) have found a significant decrease in middle cerebral artery blood flow velocity in preterm infants administered a single bolus injection of midazolam. This effect lasted up to one hour, and was directly related to a drop in the mean arterial blood pressure. Thus, it appears that the neurologic effects of midazolam may be at least partially related to transient cerebral hypoperfusion. The long-term sequalae of these effects are not known.

The mechanism of midazolam-induced hypotension was thought to be vasodilation related to levels of extravascular prostanoids and calcium (Modanlou 1997). In the study by Jacqz-Aigrain et al (Jacqz-Aigrain 1994), the number of infants with hemodynamic instability was not significantly different between the midazolam and the placebo groups (8 vs. 6), although infants in the midazolam group had significantly lower blood pressures than infants in the placebo group. Other investigators (Burtin 1991; van den Anker 1992; Ng 2002) have observed significant hypotension in several preterm infants after bolus doses and infusions of midazolam that required volume resuscitation or vasoactive drugs. In the majority of cases, fentanyl was administered concomitantly.

AUTHORS' CONCLUSIONS

Implications for practice

Definite conclusions about the effectiveness and safety of midazolam infusion (in the dose range of 30 to 60 mcg/kg/hr) as a sedative in preterm neonates cannot be made from this systematic review. The occurrence of adverse neurologic events, though they may be multifactorial in origin, were more frequently observed in the midazolam-treated infants in the studies included in this review. These adverse effects cannot be dismissed in light of previous case reports of serious neurologic and hemodynamic effects from non-randomized, uncontrolled studies, and studies on the effect of midazolam on cerebral artery blood flow velocity. The use of intravenous midazolam infusion, therefore, cannot currently be recommended in the preterm population.

Implications for research

There is a need to develop reliable, valid, and clinically useful scales to measure level of sedation in pre-verbal infants. With the development of such scales, further research on the effectiveness of sedatives such as midazolam infusion on term and preterm infants may be performed. With regards to the safety of midazolam use in infants, further studies on the short and long term adverse effects associated with the use of midazolam are needed.

ACKNOWLEDGEMENTS

Joseph Beyene, Biostatistician, University of Toronto, Ontario, Canada, for statistical analyses of the study by Anand et al (Anand 1999).

The Cochrane Neonatal Review Group has been funded in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN267200603418C.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anand 1999

Methods	Multicenter randomized, double blind, placebo-controlled pilot study (NOPAIN trial). 1. Blinding of randomization - Yes 2. Blinding of intervention - Yes 3. Complete follow up - Yes 4. Blinding of outcome measure - Yes
Participants	Preterm infants from 24-32 weeks gestational age ≤ 72 hours postnatal age who were ventilated for < 8 hours were eligible for inclusion. Exclusion criteria: major congenital anomalies, severe intrapartum asphyxia (5 minute Apgar score ≤ 3), and participation in other studies interfering with the NOPAIN trial procedures. 67 infants were randomized. Demographic data: Values presented as mean (SD). Midazolam group (n=22) Gestational age: 28.6 (2.5) wks Birth weight : 1245 (445) g Entry weight: 1224 (491) g Male (%): 54.5 Duration of infusion: 122.2 (122.1) hrs CRIB score: 5.7 (3.5) Morphine group (n=24) Gestational age: 29.2 (2.2) wks Birth weight: 1230 (475) g Entry weight: 1265 (501) g Male (%): 46.2 Duration of infusion: 81.0 (94.1) hrs CRIB score: 4.5 (3.1) Placebo (10% Dextrose) group (n=21) Gestation age: 28.1(2.2) wks Birth weight: 1049 (419) g Entry weight: 1188 (524) g Male (%): 57.1 Duration of infusion: 121.1(120.8) hrs CRIB score: 6.6 (4.0)
Interventions	Midazolam was given as 200 mcg/kg loading dose followed by infusion of 20, 40, or 60 mcg/kg/hr for those whose gestational age were 24-26, 27-29, or 30-33 weeks, respectively. Morphine was given as 100 mcg/kg loading dose, followed by infusion of 10, 20, or 30 mcg/kg/hr for those whose gestational age were 24-26, 27-29, or 30-33 weeks, respectively. Additional analgesia was given, as needed, by intravenous morphine boluses at the discretion of the clinical team. The amount and frequency of additional morphine was recorded as an outcome measure. The infusions were weaned according to a set protocol. The maximum duration of study treatment was 14 days.

Anand 1999 (*Continued*)

Outcomes	Severity of illness was measured by the CRIB score (Cockburn 1993), and the NMI (Korner 1994). Primary outcome: Incidence of adverse neurological event (neonatal death, grade III/IV intraventricular hemorrhage, periventricular leukmalacia). Secondary outcomes: Level of sedation, as measured by the COMFORT score (Ambuel 1992). Pain response to tracheal suctioning, as assessed by the PIPP (Stevens 1995). All of these scores were assessed before starting the study treatment, after 24 hours of infusion, and at 10-12 hours after treatment was discontinued. Incidence of pneumothorax, days of ventilatory support, continuous positive airway pressure, and oxygen, length of intensive care unit and hospital stay, and neurodevelopmental outcome measured by the Neurobeurobehavioral Assessment of the NAPI cluster scores (Korner 1991) at 36 weeks corrected gestational age.
Notes	Balanced randomization by blocks stratified by each participating center. Randomization performed by a 24 hour automated telephone response system. Reasons for nonenrollment were provided. Finnegan neonatal abstinence scale was performed at 12 and 24 hours after discontinuation of study infusion, and then daily.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Balanced randomization in blocks, stratified by each participating centre via a 24 hour automated telephone response system.
Allocation concealment?	Yes	Identity of study drug was concealed and blinding of both the intervention and the outcome measures were achieved.
Free of selective reporting?	Yes	Outcomes were reported on all infants enrolled in the trial.
Free of other bias?	Yes	

Arya 2001

Methods	Randomized, double-blind, placebo controlled trial. 1. Blinding of randomization - Yes 2. Blinding of intervention - Yes 3. Complete follow up - Yes 4. Blinding of outcome measure - Yes
Participants	Newborn infants < 2000 g needing mechanical ventilation during first week of life were eligible for inclusion. Exclusion criteria: encephalopathy, birth asphyxia, major malformation, maternal benzodiazepine use prior to delivery.

Arya 2001 (*Continued*)

	33 infants were randomized. 3 in each group did not complete the first 24 hours of study; 4 in each group did not complete the first 48 hours of study. Reasons for withdrawal: death (13) and extubation (1). Demographic data: Values presented as mean (SD) unless indicated. Midazolam group (n=17) Gestational age: 31.5 (2.4) wks Birth weight: 1263 (326)g Male (%): 58.8 PIP at baseline: 19.9 (5.5) cm H2O MAP at baseline: 8.7 (3.2) cm H2O Median (range) OI at baseline: 5 (1-22) Median(range) AaDO2 at baseline: 205 (13-619) Placebo group (n=16) Gestational age: 32.3 (2.2) wks Birth weight: 1337 (297)g Male (%): 75.0 PIP at baseline: 21.2 (7.1) cm H2O MAP at baseline: 9.8 (4.3) cm H2O Median (range) OI at baseline: 5 (2-55) Median(range) AaDO2 at baseline: 234.5 (59-553)
Interventions	Midazolam was given as 200mcg/kg loading dose followed by infusion of 60mcg/kg/hr. Duration of infusion and method of weaning not specified. Infants in both groups received morphine infusion at 10mcg/kg/hr during the study. The study duration was 48 hours of infusion.
Outcomes	Primary outcome: Adequacy of sedation as measured every 6 hours by a 5 item behavioural scale (facial expression, sucking, continuous motor activity, excitability and response to stimulation, excessive flexing); physiologic measures of sedation level included mean daily values of heart rate, blood pressure. Secondary outcomes: intracranial hemorrhage and epileptiform movement, hemodynamic instability (hypotension, tachycardia, oliguria) with need for volume expansion and/or vasoactive drugs, ventilation requirement (peak inspiratory and positive end-expiratory pressures, mean airway pressure and rate), days of ventilation, incidence of pulmonary air leak.
Notes	Randomization was performed using opaque envelopes containing computer-generated random numbers.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated random numbers placed in opaque envelopes.
Allocation concealment?	Yes	Placebo was manufactured with colour and vial volume similar to the study drug.

Arya 2001 (*Continued*)

Free of selective reporting?	Yes	
Free of other bias?	Yes	

Jacqz-Aigrain 1994

Methods	Randomized, double-blind, placebo controlled trial. Randomization was stratified by 2 gestational age group (<33wks and ≥33 wks). 1. Blinding of randomization - Can't tell 2. Blinding of intervention - Yes 3. Complete follow up - Yes 4. Blinding of outcome measure - Yes
Participants	Newborn infants ≤ 48 hours of age who required intubation and ventilation for respiratory distress syndrome were eligible for inclusion. Exclusion criteria: previous exposure to benzodiazepines (maternal/infant), congenital anomalies, major neurological abnormalities, low Apgar score at 5 minutes (score not defined by authors). 48 preterm infants were enrolled. 1 received midazolam previously and 1 with 5 minute Apgar score of 0 were excluded. 46 infants (25 were ≤ 33 weeks, 21 were >33 weeks gestational age) were included in the analysis. Demographic data: Values presented as mean (SD). Midazolam group (n=24) Gestational age: 32.1(2.8) wks Birth weight: 1820 (647) g Male %: 58.3 5 minute Apgar score: 9.0 (1.2) MAP at enrollment: 12 (2) mmHg FiO2 at enrollment: 49 (13) % Duration of infusion: 78.7 (30.9) hrs Placebo group (n=22) Gestational age: 32.8 (2.6) wks Birth weight: 2000 (548) g Male %: 59.1 5 minute Apgar score: 8.1 (2.3) MAP at enrollment: 13 (2) mmHg FiO2 at enrollment: 51 (16) %
Interventions	24 received midazolam infusion. For infants ≥33weeks: 60mcg/kg/hr for up to 5 days. For infants<33 weeks: 60mcg/kg/hr for 1 day, then 30mcg/kg/hr for up to 5 days. Infusion may be stopped after 48 hours if no longer required. 22 infants received a manufactured placebo. Additional sedation with fentanyl or the use of muscle relaxant was permitted; the study protocol was interrupted in such cases, but data from these infants were used in the analysis.

Jacqz-Aigrain 1994 (*Continued*)

Outcomes	Primary outcome: Adequacy of sedation as measured 4 times per day (twice by nurses and twice by physicians)by a 5 item behavioural scale (facial expression, sucking, spontaneous motor activity, excitability and response to stimulation, excessive flexing); physiologic measure of sedation level include mean daily values of hourly heart rate, systolic and diastolic blood pressures; Secondary outcomes include: Incidence of intracranial hemorrhage and epileptiform movement.; hemodynamic instability (need for fluid, albumin, vasoactive drugs); ventilation requirement (Peak inspiratory and positive end-expiratory pressures, mean airway pressure), days of ventilation, days of supplemental oxygen use, incidence of pneumothorax and pulmonary interstitial emphysema; total days of intensive care unit stay. Serum concentrations of midazolam were monitored before, 24 and 48 hours after infusion was started, and at the end of treatment.
Notes	Randomization was performed by picking of the next envelope in 2 boxes, one for each gestational age stratum. Protocol for weaning of study drug was not described.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information on sequence generation.
Allocation concealment?	Unclear	Allocation by using the next sealed envelope in the appropriate box stratified by postmenstrual age at birth (< 33 weeks or $\geq$ 33 weeks). Cannot be certain from description of the study methodology if the allocation was concealed.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

AaDO2, alveolar-arterial oxygen gradient; CRIB, clinical risk index for babies; FiO2, fraction of inspired oxygen concentration; MAP, mean airway pressure; NAPI, neurobehavioral assessment of the premature infant; NMI, neonatal medical index; OI, oxygenation index; PIP, peak inspiratory pressure; PIPP, premature infant pain profile; SD, standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Kawakami 1998	A randomized, controlled trial comparing intravenous lidocaine (1.5mg/kg) to intravenous midazolam (0.1mg/kg) in addition to lidocaine for anesthetic induction in 27 neonates undergoing surgery. It was excluded because midazolam was given as a single bolus dose and was not used as a sedative.
McCarver-May 1996	A randomized crossover trial comparing intravenous midazolam (0.2mg/kg) to oral chloral hydrate (75mg/kg) for sedation during neuroimaging studies in seven full term neonates. It was excluded because midazolam was given as a single bolus dose.
Parkinson 1997	A randomized, controlled trial comparing oral chloral hydrate (25mg/kg to 50mg/kg) with promethazine (0.5mg/kg to 1.0mg/kg) to an intravenous midazolam infusion (50mcg/kg/hr to 300mcg/kg/hr) for sedation in the critically ill. It was excluded because the population studied included children from one day to 15 years of age, and that data for the neonates could not be extracted from the study.

DATA AND ANALYSES

Comparison 1. Midazolam versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intraventricular hemorrhage (any grade)	3	122	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.87, 3.24]
2 Mortality	3	122	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.56]
3 Days of ventilation	2	89	Mean Difference (IV, Fixed, 95% CI)	3.60 [-0.25, 7.44]
4 Days of supplemental oxygen use	2	89	Mean Difference (IV, Fixed, 95% CI)	0.64 [-5.30, 6.57]
5 Pneumothorax	3	122	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.41, 2.84]
6 Length of NICU stay (days)	2	89	Mean Difference (IV, Fixed, 95% CI)	5.44 [0.40, 10.49]

Analysis 1.1. Comparison 1 Midazolam versus placebo, Outcome 1 Intraventricular hemorrhage (any grade).

Review: Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

Comparison: 1 Midazolam versus placebo

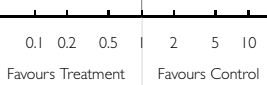
Outcome: 1 Intraventricular hemorrhage (any grade)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Anand 1999	10/22	4/21		2.39 [0.88, 6.44]
Arya 2001	0/17	0/16		0.0 [0.0, 0.0]
Jacqz-Aigrain 1994	8/24	6/22		1.22 [0.50, 2.97]
Total (95% CI)	**63**	**59**		**1.68 [0.87, 3.24]**

Total events: 18 (Treatment), 10 (Control)

Heterogeneity: $Chi^2 = 0.97$, df = 1 (P = 0.32); $I^2 = 0.0\%$

Test for overall effect: Z = 1.56 (P = 0.12)



Analysis 1.2. Comparison 1 Midazolam versus placebo, Outcome 2 Mortality.

Review: Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

Comparison: 1 Midazolam versus placebo

Outcome: 2 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anand 1999	1/22	2/21		15.2 %	0.48 [0.05, 4.88]
Arya 2001	6/17	7/16		53.7 %	0.81 [0.34, 1.89]
Jacqz-Aigrain 1994	4/24	4/22		31.1 %	0.92 [0.26, 3.23]
Total (95% CI)	**63**	**59**		**100.0 %**	**0.79 [0.40, 1.56]**

Total events: 11 (Treatment), 13 (Control)

Heterogeneity: Chi^2 = 0.24, df = 2 (P = 0.89); I^2 =0.0%

Test for overall effect: Z = 0.67 (P = 0.50)

Analysis 1.3. Comparison 1 Midazolam versus placebo, Outcome 3 Days of ventilation.

Review: Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

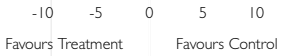
Comparison: 1 Midazolam versus placebo

Outcome: 3 Days of ventilation

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Anand 1999	22	14.2 (11.1)	21	12.2 (12.7)		29.0 %	2.00 [-5.14, 9.14]
Jacqz-Aigrain 1994	24	12.29 (10.04)	22	8.04 (5.17)		71.0 %	4.25 [-0.31, 8.81]
Total (95% CI)	**46**		**43**			**100.0 %**	**3.60 [-0.25, 7.44]**

Heterogeneity: Chi^2 = 0.27, df = 1 (P = 0.60); I^2 =0.0%

Test for overall effect: Z = 1.83 (P = 0.067)



Analysis 1.4. Comparison 1 Midazolam versus placebo, Outcome 4 Days of supplemental oxygen use.

Review: Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

Comparison: 1 Midazolam versus placebo

Outcome: 4 Days of supplemental oxygen use

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Anand 1999	22	35 (33)	21	32.3 (30.2)		9.9 %	2.70 [-16.19, 21.59]
Jacqz-Aigrain 1994	24	9.2 (9.16)	22	8.79 (12.12)		90.1 %	0.41 [-5.84, 6.66]
Total (95% CI)	**46**		**43**			**100.0 %**	**0.64 [-5.30, 6.57]**

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² =0.0%

Test for overall effect: Z = 0.21 (P = 0.83)

Analysis 1.5. Comparison 1 Midazolam versus placebo, Outcome 5 Pneumothorax.

Review: Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

Comparison: 1 Midazolam versus placebo

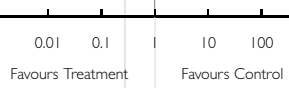
Outcome: 5 Pneumothorax

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Anand 1999	1/22	1/21		0.95 [0.06, 14.30]
Arya 2001	0/17	0/16		0.0 [0.0, 0.0]
Jacqz-Aigrain 1994	6/24	5/22		1.10 [0.39, 3.10]
Total (95% CI)	**63**	**59**		**1.08 [0.41, 2.84]**

Total events: 7 (Treatment), 6 (Control)

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² =0.0%

Test for overall effect: Z = 0.15 (P = 0.88)

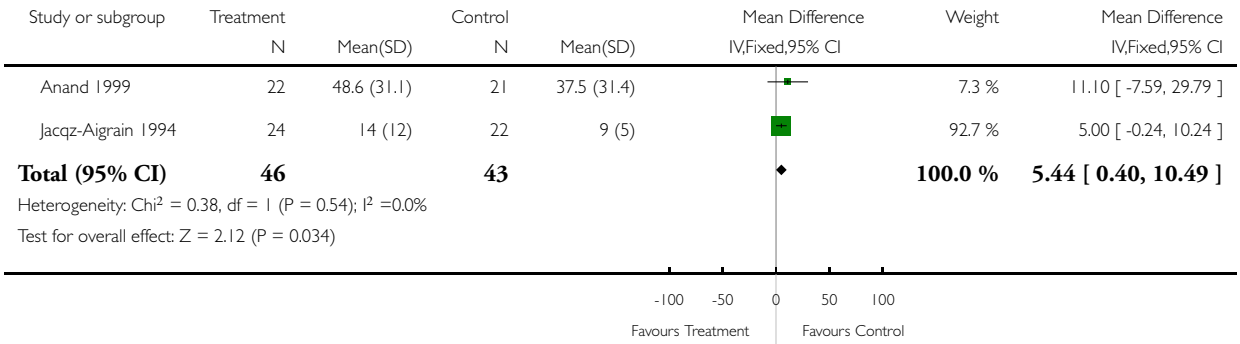


Analysis 1.6. Comparison 1 Midazolam versus placebo, Outcome 6 Length of NICU stay (days).

Review: Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit

Comparison: 1 Midazolam versus placebo

Outcome: 6 Length of NICU stay (days)



WHAT'S NEW

Last assessed as up-to-date: 8 September 2009.

9 September 2009	New search has been performed	This updates the review 'Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit' published in The Cochrane Library, Issue 1, 2003 (Ng 2003). No new trials identified.

HISTORY

Review first published: Issue 2, 2000

2 November 2008	Amended	Converted to new review format.
1 August 2006	New search has been performed	An updated search done in August 2006 found no additional studies. No change in the conclusion has been made as a result of this update.
17 September 2002	New citation required and conclusions have changed	Substantive amendment. A new search was done in September 2002, and one additional randomized controlled trial was identified for inclusion. No change in the conclusion was made as a result of this update.

CONTRIBUTIONS OF AUTHORS

E Ng:

Development and writing of protocol

Literature search and identification of trials for inclusion

Evaluation of methodologic quality of included trials

Abstraction of data independent of co-reviewer

Entering data into Revman

Writing of result section

Writing of discussion section

A Taddio:

Development of protocol

Literature search and identification of trials for inclusion

Evaluation of methodologic quality of included trials

Abstraction of data independent of co-reviewer

Verifying data entered into Revman

A Ohlsson:

Development of protocol

Literature search and identification of trials for inclusion

Verifying data entered into Revman

Revision of the final review and the 2009 update

All authors participated in the completion of the 2009 update.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Sunnybrook Health Sciences Centre, Toronto, Canada.
- The Hospital for Sick Children, Toronto, Canada.
- Mount Sinai Hospital, Toronto, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Intensive Care, Neonatal; Hypnotics and Sedatives [*administration & dosage; adverse effects]; Infant, Newborn; Infusions, Intravenous; Intensive Care Units, Neonatal; Midazolam [*administration & dosage; adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Humans